CLINICAL REVIEW

Application Type	NDA
Submission Number	21-538
Submission Code	N-000
Letter Date	May 9, 2006
Stamp Date	May 12, 2006
PDUFA Goal Date	March 10, 2007
Reviewer Name	Dragos Roman
Review Completion Date	February 21, 2007
Established Name	Somatropin
(Proposed) Trade Name	Accretropin™
Therapeutic Class	Recombinant human growth hormone
Applicant	Cangene Corporation
Priority Designation	S
Formulation	Injectable
Dosing Regimen	0.18 mg to 0.3 mg/week (for children with growth hormone deficiency) and 0.36 mg/kg/week (for children with Turner syndrome) divided into equal daily subcutaneous doses
Indication	Treatment of short stature

Intended Population Children with short stature due to) 1) growth hormone deficiency and 2) Turner syndrome

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Given that Accretropin is efficacious in improving linear growth in children with short stature due to either growth hormone deficiency or Turner syndrome, while having a safety profile similar to that of other approved recombinant human growth hormone products, it should be approved for both above-mentioned indications.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The applicant is encouraged to develop 1) a postmarketing surveillance study similar to those conducted by other manufacturers (e.g., with the goal of enhancing the long-term understanding and knowledge of Accretropin's safety profile and 2) tools and means that will evaluate and control the distribution process of Accretropin to ensure that it is prescribed by pediatric endocrinologists or physicians with expertise in pediatric growth disorders to the rightful recipients.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Accretropin is a new recombinant human growth hormone (rhGH) product generated via recombinant DNA technology in an E.coli expression system. It contains the entire 191 amino acid native GH sequence and, like other immediate-release rhGHs or somatropins it is administered daily as subcutaneous injections six times per week.

The Accretropin clinical program consists of three clinical studies: a phase I bioequivalence study (Study GA-002) and two Phase III clinical trials: one conducted in pediatric patients with growth hormone deficiency (Study GA-005/5A) and one in girls with short stature due to Turner syndrome (Study GA-007/7A). Both Phase III clinical trials were non-randomized, single-arm, open-label studies and included patients with severe short stature. Study GA-005/5A was conducted in 4 centers in Poland and Hungary and enrolled 44 patients. Study GA-007/7A was conducted in a single center in Poland and enrolled 37 patients. Since there was no control group in either Phase III study, proof of efficacy was based on comparisons with "historical" height data obtained from normally growing children or untreated girls with Turner syndrome.

The commercial Accretropin is a liquid solution containing 1 mL of a 5 mg/mL solution of growth hormone (15 IU/mL). The formulation also contains 0.75% NaCl, 0.34% Phenol (as preservative), 0.2% Pluronic F-68 (a non-ionic surfactant), and 10 mM $NaPO_4$ buffer (final pH is 6.0).

1.3.2 Efficacy

In summary, Accretropin, when administered at standard doses, was efficacious in accelerating linear growth over 3 years of continuous treatment in children with severe short stature due to GH deficiency (GHD) and/or Turner syndrome. The efficacy data that supports this conclusion is summarized by study in the following sections.

Study GA-005/5A (GHD indication)

A standard dose of Accretropin[1] given to a cohort of patients with pediatric GHD doubled the mean height velocity (HV) for the first 12 months of treatment relative to baseline (8.8 ± 2.2

[1] Dose of 0.03-0.05 mg/kg/day (0.18 to 0.3 mg/kg/week) administered as subcutaneous injections 6 days/week.

cm/year vs. 4.1 ± 1.2 cm/yr). The mean height velocities for the second and the third year of treatment were also above the baseline height velocity (7.6 ± 1.4 cm/year for the 2nd year and 6.9 ± 1.6 cm/year for the 3rd year, respectively). Thus, Accretropin added 4.76 ± 2.89 cm/yr for Months 0-12; 3.45 ±2.02 cm/yr for Months 12- 24; and 2.79 ± 2.48 cm/yr for Months 24-36, respectively, relative to baseline HV. This increment in height velocity is fully consistent with that described for other approved somatropins.

The mean height velocity values observed with Accretropin treatment in this study were higher than the mean height velocities of two reference populations of normally growing children (one Polish and one British); these "historical" comparisons made for the ITT population at Month 6, Month 12, Month 24 and Month 36 timepoints were all statistically significant (primary efficacy analysis). The same analyses conducted in the per protocol population produced concordant results.

Several other efficacy analyses further substantiate and complement the above-described observations:

- A comparison of height velocity on Accretropin treatment with a reference values of 5 cm/year (which approximates the mean HV in normally growing prepubertal children) was statistically significant through Month 36.
- The mean height velocity SDS increased from negative values at baseline to values that were above the population mean through Month 36[2].
- Mean height SDS increased from values consistent with severe short stature at baseline (-3.0 ± 0.7) to values in the low normal range at Month 36 (-1.77 ± 0.84); the cumulative change in mean height SDS after 3 years of treatment was approximately 1.27 and was comparable for both genders.
- Accretropin treatment increased the serum concentration of IGF-1 and IGFBP-3 during the three years of treatment[3]. With respect to IGF-1, it doubled the mean serum IGF-1 concentrations and increased the mean serum IGF-1 SDS from markedly negative values at baseline (-1.47 ± 1.1) to values closer to the population mean (generally between -0.5 and 0) through Month 36.

The above described acceleration in linear growth was not associated with undue acceleration of bone age maturation for the duration of the trial.

Despite methodological limitations (i.e. shortcomings in the method of collection of baseline height velocity) the totality of the efficacy data clearly confirms the effectiveness of Accretropin treatment in severely short children with GHD.

Finally, although anti-GH antibodies were observed in up to 50% of patients, the mean height velocity for patients who developed anti-GH antibodies on Accretropin treatment was comparable to that of patients who remained antibody-negative. Importantly, there was no

[2] Baseline HV SDS was -1.85. It increased to 3.5 at Month 12; 1.9 at Month 24 and 1.7 at Month 36.
[3] Both IGF-1 and IGFBP-3 are established biomarkers of GH activity.

convincing clinical evidence to suspect growth attenuation on Accretropin treatment up to 3 years of treatment.

Study GA-007/7A (Turner syndrome indication)

Accretropin treatment of Turner syndrome patients at a standard dose[4] increased more than two-fold the height velocity from 3.8 ± 0.9 cm/yr at baseline to 8.5 ± 1.7 cm/yr at Month 12. The mean HV at Month 24 (6.8 ± 1.2 cm/yr) and at Month 36 (5.8 ± 1.8 cm/yr) were also above the baseline HV. This represents an increase in HV of 4.7 ± 2.8 cm/yr for Months 0-12 and 3.4 ± 2.0 cm/yr for Months 12-24 and 2.7 ±2.4 cm/yr for Months 24-36. This increment in HV is consistent with that of other somatropins in similar cohorts of patients with Turner syndrome.

The mean height velocity on Accretropin treatment was higher than the height velocities of two reference populations of normally growing children (one Polish and one British); these "historical" comparisons were statistically significant for the Month 6, Month 12, and Month 24 timepoints but not for the Month 36 timepoint (primary efficacy analysis, ITT population). In general, per protocol and ITT analyses were concordant. A similar comparison of HV on Accretropin treatment with the historical HV of untreated Turner syndrome children (a more appropriate comparator than normally growing children) was statistically significant at all the timepoints studied up to Month 36.

Several other analyses confirmed the efficacy of Accretropin in children with Turner syndrome:

- A comparison of height velocity on Accretropin treatment with a reference values of 5 cm/year (which approximates the mean HV in normally growing prepubertal children) was also statistically significant through Month 36.
- The mean height velocity SDS increased from negative values at baseline to values that were above the population mean through Month 36[5].
- The mean height SDS increased from values consistent with severe short stature at baseline (-3.1) to values that were closer to the lower limit of the normal range at Month 36 (-2.2). The cumulative change in mean height SDS after 3 years of treatment was approximately 0.85.
- When mean height SDS on Accretropin treatment was compared with height SD scores derived from girls with Turner syndrome (a more appropriate comparison since Turner syndrome children are shorter than normal growing children), the height SDS on treatment increased from an average height (height SDS of 0.2) to a height in the upper limit of normal for Turner syndrome girls (height SDS of 1.9); the cumulative height SDS increase at 3 years was 1.7.
- Accretropin treatment increased the level of IGF-1 and IGFBP-3. Specifically it resulted in a doubling of the mean serum IGF-1 concentrations and an increase in mean serum IGF-1 SDS from markedly negative values at baseline (-1.2 ± 0.7) to values slightly above the population mean through Month 6.

[4] A dose of 0.06 mg/kg/day (0.36 mg/kg/week) administered 6 days/week.
[5] HV SDS was -2.4 at baseline. It increased to 3.0 at Month 12; 1.5 at Month 24; and 0.4 at Month 36.

The above-described acceleration in linear growth was not associated with undue acceleration of bone age maturation for the duration of the trial.

As already mentioned in reference to the GHD cohort, there were some shortcomings related to the collection of baseline height velocity information. However, the totality of the data clearly confirms the efficacy of Accretropin in severely short children with Turner syndrome.

Although up to 35% of children developed anti-GH antibodies, the mean height velocity for patients who developed anti-GH antibodies on Accretropin treatment was comparable to that of patients who did not develop antibodies through Month 36. There was no compelling clinical evidence to suspect growth attenuation on Accretropin for this duration of treatment.

1.3.3 Safety

Except for a somewhat different immunogenicity profile[6], the safety profile of Accretropin was similar to that observed for other rhGH products currently marketed. There were no new safety signals identified in this combined dataset of 81 patients (44 with GHD and 37 with Turner syndrome) treated for up to three years[7].

There was one death recorded in Study GA-005/5A: a 15-year-old with GHD developed cardiogenic shock secondary to fatty degeneration of the heart that was judged unrelated to treatment by the investigator. Cardiomyopathy due to fatty degeneration is not mentioned in any of the rhGH labels and has not been reported in postmarketing surveillance studies of rhGH[8].

No patients discontinued the trial because of adverse events. The vast majority of serious adverse events (SAEs) were background childhood illnesses and conditions. Only one of the SAEs recorded in the clinical trials was deemed "possibly related" to Accretropin treatment (insulin adjustment for high glucose levels in a patient with known type 1 diabetes mellitus)[9].

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[6] A relatively higher percentage of patients developed anti-GH antibodies at low titers without associated adverse events or growth attenuation.

[7] 243 patient-years of exposure, comparable per indication to other recently approved GH products.

[8] Ranke MB and Wilton P: Growth hormone therapy in KIGS – 10 year's experience (1999). Chapter 31: Adverse events during GH treatment: 10years's experience in KIGS, a pharmacoepidemiological survey.
Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drugs and Therapeutic Committee –J Pediatr 2003: 143: 415-21.
Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. J Clin Endocrinol Metab 2001; 86: 1868-70.
Clayton PE, Cowell CT Safety issues in children and adolescents during growth hormone therapy – a review. Growth Hormone IGF Res 2000; 10: 306-17.

[9] One patient was diagnosed with Fanconi anemia while on treatment but the screening/baseline clinical data clearly indicate that this patient had the condition at the time of enrollment. The following laboratory abnormalities were present at baseline: thrombocytopenia (38,000/mm^3) and neutropenia (2,800/mm^3). While baseline hemoglobin was at about the lower limit of normal, anemia was diagnosed at Week 8.

Most of the treatment-emergent adverse events (TEAEs) were also common childhood illnesses and conditions. Of the TEAEs that were considered treatment-related, injection site reactions were the only adverse events that could be clearly associated with the study drug[10]. The rest of the "treatment-related" adverse events were mostly adverse events known to occur in association with GH in general[11]. The few TEAEs that did not fall in this category were infrequent and inconsistently seen between the two clinical trials. Absence of a control group and the small size of the datasets limit the ability to draw additional conclusions.

There were no changes in mean values of standard analytes beyond those expected on the basis of the pharmacodynamic effect of GH in general (increase in alkaline phosphatase, IGF-I and IGFBP-3). There were no marked laboratory outliers in standard analytes. Mean vital signs were also normal and there were no outliers.

The percentage of patients who developed anti-GH antibodies during Accretropin treatment is greater than that observed with other approved immediate-release somatropins. Specifically, as many as 50% of patients in Study GA-005/5A and as many as 35% of girls in Study GA-007/7A developed anti-GH antibodies in LOCF analyses[12]. This compares unfavorably with other marketed immediate-release somatropins for which studies indicate that development of anti-GH antibodies occurs in <12% of patients and only occasionally in 20% of the patients evaluated. Importantly, however, the anti-GH antibody binding activity was relatively small and certainly below 1-2 mg/L, which is the "threshold value" under which neutralizing antibodies to GH have not been described with rhGH therapy.[13] In Study GA-005/5A the mean anti-GH antibody binding activity peaked by Months 12, declined somewhat by Month 24 and appeared to further decline by Month 36. The maximum individual antibody binding activity was 0.665 mg/L (at Week 12 and declined steadily thereafter)[14]. In Study GA-007/7A the mean anti-GH binding

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One additional patient was suspected to have increased intracranial hypertension but this is a well characterized (and labeled) adverse event associated with GH treatment.

[10] In study GA-005/5A they were recorded under several preferred terms with the following incidence rates: injection site erythema (38.6%), swelling (20.5%), bruising (11.4%), pain (6.8%), pruritus (6.8%), hemorrhage (2.3%), edema (2.3%), rash (2.3%). In study GA-007/7A they were recorded under several preferred terms with the following incidence rates: injection site erythema (29.7%), edema (5.4%), pain (2.7%), and pruritus (2.7%).

[11] Preferred terms: headache, scoliosis, hypothyroidism, myalgia, bone pain, growing pains, pain in the extremities, nausea and vomiting and headache (in the context of benign increased intracranial hypertension).

[12] In study GA005/5A anti-GH antibodies were seen as early as 8 weeks in15.9 % of all patients and further increased to 34% at Week 12, 38% at Week 24, 46.3% at Month12, 41.1% (50% in LOFC analysis) at Month 24 and 35.4% (48.3% in LOFC analysis) at Month 36. In study GA007/7A anti-GH antibodies were seen as early as 8 weeks in 16% of patients; it increased further to 29.7% patients at Week 12, 32.4% at Week 24 37.8% at Month 12. At the end of the second year 33.3% (35% in LOCF analysis) were antibody positive and after 3 years 19.3% (25.8% in LOFC analysis) were antibody positive.

[13] Ohada et al.: A case report of growth attenuation during methionyl human growth hormone treatment. Endocrinol. Japan. 34 (4), 621-626 (1987),
Pirazzoli P et al.: Follow-up of antibodies to growth hormone in 210 growth hormone-deficient children treated with different commercial preparations. Acta Paediatri 84; 1233-6, 1995.
Kaplan SL et al. Antibodies to human growth hormone arising in patients treated with human growth hormone: incidence, characteristics and effects on growth. In: *Advances in human growth hormone research: a symposium.* Washington: US Department of Health Education and Welfare, publication no NIH 74-612, 1974; 725-47.

[14] 0.357 mg/L at Week 24; 0.399 mg/L at Month 12, 0.242 mg/L at Month 24 and 0.152 mg/L Month 36 .

activity peaked by Month 12, remained relatively stable through Year 1 and 2, respectively and decreased at Month 36. The maximum individual antibody binding activity was 0.219 mg/L at Month 6[15].

Very importantly, the mean height velocities in anti-GH antibody positive and anti-GH antibody negative patients were comparable through Month 36. There were no clinical signs/symptoms suggestive of allergy, no differences in absolute eosinophil counts in patients with or without antibodies and no growth attenuation[16].

It is not clear why a larger percentage of patients appear to develop low titers relative to other somatropins. The chemistry review indicates that Accretropin has acceptable levels of impurities.

1.3.4 Dosing Regimen and Administration

Indication-specific regimens of GH have been established over the last 20 years of recombinant human GH use. The dose regimens used in pediatric GHD patients[17] and Turner syndrome patients[18] in the Accretropin clinical program are standard for each indication[19].

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

1.3.6 Special Populations

This application does not include any formal studies that evaluate the effect of gender, age, race, or co-morbid states (such as renal or hepatic failure) on the efficacy and safety of Accretropin.

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[15] 0.190 mg/L at Months 12 and 0.243 mg/L at Month 24 and 0.156 mg/L at Month 36.
[16] The mean levels and the mean change in absolute eosinophil counts (through Month 6) were similar for anti-GH positive and negative patients (and comparable to baseline counts). Importantly, the maximum eosinophil counts were also comparable.
[17] For Study GA-005/5A: 0.03 to 0.05 mg/kg/day once daily 6 times per week (0.18-0.30 mg/kg/week) for GHD and 0.06 mg/kg/day once daily 6 times per week for Turner syndrome.
[18] For Study GA-007/7A: 0.06 mg/kg/day once daily 6 times per week for Turner syndrome.
[19] Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone Deficiency in children. GH Research Society, 2000).
Tanaka T et. al: Diagnosis and management of growth hormone deficiency in childhood and adolescence – Part 2: growth hormone treatment in growth hormone deficient children. Growth Hormone & IGF Research 12, 323-41 (2002).

Efficacy analyses by gender indicated similar responses for the primary efficacy variable in boys and girls in Study GA-005/5A.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The drug substance in Accretropin is the native 191 amino acid sequence of human growth hormone expressed and [redacted] in an E.coli [redacted]. The Accretropin drug product contains rhGH, sodium chloride, phenol, sodium phosphate [redacted], sodium phosphate [redacted], and [redacted], all as a sterile clear liquid for injection supplied in [redacted]-mL glass vials.

2.2 Currently Available Treatment for Indications

Recombinant human GH (generic name: somatropin) is currently the only marketed product for the treatment of short stature[20]. Table 1 summarizes the available rhGH drug products currently marketed in the US and the indications (pediatric and adult) for each of them.

Table #1: Marketed rhGH products in the US

Product	Manufacturer	Indications
Nutropin AQ and Depot	Genentech	Peds GHD, CRI, TS, AGHD
Humatrope	Eli Lilly	Peds GHD, TS, AGHD, SHOX
Norditropin	Novo Nordisk	Peds GHD
Genotropin	Pfizer	Peds GHD, AGHD, PWS, SGA
Saizen	Serono	Peds GHD
Serostim	Serono	AIDS wasting
Tev-Tropin	Ferring	Peds GHD
Omnitrope	Sandoz	Peds and AGHD

Abbreviations: Peds GHD = pediatric growth hormone deficiency; CRI = chronic renal failure up to the point of transplantation; TS = Turner Syndrome; AGHD = adult growth hormone deficiency; SHOX = short stature homeobox-containing gene; PWS = Preder Willi Syndrome; SGA = small for gestational age children who do not manifest catch-up growth by 2 years of age.

2.3 Availability of Proposed Active Ingredient in the United States

Refer to Table 1, above. The following rhGH are approved for the indication of short stature due to pediatric GHD: Humatrope, Genotropin, Norditropin, Nutropin, Nutropin AQ, Saizen, Tev-Tropin, and Omnitrope. The following rhGH are approved for the indication of short stature due to Turner syndrome: Humatrope, Genotropin, Nutropin, and Nutropin AQ. All rhGH products currently on the market contain the native GH sequence (they all are somatropin).

[20] Methionyl-GH (generic name: somatrem; marketed as Protropin), which was the first approved rhGH product is no longer marketed in the US. The Protropin NDA was withdrawn by Genentech on [redacted] 16, 2006.

2.4 Important Issues With Pharmacologically Related Products

Recombinant human GH has been used in approximately 100,000 children to date (GH Research Society, 2001) and its safety profile is well characterized. Several adverse events have been recognized to be associated with rhGH therapy in children: intracranial hypertension (pseudotumer cerebri), edema, slipped capital femoral epiphysis, worsening of scoliosis, gynecomastia, hyperglycemia, and a possible increased risk of leukemia in children with underlying conditions that already predispose them to develop malignancies.[21]

2.5 Presubmission Regulatory Activity

The Division met with the sponsor for a pre-IND meeting (August 5, 1999) and a pre-NDA meeting (June 17, 2004). At each meeting the applicant received specific advice concerning regulatory requirements necessary to provide a fileable and reviewable NDA application.

Issues discussed included trial design and duration of treatment, efficacy endpoints, PK/PD endpoints, evaluation of immunogenicity, what represents an adequate historical control for efficacy analyses.

The following issues were discussed at the June 17, 2004 pre-NDA meeting (refer to the Meeting Minutes in DFS for details):

- The applicant has been informed that the Division and the Agency do not have an official position on follow-on biologics, in general, and follow-on GH in particular and, therefore, the sponsor was encouraged to submit a 505(b)(1) application instead of a 505(b)(2) application[22].
- CMC advice addressed questions related to changes made to the formulation of the commercial drug product relative to that of the preclinical and clinical drug product.
- The following comments were provided to the sponsor in response to clinical questions: 1) at least 12-months of clinical data are required for registration; 2) a comparison of efficacy data with historical data should be provided; 3) due to the fact that the immunogenicity data were obtained with the development product, a 6-month immunogenicity study may be required in phase IV; 4) an analysis of change in height velocity SDS on treatment relative to height velocity SDS at baseline should be presented for each clinical study; 5) efficacy variables should be presented as standard deviation scores.

[21] Update of the guidelines for the use of growth hormone in children: the Lawson Wilkins Endocrinology Society Drug and Therapeutics Committee. J Pediatr 143: 415-21 (2003).
[22] Consequently the applicant filed a 505(b)(1) application.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There were several formulation changes made during the development of Accretropin with respect to the concentration of phenol. Specifically, the phenol concentration was [redacted] in the commercial product to 0.34% from [redacted] in the phase II/III trials and [redacted] in the preclinical and phase I clinical trial, respectively. T[redacted]. The concentrations of hGH, sodium phosphate, sodium chloride, and [redacted] remained unchanged during the Accretropin development.

The commercial Accretropin is a liquid solution containing 1 mL of a 5 mg/mL solution of growth hormone (15 IU/mL). The formulation also contains 0.75% NaCl, 0.34% Phenol (as preservative), 0.2% Pluronic F-68 (a non-ionic surfactant), and 10 mM $NaPO_4$ buffer (final pH is 6.0).

The physico-chemical characterization of Accretropin was extensive and included molecular mass determination (by[redacted] mass spectroscopy), peptide mapping, CD and NMR spectroscopy as means of assessing and verifying the molecular structure. Impurity profiles were characterized by[redacted].

The biological activity of Accretropin has been measured using a cell proliferation bioassay using the Nb2 rat lymphoma cell line. The biological activity of somatropin is determined using the WHO International Standard (NIBSC Code 98/574) as the reference standard, and expressed in International Units/mg (IU/mg).

The CMC reviewer recommends approval[23].

3.2 Animal Pharmacology/Toxicology

The following preclinical toxicology studies were included:

- A single-dose and 10-day repeated dose toxicity study in rats (via subcutaneous injection)
- A 30-day subcutaneous injection toxicity study in rats

[23] The CMC review indicates that a level of E. coli proteins **is** acceptable from a CMC point of view and is controlled at [redacted] ng/mg at release.

- A 10-day weight gain (potency) study in hypophysectomized rats.

The applicant requests a waiver for additional non-clinical pharmacology and toxicology testing under 21.CFR 314.90 on the basis that the "pharmacology and toxicology of rhGH has been well established."

3.3 Other consults

The statistical review is pending at this time. Preliminary discussions with the statistical reviewer do not indicate any objections to approval of Accretropin.

A DMETS consult completed on February 2, 2007 found no objection to the use of the proprietary name Accretropin.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data evaluated in this review are from three clinical studies conducted with Accretropin:

- A pharmacokinetic/bioequivalence study (Study GA-002) that compared Accretropin to Humatropin (an approved GH product)
- A 36-month efficacy and safety study conducted in children with short stature due to GH deficiency (Study GA-005/5A)
- A 36-month efficacy and safety study conducted in children with short stature due to Turner syndrome (Study GA-007/7A).

4.2 Tables of Clinical Studies

A summary of the clinical studies that constitute the Accretropin clinical program is presented in Table 2.

Table 2: Summary of the clinical studies of Accretropin

Name of study	Main characteristics
GA-002	A Phase I, crossover pharmacokinetic/bioequivalence study that compared Accretropin (4 mg) to Humatropin (4 mg) in healthy volunteers.
GA-005/5A	A Phase III, multicenter, single-arm, open-label, non-randomized, historically controlled, study conducted in 44 patients with GHD for 36 months.
GA-007/7A	A Phase III, single center, single-arm, open-label, non-randomized, historically controlled, study conducted in 37 patients with Turner syndrome for 36 months.

4.3 Review Strategy

The review focuses on the two Phase 3 clinical trials submitted (GA-005/5A and GA-007/7A). The results were interpreted in the context of our current knowledge of the efficacy and safety of GH in general.

4.4 Data Quality and Integrity

The clinical protocol specified clearly the responsibilities of the investigators, the procedures for collecting and handling the clinical information (including Case Report Forms), and the responsibilities of the Medical Monitor. The study sites were monitored by Cangenes's clinical research scientist and by a contract research organization. For Study GA-005/5A Cangene Corporation performed an audit on April 14-16, 2003 at site 100 (Warsaw, Poland); there were no audits performed by [redacted] For Study GA-007/7A site audits were done by both Cangene Corporation (on April 14-16, 2003) and by [redacted]. The submission describes the general methodology used to insure the quality and integrity of the data. The data submitted appears complete and internally consistent. There were no major inconsistencies between different parts of the submission (numerical or otherwise).

A DSI inspection was conducted at the largest site, which enrolled 24 subjects in Study GA-005/5A and thirty-seven subjects in Study GA-007/7A. Several protocol deviations and violations were observed. However, the overall conclusion was that

> The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indications.

4.5 Compliance with Good Clinical Practices

The applicant states that the study was conducted "in accordance with the International Conference on Harmonizarion (ICH) and Good Clinical Practices (GCP) guidelines." The applicant states that "all studies were conducted according to the current GCP guidelines and related Cangene Corporation SOPs." The protocol was consistent with this statement. The study protocol (including amendments) state that the informed consent was to be reviewed and approved by a Research Ethics Board.

4.6 Financial Disclosures

The applicant submitted FDA Form 3454 and certified that there have been no financial agreements between Cangene Corporation and the nine clinical investigators that participated in the Accretropin development program that may have affected the outcome of the studies. The

applicant further certified that none of the clinical investigators had a proprietary interest in Accretropin and none received significant payments as defined in 21 CFR 54.2 (f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The applicant conducted a phase I, randomized, double-blind, crossover, single-dose bioavailability study (Study GA-002) in healthy adult male volunteers aged 18-55 years whose endogenous GH secretion was suppressed by a somatostatin infusion[24]. Patients received a single 4-mg dose of Accretropin and Humatrope, respectively, with a 7-day wash out period between doses. The Accretropin to Humatrope ratios for AUC_{0-24} and C_{max} were within the 90% confidence interval of 0.80 and 0.125 (94.23 for AUC_{0-24} and 103.84 for C_{max}, respectively), thus establishing bioequivalence between them[25]. The comparative bioequivalence data are summarized in Table 3. Although not displayed in this review, the 24-hour profile of the mean GH concentrations was visually very similar for both rhGH products.

Importantly, the study was conducted in 1999 with a formulation that is slightly different in the phenol concentration relative to the proposed commercial formulation (vs. 0.34%).

Table 3: Bioequivalence between Accretropin and Humatrope (Study GA-002)

	Accretropin	Humatrope	Ratio of Geometric mean	90% Confidence Interval
Uncorrected for measured drug content				
AUC (0-t)*	232.93	247.2	94.23	88.7-100.10
AUC (0-inf)*	249.63	257.67	96.88	93.28-100.61
C_{max}**	28.18	27.14	103.84	95.73-112.63
Corrected for measured drug content				
AUC (0-t)*	234.23	243.12	96.35	90.81-102.23
AUC (0-inf)*	251.03	253.42	99.06	95.46-102.81
C_{max}**	28.34	26.69	106.17	98.05-114.97

*ng.h/mL
**ng/mL
Source" Table 2.5.3.1a.

[24] The infusion rate of somatostatin was 25 µg/hr for 24 hours. Such infusion rate results in an 84% inhibition of endogenous GH (doubling and tripling of the infusion rates increase only minimally the level of suppression to: 86% and 90%, respectively).
[25] The two rhGH have different excipients. Although the bioavailability of Accretropin was not formally calculated, it is assumed to be that of Humatrope (75%) and similar with other approved GH drug products (63% for Genotropin and 72% for Saizen).

5.2 Pharmacodynamics

The pharmacodynamic endpoints (secondary endpoints) evaluated in study GA-002 were insulin-like growth factor-1 (IGF-I), insulin-like growth factor binding protein-3 (IGFBP-3), and serum glucose. IGF-1 and IGFBP-3 were also evaluated as secondary endpoints during the two clinical trials GA-0005/5A and GA-007/7A (refer to Section 6.14 for details). Both IGF-1 and IGFBP-3 are standard pharmacodynamic (PD) endpoints in rhGH efficacy trials in humans.

Following administration of 4-mg of Accretropin, the serum IGF-1 concentration increased within 8 hours and serum IGFBP-3 increased within 24 hours. This observation is consistent with data from other rhGH applications and literature publications. Table 4 summarizes descriptively the PD results for IGF-1, IGFBP-3, and glucose for the 24 hour endpoint. The changes in these three parameters were similar for Accretropin and Humatrope. Although not displayed in this review, the 24-hour profiles of the mean IGF-I concentrations were visually very similar for both drug products.

Table 4: PD endpoints in study GA-002

Variable	Treatment	Serum concentration at baseline	Serum concentration after 24 hours	AUC_{0-24}	AUC_{0-24} Ratio (%)
IGF-I	**Accretropin**	151.2 µg/L	394.3 µg/L	6133.56 µg.h/L	98.94
	Humatrope	151.4 µg/L	412.9 µg/L	6273.99 µg.h/L	
IGFBP-3	**Accretropin**	2848.6 µg/L	3385.0 µg/L	70720.45 µg.h/L	97.14
	Humatrope	2997.5 µg/L	3445.7 µg/L	73234.85 µg.h/L	
Glucose	**Accretropin**	5.5 mmol/L	4.8 mmol/L	140.45 mmol.h/L	101.47
	Humatrope	5.4 mmol/L	4.8 mmol/L	138.68 mmol.h/L	

Source: Table 2.7.2.24a

5.3 Exposure-Response Relationships

No analyses of exposure-response were submitted with this application. The rhGH doses for pediatric GHD and Turner syndrome have been well characterized in multiple clinical trials published during the last two decades. The dose regimens selected by the applicant in clinical trials GA-005/5A and GA-007/7A are consistent with those approved for other rhGH products.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant is seeking Accretropin approval for two indications:

- [redacted]treatment of pediatric patients who have growth failure due to an inadequate secretion of normal growth hormone (*Growth Hormone Deficiency*)
- Treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed (*Turner Syndrome*).

6.1.1 Methods

6.1.2 General Discussion of Endpoints

The primary and secondary endpoints of clinical studies GA-005/5A and GA-007/7A are standard endpoints evaluated in pediatric statural studies. They have been validated over decades in several populations of children with short stature treated with different GH products.

6.1.3 Study Design

Objective, trial design and patient population

The objectives of clinical trials GA-005/5A and GA-007/7A were to establish the efficacy and safety of Accretropin in children with GHD (trial GA-005/5A) and Turner syndrome (trial GA-007/7A). Both clinical trials used a similar design. They were single-arm, open-label, non-randomized, historically controlled studies and lasted a total of 36 months[26]. Study GA-005/5A was a multicenter study conducted at four sites in Poland and Hungary[27]. Study GA-007/7A was a single center study conducted in Poland. The range of Accretropin doses for study GA-005/5A was 0.18 to 0.30 mg/kg/week divided equally in 6 daily subcutaneous injections of 0.03 to 0.05

[26] Each study had two sequential components. The first part of the study was from baseline to Month 6 and was followed by an extension for 30 additional months (Month 6 to Month 36). For the purpose of this review, unless otherwise specified, the two components are considered one study only. For instance Study GA-005 and its extension GA-005A are referred to as Study GA-005/5A. Similarly, studies GA-007 and its extension GA-007A are referred to as Study GA-007/7A.

[27] The four sites were as follows: Site 100 in Warsaw (24 patients), site 200 in Budapest (14 patients), site 300 in Budapest (4 patients) and site 400 in Pecs (2 patients).

mg/kg given at bedtime[28]. In study GA-007/7A patients with Turner syndrome received 0.36 mg/kg/week of the study drug (0.06 mg/kg/day) given at bedtime subcutaneously. Study GA-005/5A enrolled 44 subjects. Study GA-007/7A enrolled 37 subjects. In both studies patients were prepubertal and naïve to GH therapy at enrollment.

Inclusion criteria

Study GA-005/5A

The inclusion criteria for study GA-005 were as follows:

- prepubertal male and female children diagnosed with GHD (maximum stimulated GH < 10 μg/L) proven by two pharmacological provocation tests[29]
- height < -2 SDS for chronological age (using appropriate national and international standard curves) and spontaneous height velocity < - 1 SDS assessed over an interval of at least six months before enrollment
- documented bone age radiograph being ≤ 30% of the chronological age
- euthyroidism (patients on thyroid replacement therapy were allowed to enroll if they had normalized thyroid function and received replacement for ≥ 3 months)
- normal karyotype (46, XX) for female children
- signed informed consent/assent

All patients who completed trial GA-005 who were deemed compliant, remained prepubertal and signed informed consent/assent were allowed to continue in the extension trial GA-005A. During the extension phase of the study (i.e. Study GA-005A) all patients who reached puberty before the 36 months of the trial were to be terminated prematurely.

Study GA-007/7A

The inclusion criteria for study GA-007 were as follows:

- prepubertal female children (Tanner I-breast) diagnosed with Turner's syndrome by karyotype, aged 8-12 years
- height < -2 SDS for chronological age (using appropriate national and international standard curves) and spontaneous height velocity < - 1 SDS assessed over an interval of at least six months before enrollment
- euthyroidism (patients on thyroid replacement therapy were allowed to enroll if they had normalized thyroid function and received replacement for ≥ 3 months)
- signed informed consent/assent

[28] Slightly different doses were used in Poland and Hungary in order to "accommodate physician preferences within the two countries". Specifically, subjects in Poland received 0.05 mg/kg/day while subjects in Hungary received slightly lower doses: 0.03-0.04 mg/kg/day. The drug product was injected with a 0.5 or 1 ml syringe via a 29G needle.

[29] Any two tests from the following: insulin, dopamine/glucagon, or clonidine/arginine stimulation assays.

All patients who completed trial GA-007 and signed informed consent/assent were allowed to continue in the extension trial GA-007A.

Exclusion criteria

Study GA-005/5A

In study GA-005 patients were excluded if they had "normal variant short stature"[30], Turner syndrome, syndromic short stature (e.g. chondrodysplasias), active malignancy, HIV or other chronic infections, or if they had received rhGH or other drugs known to affect growth[31]. In the extension study GA-005A patients were excluded if they were pubertal or if they were deemed non-compliant in the previous study.

Study GA-007/7A

In study GA-007 patients were excluded if they met any of the following criteria: received any form of GH, had syndromic short stature other than Turner syndrome (e.g chondrodysplasias), received prohibited hormones or medications (e.g estrogens, adrenal androgens, Ritalin/Cyalert) prior to enrollment, had chronic illnesses that could impair growth, had HIV or active malignancy, were hypothyroid.

Protocol amendments

Study GA-005/5A

The protocol for Study GA-005 was initially issued on November 10th, 1999: the protocol for the extension (Study GA-005A) was issued on August 2, 2000. There were 4 protocol amendments issued to Study GA-005 and 5 protocol amendments issued to Study GA-005A (summarized in Table 5). The study lasted between June 2000 and January 2004. The amendments had no impact on the efficacy and safety plan and analyses.

Table #5 Protocol Amendments for Study GA-005/5A

Amendment number	Amendment date	Main changes
Study GA-005		
1	December 8th, 1999	Changed the GH dose to be administered from 0.06 mg/kg/day to a range of 0.03 to 0.05 mg/kg/day.
2	January 19, 2000	Changed the inclusion criterion for the lower limit of age at enrollment (from "6 months [of age] to puberty" to "prepubertal male or female children"; also included minor text clarifications.
3	September 18th, 2000	Allowed the use of an auto injector for the administration of the drug.

[30] Normal variant short stature was defined as a current height and adult height prediction < 3rd percentile. (approximately -2SD), a birth weight > 2.5 kg, no organic cause for growth retardation, and average peak GH > 12 ng/ml.
[31] Anabolic steroids were allowed after a 3-month washout.

4	October 23rd, 20000	Allowed flexibility in the timing of drug administration prior to the scheduled follow-up visits.
Study GA-005A		
1	September 18, 2000	Allowed the use of an auto injector for the administration of the drug.
2	October 23rd, 20000	Allowed flexibility in the timing of drug administration prior to the scheduled follow-up visits. Allowed to stop the treatment when the investigator deemed that it was no longer indicated.
3	October 30, 2000	Added testing of IGF-I and IGFBP-3 every 6 months.
4	September 26, 2002	Changed the definition of SAE to harmonize it with ICH and WHO definitions
5	May 2, 2003	Added another principal investigator at one of the existing sites.

Source: Module 5: Clinical Study Reports; 16.1.1.

Study GA-007/7A

The protocol for Study GA-007 was initially issued on November 10th, 1999: the protocol for the extension (Study GA-007A) was issued on August 2, 2000. There were 4 protocol amendments issued to Study GA-007 and 5 protocol amendments issued to Study GA-007A. The protocol amendments are summarized in Table 6. The study lasted between August 2000 and March 2004. The amendments had no impact on the efficacy and safety plan and analyses.

Table 6: Protocol Amendments for Study GA-007/7A

Amendment number	Amendment date	Main changes
Study GA-007		
1	December 8th, 1999	Changed the age inclusion criterion from "9 to 11 years of chronological age" to "above 8 and below12 years of chronological age"; clarified language describing the karyotype requirements for a diagnosis of Turner syndrome.
2	January 10, 2000	Made minor text clarifications.
3	September 18th, 2000	Allowed the use of an auto injector for the administration of the drug.
4	October 23rd, 20000	Allowed flexibility in the timing of drug administration prior to the scheduled follow-up visits.
Study GA-007A		
1	August 28, 2000	Changed the age inclusion criterion from "9 to 11 years of chronological age" to "8 1/2 to 12 1/2 years of chronological age".
2	September 18th, 2000	Allowed the use of an auto injector for the administration of the drug.
3	October 23rd, 20000	Allowed flexibility in the timing of drug administration prior to the scheduled follow-up visits. Allowed to stop the treatment when the investigator deemed that it was no longer indicated.
4	September 26, 2002	Changed the definition of SAE to harmonize it with ICH and WHO definitions
5	May 2, 2003	Added another principal investigator at one of the existing sites.

Source: Module 5: Clinical Study Reports; 16.1.1.

Compliance

Study GA-005/5A

Drug use was recorded by the investigator and the parent/guardian. Subjects were required to return all used vials of study drug to the investigator and site personnel completed drug accountability forms. The number of used vials was reconciled against dispensing records. The subjects (or parents/guardians) were required to keep track of each study administration in a diary that was used as a source of documentation for compliance to the treatment.

Study GA-007/7A

Same as for study GA-005/5A, above.

Efficacy assessments and statistical plan

Study GA-005/5A

Most efficacy endpoints were height related. The statistical analysis section of the protocol states that

> The effectiveness of therapy will be evaluated by comparing pre-treatment annualized growth rates to annualized growth velocity during 6 month of therapy. Linear growth rates will also be compared to age and gender matched group tables for healthy children (Tanner) as well as to local national standards. Secondary analyses will involve analysis of weight gain, changes in mean laboratory values and incidence of related adverse events.
>
> If suitable, a primary analysis will consist of a paired t-test comparing each subject's pre-study and on-study growth rates. The secondary analysis will be a one-sample t-test comparing each subject's on study growth rate to a referent value of 5 cm/year [32]... Appropriate statistical analyses will be conducted on pharmacodynamic (PD) and antigenicity (anti-hGH and anti-ECP) data….

The extension component of the trial extended the efficacy analyses for up to 36 months. There were no plans for interim analyses.[33]

---

[32] This height velocity referent value of 5 cm/year is derived from Tanner et al. (Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. Arch.Dis.Child. 1966 Dec; 41: 613-35). It was based on the average linear height velocity for children between ages 6 and 12 years of age (5.6 ± 0.39 cm/yr). The null hypothesis was that there will be no difference in the height velocity in response to GH therapy (i.e. annualized growth velocity will be approx. 5 cm/yr). The alternative hypothesis was that GH therapy will increase the annualized height velocity to 10 cm/yr (i.e. a difference in growth rate of 5 cm/yr) based on a reported first year height velocity of 9.4 ± 1.9 cm/yr following 12 months of Humatrope therapy (with a baseline height velocity of 4.0 ± 1.3 cm/yr in the reference study).

[33] In response to a request from the Hungarian Regulatory Authority the applicant conducted an analysis of the growth rate of the first seven subjects that completed 24 weeks of treatment ("6-month safety report", March 2001). Subsequent safety update were presented every 6-months to the Hungarian Regulatory Authority until the completion of the study.

In the study report the applicant states the following:

> Pre-treatment height velocity of children enrolled into this study was collected, but collection of the data was not accomplished in a standardized manner consistent with GCP, or per protocol. Growth data was collected by the child's physician in the subjects' charts, and was not collected during a standardized period. Various physicians also collected these data at various locations, and the subjects' heights were not measured at identical intervals prior to administration of [redacted]. Due to the manner in which these data were collected, it was determined that pre-treatment height velocities would be used only as supporting information for the primary endpoint (i.e. to calculate baseline height velocity for subjects in study GA-005/5A). It was also included for completeness, and to be compliant with analyses indicated in the protocol. In addition, one of the inclusion criteria was that children had a height velocity ≤ -1 SD from normal, and a height of ≤ -2 SDS from normal. The investigator stipulated that each subject enrolled in the study met these criteria. The baseline SDS for height was calculated in a post hoc analysis, and all except 1 of the children enrolled into this study met the inclusion height criteria.

Study GA-007/7A

Same as for study GA-005/5A, above. No interim analyses were performed.

Safety assessments

Study GA-005/5A

In addition to physical exams (including vital signs) and adverse events[34], safety assessments included standard chemistry and hematology analytes, serum IGF-I, IGFBP-3 and GH concentrations, antibodies to GH and host cell (E.coli) polypeptides, LH, FSH, TSH, T_4 levels, and urinalysis. Such evaluations were scheduled at baseline and weeks 8, 12, and 24 during the GA-005 part of the study and at months 6, 9, 12, 18, 24, 30 and 36 during the GA-005A extension.

Study GA-007/7A

Same as for study GA-005/5A, above.

Disposition of patients

Study GA-005/5A

Forty-four patients were enrolled and received study medication in Study GA-005/5A. Of these, 42 patients completed 24 weeks; two subjects[35] were withdrawn from study at Week 12 for non-compliance[36]. Only 41 patients were enrolled in Study GA-005A; one patient[37]

[34] Adverse events were coded using the MedDRA Dictionary Version 6.0.
[35] Patients 122 and 213.
[36] This was done in accordance with the protocol.
[37] Subject 120.

did not enter this extension phase of the study after being diagnosed with Fanconi anemia. The following patients did not complete Study GA-005A:

- Subject 205 died after the Month 12 visit (cardiogenic shock secondary to fatty degeneration of the heart).
- Subject 303 withdrew consent at Month 18 due to "perceived lack of effect."
- Subject 119 withdrew at Month 30 after being diagnosed with hypertension secondary to a hypoplastic right renal artery.
- Nine subjects[38] were withdrawn at Month 24 and 5 additional subjects[39] were withdrawn at Month 30 because they reached puberty (this was done according to the protocol).

The subject disposition data are summarized in Table 7.

Table 7: Patient disposition- Study GA-005/5A

Study	Enrolled	Withdrawn	Completed
GA-005*	44	2	42
GA-005A**	41	16	25

Source: Module 5: Clinical Study Report. Table 10-1.
*Months 0-6.
** Months 6-36.

Study GA-007/7A

All 37 subjects enrolled completed Study GA-007 and continued into the extension study GA-007A. Thirty-six patients completed 36 month of treatment. One subject (530) was withdrawn for non-compliance after the Month 18 visit (she did not return for subsequent visit and was lost to follow-up). Another subject (510) completed treatment for 36 months but did not have a final evaluation for efficacy.

Protocol violations and deviations

Study GA-005/5A

Protocol violations are summarized in Table 8. Several violations of inclusion criteria were recorded, such as those related to euthyroidism (6 patients), height SDS (1 patient), peak stimulated GH concentration (1 patient), presence of chronic infection or disease (1 patient), bone age (1 patient), missing karyotype (1 patient), and using drug(s) that may interfere with growth (2 patients). Other common violations were related to the timeframe of reporting SAEs. The most common protocol deviations that did not involve inclusion criteria were those related to missing laboratory values and having study visits outside the defined visit date[40]. It should be noted that several of the violations in the inclusion criteria (such as euthyroidism, chronic infections, use of some drugs that may slow growth) should not confound negatively the efficacy

[38] They are subjects 113, 114, 117, 201, 202, 203, 215, 302, and 304.
[39] They are subjects 102, 109, 123, 124, and 204. Clarified in the submission entitled "Amendment # 8.
[40] ± 4 days for study GA-005 and ± 14 days for Study GA-005A.

because they are not expected to accelerate growth (on the contrary they can slow it down by having a negative effect on IGF-1 levels).

Table 8: Protocol violations – Study GA-005/5A

Protocol violation	No. of subjects	Subject ID
Did not meet inclusion criterion of euthyroidism	6	107, 115, 116, 205, 214, 302
Did not meet inclusion criterion of height < -2SD	1	205*
Did not meet inclusion criterion of GHD (GH <10 µg/L)	1	207
Did not meet inclusion criterion of assessment period of at least six months for stature and height velocity	1	211
Chronic hepatitis B infection	1	116
Erroneously entered in the study (Fanconi's anemia diagnosed after start of the study	1	120
Subject received drugs that are known to affect growth	2	105, 108
SAE reported outside the required timeframe	8	109, 111, 113, 115, 116, 119, 120, 121
Did not meet inclusion criteria of < 30% chronological bone age	1	124
Karyotype information not available	1	123

Source: Module 5: Clinical Study Report. Table 10-2.
*Baseline height SDS: -1.94.

Study GA-007/7A

Protocol violations are summarized in Table 9. The most common protocol violations were those related to failure to meet appropriate inclusion criteria (such as euthyroidism, specific height and age criterion, and absence of chronic illnesses). The most common protocol deviations were those related to attendance of study visits outside the defined visit date.

Table 9: Protocol violations – Study GA-007/7A

Protocol violation	No. of subjects	Subject ID
Did not meet inclusion criterion of euthyroidism	6	511, 524, 527, 529, 534, 536
Did not meet inclusion criterion of height < -2SD	2	507*, 536**
Did not meet inclusion criterion of age 8 to 12 years	6	522, 533, 534, 535, 536, 537
Did not meet inclusion criterion of absence of clinically significant gastrointestinal condition	1	508
SAE reported outside the required timeframe	2	508, 520
Met exclusion criterion of active chronic infection (chronic hepatitis C infection)	1	514

Source: Module 5: Clinical Study Report. Table 10-1.
*Height SDS: -1.92
** Height SDS -1.85.

Datasets analyzed

Study GA-005/5A

The efficacy datasets are:

- the intent-to-treat (ITT) population made of all subjects who receive study medication
- the per protocol (PP) population, which includes all subjects of the ITT population who did not violate the protocol in a "clinically meaningful manner"

Study GA-007/7A

Same as for study GA-005/5A.

6.1.4 Efficacy Findings

Demographics and baseline characteristics

Study GA-005/5A

The main demographic and auxological patient characteristics at baseline are presented in Table 10. The patients enrolled in this clinical trial had severe short stature (mean height SDS: -3.0; range -5.1 to -1.9), had slow growth rates (mean pre-treatment height velocity SDS: -1.85) and had IGF-1 levels in the low normal range. There were slightly more males than females enrolled (59.1% vs. 40.9%). Consistent with the demographics of the countries where the studies were conducted (Poland and Hungary) all patients enrolled in the trial were Caucasian.

Table 10: Baseline demographic and auxological characteristics – Study GA-005/5A

Chronological Age (years)	
N	44
Mean ± SD	8.5 ±2.51
(range)	(4.0 to 14.0)
Height (cm)	
N	44
Mean ± SD	115.3 ± 13.39
(range)	87.6 to 150.5
Height SDS	
N	44
Mean ± SD	-3.0 ± 0.79
(range)	(-5.1 to -1.9)
Height velocity (cm/yr)	
N	44
Mean ± SD	4.1 ± 1.2
(range)	(1.2 to 7.2)
Height velocity SDS	
N	44
Mean ± SD	-1.85 ± 1.47

(range)	(-6.31 to 1.29)
IGF-1 (ng/mL)	
N	44
Mean ± SD	136.1 ± 61.12
(range)	(86.0 to 309.0)
IGF-1 SDS	
N	42*
Mean ± SD	-1.47 ± 1.1
(range)	(-4.19 to 0.4)
IGFBP-3 (µg/mL)	
N	44
Mean ± SD	2.8 ± 0.98
(range)	(1.4 to 5.8)
Gender (N, %)	Female: 18 (40.9) Male 26 (59.1)

Source: Module 5: Clinical Study Report. Table 14-1 and text.
*Mean from the ITT population.

Study GA-007/7A

The main demographic and auxological patient characteristics at baseline are presented in Table 11. The patients enrolled in the clinical trial had severe short stature (mean height SDS: -3.2; range: -5.6 to -1.9) and had slow growth rates (mean pre-treatment height velocity SDS: -1.2). All patients enrolled were Caucasian; this is consistent with the demographics of the countries where the studies were conducted (Poland and Hungary). 100% of the patients in the study were females, consistent with the fact that Turner syndrome manifests only in girls.

Table 11: Baseline demographic and auxological characteristics – Study GA-007/7A

Chronological Age (years)	
N	37
Mean ± SD	8.9 ±1.71
(range)	(5.0 to 12.0)
Height (cm)	
N	37
Mean ± SD	117.8 ± 7.10
(range)	101.5 to 130.8
Height SDS	
N	37
Mean ± SD	-3.2 ± 0.89
(range)	(-5.6 to -1.9)
Height velocity (cm/yr)	
N	37
Mean ± SD	3.8 ±0.966
(range)	(1.8 to 6.4)
Height velocity SDS ("Tanner standards")*	
N	37
Mean ± SD	-2.4 ± 1.5
(range)	(-5.7 to – 1.3)
Height velocity SDS ("Turner standards")**	
N	37
Mean ± SD	-0.2 ±0.8

(range)	(-2.2 to – 2.3)
IGF-1 (ng/mL)	
N	37
Mean ± SD	154.6 ± 59.63
(range)	(86.0 to 308.0)
IGF-1 SDS	
N	37
Mean ± SD	-1.2 ± 0.75
(range)	(-2.8 to 0.39)
IGFBP-3 (µg/mL)	
N	37
Mean ± SD	3.4 ± 0.62
(range)	(2.1 to 4.6)

Source: Module 5: Clinical Study Report. Table 14-1 and "Amendment # 8".
*Calculated relative to normal growing children ("Tanner standards").
** Calculated relative to children with Turner syndrome.

Primary efficacy analysis

Study GA-005/5A

The applicant presents as primary efficacy analysis an analysis that compares the annualized height velocity on treatment to a "historical" height velocity calculated from age and gender matched national standards from Poland and Hungary, respectively ("local" height velocity) and from age and gender matched international standards[41] ("international" height velocity). The applicant could not conduct, as planned, a comparison of height velocity on trial with pre-trial height velocity since the pre-trial height data (and therefore baseline height velocity data) were not collected in a consistent manner in all patients. It is important to mention that both above mentioned analyses are protocol-specified and the protocol does not describe clearly which of these two analyses was supposed to be the primary analysis.

The applicant proposes that the standards for normal children had to be used as historical reference for such comparisons because longitudinal growth standards do not exist for untreated children with GHD[42]. Table 12 summarized these analyses for the *ITT population*. In both analyses the height velocity on treatment was higher than the height velocity of age and gender matched national and international standards. All comparisons were statistically significant. Height velocity doubled during the first year of Accretropin treatment and was maintained above baseline for each of the three years of treatment.

[41] Tanner et all, 1966.
[42] The applicant also proposes that, although both local and international standards are used to assess height velocity, it was the "local growth standards [that] were used in forming any conclusions" because they are "more relevant, up to date, and applicable to the populations assessed", while the international Tanner standards reflect growth data collected over 35 years ago.

Table 12: Comparison of height velocity on Accretropin treatment (Study GA-005/5A) with local and international standards for HV (ITT population).

	Annualized HV on treatment (cm/yr) N Mean (SD)	"Local" HV (cm/yr) N Mean (SD)	P-values for comparisons of HV on treatment with "local" HV	"International" HV (cm/yr) N Mean (SD)	P-values for comparison of HV on treatment with "international" HV
Baseline	42 4.09 (1.19)	NA	NA	NA	NA
Baseline to Month 6	42 9.5 (2.4)	42 6.0 (1.1)	< 0.0001	42 5.9 (1.0)	< 0.0001
Baseline to Month 12	41 8.8 (2.2)	41 6.0 (1.1)	< 0.0001	41 5.9 (1.0)	< 0.0001
Month 12 to Month 24	34 7.6 (1.4)	34 5.7 (1.2)	< 0.0001	34 5.6 (1.1)	< 0.0001
Month 24 to Month 36	26 6.9 (1.6)	26 5.2 (1.6)	< 0.0004	25* 5.6 (0.8)	< 0.0006

Source: Module 5: Clinical Study Report. Tables 11-1, 11-2, 11-4, and 11-5.
*One subject (108) was 16.5 years old at 36 months (reportedly Tanner standards for females do not include, the age of this patient). Therefore an "international" HV could not be calculated for this patient.
HV = height velocity. NA = not available

Table 13 presents the same efficacy analysis conducted in the *per protocol* population[43]. In general, it replicates the results observed in the *ITT population*.

Table 13: Comparison of height velocity on Accretropin treatment (Study GA-005/5A) with local and international standards for HV (PP population).

	Annualized HV on treatment (cm/yr) N Mean (SD)	"Local" HV (cm/yr) N Mean (SD)	P-values for comparison of HV on treatment with "local" HV	"International" HV (cm/yr) N Mean (SD)	P-values for comparison of HV on treatment with "international" HV
Baseline to Month 6	27 9.5 (2.4)	27 6.2 (0.9)	< 0.0001	27 6.1 (0.9)	< 0.0001
Baseline to Month 12	26 8.8 (2.2)	26 6.2 (0.9)	< 0.0001	26 6.2 (0.9)	< 0.0001
Month 12 to Month 24	21 7.5 (1.3)	21 6.0 (0.6)	< 0.0001	21 5.9 (0.8)	< 0.0001
Month 24 to Month 36	16 6.9 (1.7)	16 5.5 (1.1)	< 0.0152	16 5.7 (0.6)	< 0.0085

Source: Module 5: Clinical Study Report. Tables 14-2, 14-3, 14-4, and 14-5; updated in Amendment #8.
HV = height velocity.

[43] This analysis excludes: patients 212 and 301 who were enrolled but did not receive study medication; patients 122 and 213 who were withdrawn from the study at Week 12 due to non-compliance; patients 205 and 124 who violated the height and bone age criterion, respectively; subjects 107, 115, 116, 205, 214 and 302 who were not euthyroid at baseline. In addition, the following patients had baseline SDS for growth velocity above -1 SDS: GD-101, GD-103, GD-108, GD-113, GD-114, GD-207, GD-211 and GD-215.

The applicant also reports that the results of a protocol-defined analysis that compares the height velocity of subjects in the trial with a referent value of 5 cm/year reached statistical significance ((p<0.0001) at all the timepoints analyzed (Month 6 through Month 36). The referent value of 5 cm/year approximates the average height velocity in middle childhood.

At the request of this reviewer the applicant provided an analysis of on-trial height velocity (cm/yr and SDS) relative to baseline height velocity. As indicated by Table 14, the change in HV reached statistical significance for each of the timepoints evaluated during the trial.

Table 14: Height velocity change on Accretropin treatment relative to baseline (Study GA-005/5A)

Change from Baseline (cm/year)			
Timepoint	**Mean (SD)**	**95% CI**	**p-value***
Week 24	5.46 (3.01)	4.53, 6.40	<0.0001
Month 12	4.76 (2.89)	3.84, 5.67	<0.0001
Month 24	3.45 (2.02)	2.75, 4.16	<0.0001
Month 36	2.79 (2.48)	1.79, 3.79	<0.0001
Change from Baseline (SDS)			
Timepoint	**Mean (SD)**	**95% CI**	**p-value***
Week 24	6.22 (3.70)	5.06, 7.37	<0.0001
Month 12	5.42 (3.97)	4.16, 6.67	<0.0001
Month 24	3.69 (2.75)	2.72, 4.67	<0.0001
Month 36	3.54 (3.38)	2.17, 4.90	<0.0001

*Paired t-test

A descriptive comparison of height velocity results by country indicated that patients treated in Poland (23 patients treated at one site) had higher height velocities relative to patients treated in Hungary (19 patients treated at 3 sites)[44]. This is consistent with the fact that the Accretropin dose regimen was higher for patients enrolled in Poland (0.05 mg/kg/day) than that for patients enrolled in Hungary (0.03-0.04 mg/kg/day).

Another descriptive analysis indicates comparable height velocity changes on treatment for boys and girls. The height velocity for boys was only slightly higher than that of girls[45].

Study GA-007/7A

The same efficacy analyses for HV described in trial GA-005/5A were conducted in clinical trial GA-007/7A. In addition, a post hoc "historical" comparison of height velocity on trial to that of

[44] The mean height velocities (Poland vs. Hungary) were as follows: 10.1 vs. 8.7 cm/yr at 6 months, 9.6 vs. 7.9 cm/yr for baseline to Month 12, 8.1 vs. 6.7 cm/yr for Month 12 to Month 24, and 7.6 vs. 6.0 for Month 24 to Month 36.

[45] The mean height velocities (boys vs. girls) were as follows: 9.7 vs. 9.2 cm'yr at 6 months, 9.0 vs. 8.6 cm/yr for baseline to Month 12, 7.6 vs. 7.6 cm/syr for Month 12 to Month 24, and 7.2 vs. 6.5 for Month 24 to Month 36.

Polish standards of HV for untreated girls with Turner syndrome[46] was completed. The results of the primary efficacy analyses conducted in the *ITT population* are summarized in Table 15. In both analyses the height velocity on treatment was higher than the height velocity of age and gender matched national and international standards. The comparisons were statistically significant at Month 12 and Month 24 but not at Month36.

Table 15: Comparison of height velocity on Accretropin treatment (Study GA-007/7A) with local and international standards for HV (ITT population).

	Annualized HV on treatment (cm/yr) N Mean (SD)	"Local" HV (cm/yr) N Mean (SD)	P-values for comparison of HV on treatment with "local" HV	"International" HV (cm/yr) N Mean (SD)	P-values for comparison of HV on treatment with "international" HV
Baseline to Month 6	37 8.8 (2.5)	37 5.9 (0.6)	< 0.0001	37 6.0 (0.6)	< 0.0001
Baseline to Month 12	37 8.5 (1.7)	41 5.9 (0.6)	< 0.0001	37 6.0 (0.6)	< 0.0001
Month 12 to Month 24	36 6.8 (1.2)	25 5.7 (1.9)	< 0.007	36 5.7 (0.9)	< 0.0001
Month 24 to Month 36	35 5.8 (1.8)	30 5.2 (2.2)	< 0.237	35 5.4 (1.7)	< 0.341

Source: Module 5: Clinical Study Report. Tables 11-1, 11-2, 11-5, and 11-6.
HV = height velocity.

Table 16 presents the same efficacy analysis conducted in the *per protocol population*[47]. The data confirms the results of the *ITT analysis*.

Table 16: Comparison of height velocity on Accretropin treatment (Study GA-007/7A) with local and international standards for HV (PP population).

	Annualized HV on treatment (cm/yr) N Mean (SD)	"Local" HV (cm/yr) N Mean (SD)	P-values for comparisons of HV on treatment with "local" HV	"International" HV (cm/yr) N Mean (SD)	P-values for comparisons of HV on treatment with "international" HV
Baseline to Month 6	24 8.7 (2.8)	24 5.9 (0.2)	< 0.0001	24 6.1 (0.7)	< 0.0002
Baseline to Month 12	24 8.5 (1.8)	24 5.9 (0.2)	< 0.0001	24 6.1 (0.7)	< 0.0001
Month 12 to Month 24	23 6.8 (1.2)	23 5.7 (1.8)	< 0.034	23 5.7 (0.5)	< 0.0013

[46] From Wisniewski et al., 2002.
[47] This analysis excludes: patients 507 and 536 who violated the height inclusion criterion; subjects 522, 533, 534, 535, 536 and 537 who violated the age inclusion criterion, subject 508 who had a clinically significant gastrointestinal condition; patients 511, 524, 527, 529, 534 and 536 who were not euthyroid at baseline. In addition, the following patients had baseline SDS for growth velocity above -1 SDS: GF-507, GF-521 and GF-527.

Month 24 to Month 36	22 5.8 (2.2)	18 4.8 (2.0)	< 0.1355	22 5.4 (1.6)	< 0.4903

Source: Module 5: Clinical Study Report. Tables 11-3, 11-4, 11-7, and 11-8.
HV = height velocity.

A per-protocol analysis that compared growth velocity on treatment to a predefined height velocity of 5 cm/yr indicates that the HV on trial was significantly higher throughout the entire trial ($p<0.0001$).

The applicant presents the results of a post hoc "historical" analysis that compares on-trial HV with "local" (i.e. Polish) HV growth standards for girls with Turner syndrome (Table 17). This reviewer agrees that a comparison with Turner syndrome-specific growth references is more appropriate than using growth references of normally growing children (Turner syndrome children grow slower than normal children along lower "growth channels"). In this comparison the height velocity of girls with Turner syndrome treated with Accretropin was greater than that of untreated girls at all timepoints ($p<0.0001$).

Table 17: Comparison of height velocity on Accretropin treatment (Study GA-007/7A) with local standards for HV obtained from untreated patients with Turner syndrome (ITT population).

	Annualized HV on treatment (cm/yr) **N** **Mean (SD)**	**Turner syndrome "local" HV (cm/yr)** **N** **Mean (SD)**	**P-values for comparisons of HV on treatment with "local" HV for Turner syndrome patients**
Baseline to Month 6	37 8.8 (2.5)	37 4.0 (0.7)	< 0.0001
Baseline to Month 12	37 8.5 (1.7)	41 4.0 (0.7)	< 0.0001
Month 12 to Month 24	36 6.8 (1.2)	35 3.7 (1.2)	< 0.0001
Month 24 to Month 36	35 5.8 (1.8)	30 3.7 (0.9)	< 0.0001

Source: Module 5: Clinical Study Report. Tables 11-9, and 11-10.
HV = height velocity.

At the request of this reviewer the applicant provided an analysis of on-trial height velocity (cm/yr and SDS) relative to baseline height velocity. As indicated by Table 18, the change in HV reached statistical significance for each of the timepoints evaluated during the trial.

Table 18: Height velocity change on Accretropin treatment relative to baseline (Study GA-007/7A)

Change from Baseline (cm/year)			
Timepoint	**Mean (SD)**	**95% CI**	**p-value***
Week 24	5.02 (2.74)	4.11, 5.94	<0.0001
Month 12	4.74 (2.00)	4.07, 5.40	<0.0001
Month 24	3.05 (1.32)	2.60, 3.49	<0.0001
Month 36	2.04 (1.99)	1.35, 2.72	<0.0001
Change from Baseline (SDS)			

Timepoint	Mean (SD)	95% CI	p-value*
Week 24	5.79 (3.72)	4.55, 7.03	<0.0001
Month 12	5.49 (2.78)	4.57, 6.42	<0.0001
Month 24	3.94 (2.87)	2.97, 4.91	<0.0001
Month 36	2.81 (4.33)	1.28, 4.34	0.0007

*Paired t-test

Secondary efficacy analyses

Study GA-005/5A

Height velocity SDS

The results of this post hoc analysis are presented in Table 19. The mean HV SDS[48] increased from a negative baseline value (-1.8) to above normal values through Month 36 (ranging from 4.3 to 1.7). A characteristic "catch up" phenomenon is observed with a rapid acceleration in HV in the first year of treatment followed by a gradual slowdown that ultimately results in HV SDS values in the high normal range (and higher than those observed at baseline).

Table 19: Height velocity SDS and change in height velocity SDS (ITT population) – Study GA-005/5A

	Height Velocity SDS N Mean (SD)	Change in height velocity SDS* Mean (SD)
Baseline	42 -1.85 (1.4)	NA
Month 6	42 4.3 (3.3)	6.2 (3.7)
Month 12	41 3.5 (3.5)	5.4 (3.9)
Month 24	33 1.9 (2.3)	-1.7 (2.8)
Month 36	26 1.7 (2.8)	-0.38 (2.6)

Source: Module 5: Clinical Study Report. Table 11-12.
*The change in height SDS was calculated relative to baseline for Month 6 and 12, relative to Month 12 for Month 24, and relative to Month 24 for Month 36.

Height SDS

An analysis of height SDS and change in height SDS[49] is summarized in Table 20. The mean baseline height SDS was -3.039 ± 0.79 and increased to -2.7 ± 0.75 at 6 months, -2.46 ± 0.70 at Month 12, -2.12 ± 0.82 at Month 24, and -1.77 ± 0.8 at Month 36. The mean height SDS at Month 36 (-1.77) reached the normal range (defined statistically as 2 SD above and below the population mean). The net increase in height SDS was 0.34 ± 0.44 at Month 6; 0.59 ± 0.53 at

[48] Calculated from the HV of "international" standards of normally growing children of Tanner et. al.
[49] Height SDS calculations were based on local growth standards from Poland and Hungary.

Month 12; 0.35 ± 0.28 at Month 24 and 0.33 ± 0.34 at Month 36. This resulted in a cumulative height SDS increase of approximately 1.27 SDS. The increase in height SDS was similar for both genders[50]. It was higher for patients treated in Poland relative to those treated in Hungary[51] (Polish children received higher GH doses).

Table 20: Height SDS and height SDS change in trial GA-005/5A

Descriptive statistics	Height SDS						
	Baseline	Month 12	Change at Month 12	Month 24	Change at Month 24	Month 36	Change at Month 36
N	42	41	41	34	34	31	26
Mean (SDS)	-3.0 (0.7)	-2.4 (0.7)	0.59 (0.5)	-2.1 (0.8)	0.35 (0.28)	-1.77 (0.84)	0.33 (0.3)
Range	-5.0 to -1.9	-4.1 to -1.2	-0.09 to 2.3	-4.0 to -0.5	-0.08 to 0.9	-3.4 to - 0.04	-0.1 to 1.1

Source: Module 5: Clinical Study Report. Tables 11-8 and 11-9.

Serum IGF-1

Serum IGF-1 concentrations were measured during the study at various timepoints and are displayed in Table 21 (both as ng/ml and standard deviation score). The mean IGF-1 standard deviation score was low normal at baseline (-1.47). On Accretropin treatment the mean IGF-1 SD score increased to values that approached the population mean. By Week 8 of treatment (the first post-baseline assessment) the mean IGF-1 concentrations increased by approximately 67%. By Month 12 and beyond, IGF-1 concentrations doubled and were subsequently maintained at similar levels on all subsequent measurements.

Table 21: Serum IGF-1 concentration and standard deviation score (SDS) in Study GA005/5A

Statistics	Baseline	Week			Month				
		8	12	24	12	18	24	30	36
Serum IGF-1 concentrations (ng/ml)									
n	42	42	41	42	41	37	38	26	26
Mean (SD)	136.19 (61.67)	227.26 (114.70)	238.42 (155.73)	243.50 (173.35)	282.73 (185.67)	301.97 (177.07)	359.21 (228.42)	308.19 (164.50)	340.92 (142.94)
Serum IGF-I SDS									
n	42	42	41	42	41	37	38	26	26
Mean (SD)	-1.47 (1.10)	-0.52 (1.14)	- 0.44 (1.10)	-0.51 (1.19)	-0.46 (1.39)	-0.25 (1.20)	-0.02 (1.18)	-0.24 (0.90)	0.00 (0.87)

Source: Module 5: Clinical Study Report. Tables 11-17 and 11-18.

In a gender analysis, girls displayed higher mean IGF-1 serum concentrations (ng/ml) relative to boys for all but one of the assessments. This was not confirmed when IGF-1 SD scores were

[50] Increase in height SDS (boys vs. girls) was as follows: 0.34 ± 0.45 vs. 0.3 ± 0.43 at 6 months; 0.66 ± 0.5 vs. 0.50 ± 0.5 at 12 months; 0.344 ± 0.25 vs. 0.37 ± 0.32 at Month 24 and 0.34 ± 0.30 vs. 0.32 ± 0.4 at Month 36.
[51] Increase in height SDS (Poland- vs. Hungary-treated children) was as follows: 0.4 ± 0.5 vs. 0.22 ± 0.23 at Month 6, 0.76 ± 0.6 vs. 0.4 ± 0.3 at Month 12, 0.38 ± 0.3 vs. 0.3 ± 0.2 at Month 24 and 0.45 ± 0.3 vs. 0.16 ± 0.1 at Month 36.

compared. Poland-treated children had higher mean IGF-1 concentrations (ng/ml) relative to those treated in Hungary; this difference was not as obvious when standard deviation scores were compared between the two countries.

Serum IGFBP-3

Serum IGFBP-3 concentrations were also measured during the study and are displayed in Table 22. They showed an increase on GH treatment which was noted at the first post-baseline measurement (Week 8), followed by a small further increase at the next timepoints that was maintained on all subsequent measurements. Standard deviation scores were not provided.

Table 22: Serum IGFBP-3 concentration (µg/ml)

Statistics	Baseline	Week			Month				
		8	12	24	12	18	24	30	36
n	42	42	41	42	41	37	38	26	26
Mean (SD)	2.84 (1.00)	3.85 (1.24)	4.07 (1.23)	4.18 (1.23)	4.49 (1.24)	4.43 (1.28)	4.18 (0.96)	4.16 (0.86)	4.21 (0.98)

Source: Module 5: Clinical Study Report. Tables 11-19.

Study GA-007/7A

Height velocity SDS

An analysis of HV SDS using the Tanner "international" standards as reference for standard deviation score calculations is presented in Table 23. HV SDS increased from below normal baseline value (-2.4) to above normal values through Month 12 (3.0) and normal values through Months 24 and 36 (1.5 and 0.4, respectively). A characteristic "catch up" phenomenon is observed with a rapid acceleration in the first year of treatment followed by a gradual reduction in HV SDS values which remained still in the normal range (and higher than baseline HV SDS).

Table 23: Height velocity SDS and change in height velocity SDS (ITT population) –Study GA-007/7A

	Height Velocity SDS N Mean (SD)	Change in height velocity SDS Mean (SD)
Baseline	37 -2.4 (1.5)	NA
Month 6	37 3.3 (3.8)	5.7 (3.7)
Month 12	37 3.0 (2.5)	5.4 (2.7)
Month 24	36 1.5 (1.8)	-1.6 (2.8)
Month 36	33 0.4 (3.2)	-0.8 (2.6)

Source: Module 5: Clinical Study Report. Table 11-15.
The change in height SDS was calculated relative to baseline for Month 6 and 12, relative to Month 12 for Month 24, and relative to Month 24 for Month 36.

NA= not applicable.

Height SDS

An analysis of height SDS and change in height SDS is summarized in Table 24[52]. The mean baseline height SDS was -3.1 ± 0.8 and increased to -2.8 ± 0.9 at 6 months, -2.6 ± 1.1 at Month 12, -2.4 ± 1.2 at Month 24, and -2.2 ± 1.2 at Month 36. The net increase in height SDS was 0.33 ± 0.4 at Month 6; 0.5 ± 0.4 at Month 12; 0.2 ± 0.4 at Month 24 and 0.15 ± 0.4 at Month 36. This results in a cumulative height SDS increase of 0.85 SDS for three years of treatment.

Table 24: Height SDS and change in height SDS in trial GA-007/7A

Descriptive statistics	Height SDS						
	Baseline	Month 12	Change at Month 12	Month 24	Change at Month 24	Month 36	Change at Month 36
N	37	37	37	36	36	35	35
Mean (SDS)	-3.1 (0.8)	-2.6 (1.1)	0.5 (0.4)	-2.4 (1.2)	0.2 (0.4)	-2.2 (1.2)	0.15 (0.4)
Range	-5.6 to -1.8	-5.9, -0.7	-0.4 to 1.4	-5.3 to -0.2	-0.8 to 1.1	-5 to - 0.08	-0.6 to 0.9

Source: Module 5: Clinical Study Report. Tables 11-11 and 11-12.

The applicant presents another analysis of height SDS in which height SDS was calculated using the growth standards for untreated Polish girls with Turner syndrome (Wisniewski et al., 2002) instead of the growth standards of normally growing Polish girls (Table 25). The baseline height SDS indicates that the patients enrolled in the trial were average height relative to the population mean for Turner syndrome children (height SDS of 0.2). The height increased relative to the Turner population children by 0.37 ± 0.4 at Month 6, 0.7 ± 0.3 at Month 12, 0.5 ± 0.3 at Month 24, and 0.4 ± 0.3 at Month 36. For the whole duration of treatment the height SDS increase was 1.7 ± 0.6.

Table 25: Height SDS relative to the Polish Turner syndrome standards - trial GA-007/7A

Descriptive statistics	Height SDS						
	Baseline	Month 12	Change at Month 12	Month 24	Change at Month 24	Month 36	Change at Month 36
N	37	37	37	36	36	35	35
Mean (SDS)	0.2 (0.6)	0.9 (0.8)	0.7 (0.3)	1.4 (0.9)	0.5 (0.3)	1.9 (1.1)	0.4 (0.3)
Range	-1.8 to 1.2	-1.3, 2.5	0.06 to 1.4	-0.6 to 3.6	-0.2 to 1.0	-0.5 to 4.4	-0.3 to 1.0

Source: Module 5: Clinical Study Report. Tables 11-13 and 11-14.

The two analyses of height SDS indicate that the patients with Turner syndrome who received Accretropin had heights that were still below the average height compared to the normal children but above the average height when compared to an untreated population of girls with Turner syndrome.

[52] Height SDS calculation was based on local growth standards for normally growing Polish girls.

Serum IGF-1

Serum IGF-1 concentrations were measured during the study up to Week 24 (Month 6) and are displayed in Table 25. By Week 8 (the first on-trial assessment) the serum IGF-1 concentration almost doubled and subsequently it was maintained at comparable levels through Week 24. The IGF-1 serum concentrations are also presented as standard deviation score (calculated relative to normal healthy children). At baseline the IGF-1 SD score was low normal (-1.47); on treatment it increased to positive values close to the population mean.

Table 26: Serum IGF-1 concentration and standard deviation score (SDS)

Statistics	Baseline	Week 8	Week 12	Week 24
Serum IGF-1 concentrations (ng/ml)				
n	37	37	37	37
Mean (SD)	154.65 (59.63)	309.22 (119.76)	303.03 (125.11)	353.92 (187.58)
Serum IGF-I SDS				
n	37	37	37	37
Mean (SD)	-1.2 (0.7)	0.2 (0.8)	0.06 (1.1)	0.1 (1.3)

Source: Module 5: Clinical Study Report. Tables 11-20 and 11-21.

Serum IGFBP-3

Serum IGFBP-3 concentrations during Study GA-007 are displayed in Table 27. An increase of mean IGFBP-3 serum concentrations on treatment was observed with the first post-baseline measurement at Week 8 and was maintained at all subsequent measurements through Month 6.

Table 27: Serum IGFBP-3 concentrations (µg/ml)

Statistics	Baseline	Week 8	Week 12	Week 24
n	37	37	37	37
Mean (SD)	3.3 (0.6)	4.6 (0.8)	4.7 (0.9)	4.6 (0.8)

Source: Module 5: Clinical Study Report. Tables 11-22.

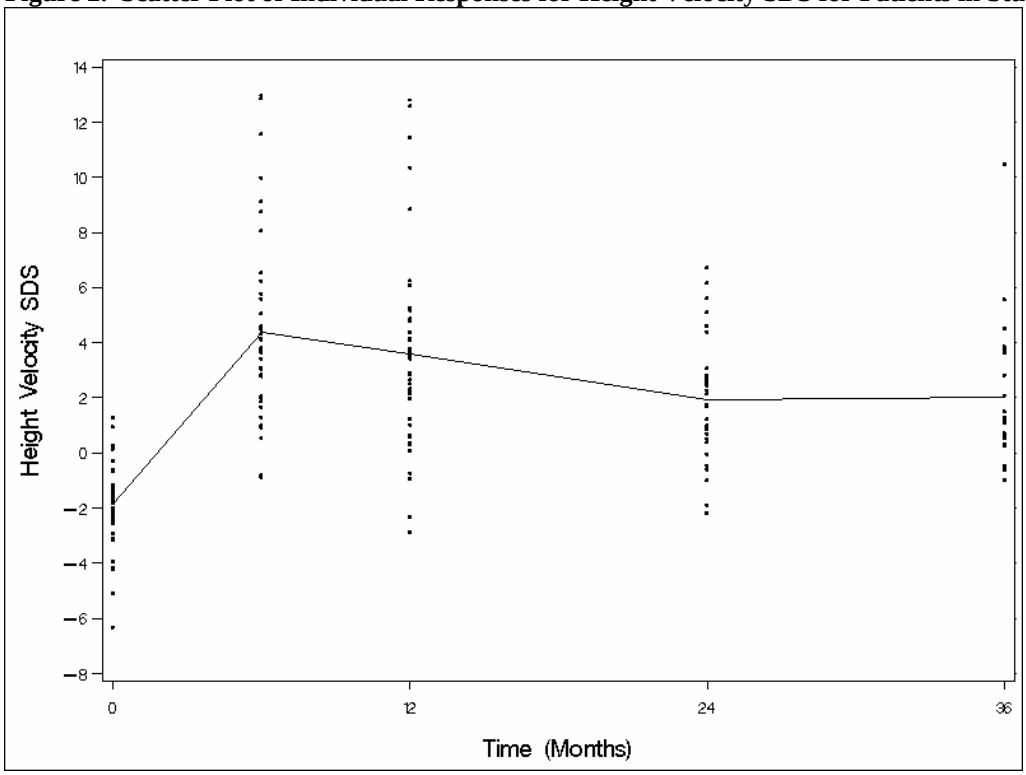
Individual efficacy analysis

Study GA-005/5A

At the request of this reviewer the applicant has provided additional data describing the individual patient responses for the primary efficacy variable (height velocity) during Accretropin treatment. Applicant's Figure 2 of the "Amendment # 8" submission illustrates the distribution of height velocity SD scores at baseline, Month 6, Month 12, Month 24 and Month 36. The continuous line represents the mean values and dots represent individual patient values (as expected, following an initial acceleration in HV or "catch up" phase, there is a slowdown or

"catch down" phase but, importantly, the HV remains above that observed at baseline). The distribution of individual values illustrate a good response on Accretropin treatment.

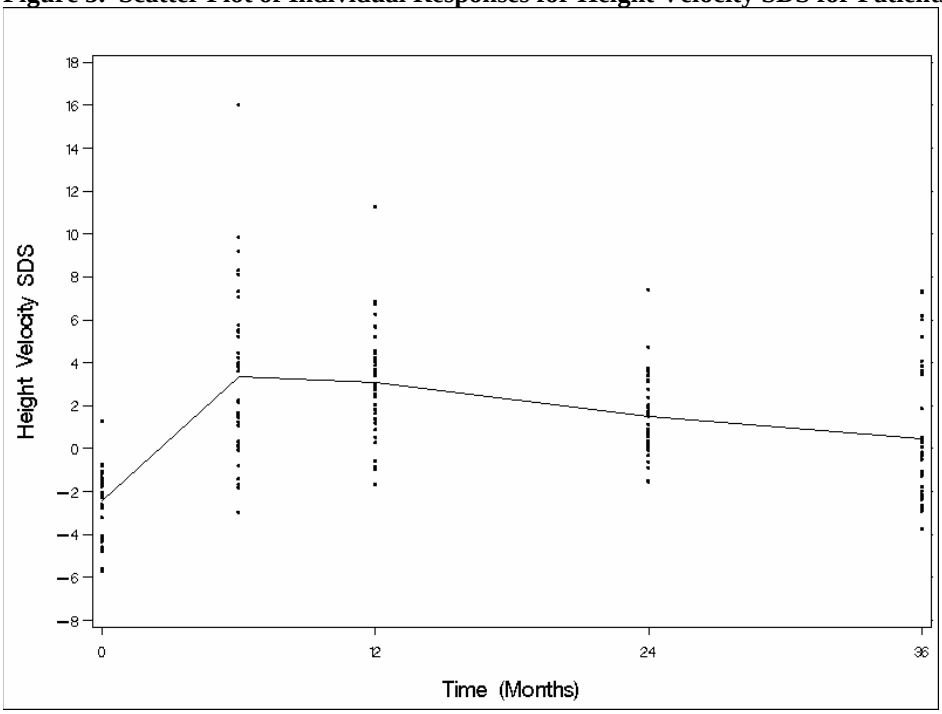
Figure 2. Scatter Plot of Individual Responses for Height Velocity SDS for Patients in Study GA-005/5A



Study GA-007/7A

Applicant's Figure 5 of the "Amendment # 8" submission illustrates the distribution of height velocity SD scores at baseline, Month 6, Month 12, Month 24 and Month 36 in patients with Turner syndrome. The continuous line represents the mean values and dots represent individual patient values (as expected, following an initial acceleration in HV or "catch up" phase, there is a slowdown or "catch down" phase but, importantly, the HV remains above that observed at baseline). The distribution of individual values illustrate a good response on Accretropin treatment.

Figure 5. Scatter Plot of Individual Responses for Height Velocity SDS for Patients in Study GA-007/7A



Efficacy data and immunogenicity

Study GA-005/5A

Since up to 50% of patients enrolled in this study developed anti-GH antibodies by Months 24 and 36, the applicant provides descriptive statistics for height velocity at the end of study GA-005A (i.e. Month 6) for patients with and without anti-GH antibodies[53]. These data suggest that the anti-GH antibodies did not result in growth attenuation at this timepoint (Table 28).

Table 28: Annualized height velocity (cm/yr) at Month 6 for patients with and without anti-GH antibodies in Study GA-005/5A

	Height velocity at Month 6 (cm/year)	
	Anti-GH antibody positive	**Anti-GH antibody negative**
N	18	24
Mean (SD)	9.3 (1.6)	9.8 (2.9)
Median	9.5	9.2
Minimum	6.5	5.1

[53] At this particular timepoint 38% of patients were antibody-positive.

Maximum	13.1	16.8

Source: Table 12-9 in Clinical Study Report for Study GA-005/5A.

At the request of this reviewer the applicant provided data through Month 36 (Table 29). This additional data do not indicate growth attenuation through Month 36.

Table 29: Summary Statistics for Height Velocity (cm/yr) in Patients with and without Anti-GH antibodies at Month 12, 24 and 36 in Studies GA-005/5A –ITT Population

	Annualized height velocity (cm/yr) at Month 12		Annualized height velocity (cm/yr)at Month 24		Annualized height velocity (cm/yr) at Month 36	
	antibody positive	antibody negative	antibody positive	antibody negative	antibody positive	antibody negative
N	19	22	14	20	9	16
Mean (SD)	8.7 (1.5)	9.0 (2.8)	7.9 (1.3)	7.4 (1.4)	7.8 (1.7)	6.3 (1.2)
Median	8.908	8.434	7.738	7.117	7.554	5.992
Minimum	5.956	4.789	6.184	5.183	6.184	4.733
Maximum	12.835	16.111	10.596	10.094	11.519	9.158

Source: Table 14 in submission "Amendment # 8.

Study GA-007/7A

Up to 35 % of patients enrolled in this study developed anti-GH antibodies by Months 24. The applicant provides descriptive statistics for height velocity at the end of study GA-007A (i.e. Month 6) with and without anti-GH antibodies[54]. This data suggests that the anti-GH antibodies did not result in growth attenuation for this timepoint (Table 30).

Table 30: Annualized height velocity (cm/yr) at Month 6 for patients with and without anti-GH antibodies in Study G7-007A

	Height velocity at Month 6 (cm/year)	
	Anti-GH antibody positive	Anti-GH antibody negative
N	15	22
Mean (SD)	9.6 (1.8)	8.3 (2.9)
Median	8.9	7.8
Minimum	7.1	4.0
Maximum	13.3	17.9

Source: Table 12-7 in Clinical Study Report for Study GA-007/7A.

At the request of this reviewer the applicant provided data through Month 36 (Table 31). This additional data do not indicate growth attenuation through Month 36.

[54] At this particular timepoint 32% of patients were antibody-positive.

Table 31: Summary Statistics for Height Velocity (cm/yr) in Patients with and without Anti-GH antibodies at Month 12, 24 and 36 in Studies GA-007/7A–ITT Population

	Annualized height velocity (cm/yr) at Month 12		Annualized height velocity (cm/yr)at Month 24		Annualized height velocity (cm/yr) at Month 36	
	antibody positive	antibody negative	antibody positive	antibody negative	antibody positive	antibody negative
N	14	23	12	24	6	25
Mean (SD)	8.791 (1.381)	8.418 (1.895)	7.162 (1.135)	6.700 (1.242)	6.318 (1.644)	5.564 (1.568)
Median	8.495	8.122	7.454	6.563	6.357	5.374
Minimum	6.451	5.673	4.985	4.362	4.056	0.735
Maximum	11.465	14.473	8.817	9.038	8.273	8.690

Source: Table 14 in submission "Amendment # 8.

Efficacy data for protocol violators

Study GA-005/5A

According to the study protocol patients were supposed to have been euthyroid or to have had normal thyroid function on thyroid replacement at baseline. Six patients were "erroneously entered into the study" with a variety of abnormalities in thyroid hormone levels at baseline and later were identified as protocol violators[55]. In addition, two patients received prohibited medication on study[56]. Table 32 presents the height velocity for each of these patients along with the mean HV for the historical control ("international" standard from Tanner et al.). It indicates that the listed patients had on-treatment height velocity values that were higher than those of the historical control for all but one measurement.

Table 32: Height velocity for protocol violators in Study GA-005

	Height velocity (cm/yr)		
	Year 1	Year 2	Year 3
Individual Patients			
Patient 107	8.48	6.32	7.52
Patient 115	12.82	9.93	9.19
Patient 116	16.11	10.09	9.16
Patient 205	7.60	NA	NA
Patient 214	9.54	6.93	5.35
Patient 302	9.75	8.26	NA
Patient 108	8.26	7.85	8.13
Patient 124	7.92	7.05	7.05
Control			
International standard Mean (± SD)	5.9 ±1.0	5.6 ± 1.2	5.7 ±0.6

[55]Patients 107, 115, 116, 205, 214 and 302.
[56] Patient 108 was started on estradiol at Month 30 and patient 124 started triptorelin/leuprorelin treatment after the Week 8 visit.

Source: Table 14-35
NA=Not available.

Study GA-007/7A

As in Study GA-005A, patients enrolled in study GA-007/7A were supposed to have been euthyroid or to have had normal thyroid function on thyroid replacement at baseline. Six patients were "erroneously entered into the study" despite not being euthyroid at baseline[57]. In addition, three patients were treated with GnRH-agonists to delay puberty[58]. Table 33 displays the individual height velocity on trial for these protocol violators and provides as reference the height velocity of untreated Polish girls with Turner syndrome. It indicates that the listed patients had on treatment height velocity values that were all higher than those of the historical controls (i.e. Turner syndrome patients).

Table 33: Height velocity for protocol violators in Study GA-007

	Height velocity (cm/yr)		
	Year 1	**Year 2**	**Year 3**
Individual Patients			
Patient 511	8.89	7.32	5.85
Patient 524	9.09	8.25	5.70
Patient 527	6.55	6.58	6.23
Patient 529	10.46	8.63	4.99
Patient 534	6.92	5.31	5.12
Patient 536	8.82	6.72	6.99
Patient 505	10.04	7.15	7.02
Patient 507	10.36	8.75	5.89
Patient 532	9.76	7.19	5.23
Control			
Turner syndrome Polish standard Mean (± SD)	4.0 ±0.7	3.7 ±1.2	3.7 ±0.9

Source: Table 14-2

Bone age advancement

At the request of this reviewer the applicant provided an analysis of bone age (BA)/chronological age ratio and change in BA/change in CA ratio on Accretropin treatment.

[57] Patients 511, 524, 527, 529, 534 and 536.
[58] Patient 505 started Leuprolin approximately 20 weeks on trial. Patients 507 and 532 started Triptorelin treatment at Month 18 and Month 12 visit, respectively.

Study GA-005/5A

As illustrated in Table 34 children with GHD had bone age advancement that was somewhat faster than that of chronological age. This is to be expected since GHD children have BA delay and at GH treatment initiation they display a "catch up" phenomenon.

Table 34 : Bone age advancement on Accretropin children (Study GA-005/5A)

Variable		Baseline	Month 12	Month 24	Month 36
Bone age / Chronological age ratio (%)	N	39	25	30	20
	Mean(SD)	64.5 (16.32)	67.8 (15.97)	78.5 (13.86)	83.7 (12.02)
	Min – Max	19 – 101	23 – 97	41 – 100	67 – 108
Bone age advancement / Chronological age advancement ratio (%)	N	N/A	25	30	20
	Mean(SD)		102.2 (97.23)	151.2 (67.44)	137.2 (47.61)
	Min – Max		-250.0 – 283.0	0.0 – 275.0	62.5 – 224.1

Source: Amendment # 10.

Study GA-007/7A

Table 35 illustrates bone age analyses for the Turner syndrome children (bone age delay is not a feature of Turner syndrome). On Accretropin treatment bone age and chronological age advanced concordantly.

Table 35 : Bone age advancement on Accretropin children (Study GA-007/7A)

Variable		Baseline	Month 12	Month 24	Month 36
Bone age / Chronological age ratio (%)	N	25	19	19	16
	Mean(SD)	91.0 (12.23)	91.7 (10.98)	94.6 (8.35)	93.1 (8.63)
	Min – Max	65 – 118	61 – 108	77 – 108	76 – 104
Bone age advancement / Chronological age advancement ratio (%)	N	N/A	19	19	16
	Mean(SD)		87.1 (80.04)	111.8 (46.72)	91.0 (33.20)
	Min – Max		-142.9 – 220.0	31.3 – 200.0	38.5 – 142.3

Source: Amendment # 10.

Comparison of efficacy of Accretropin with other rhGH products

Study GA-005/5A

The applicant provides a tabulated summary of efficacy data obtained with several approved rhGH products in pediatric GHD clinical trials (Table 36). Although different doses and regimens were evaluated in these trials, the results obtained with Accretropin in Study GA-005/5A are within the range of observations made with other marketed rhGH products when used in treating children with GHD.

Table 36: First-year height velocity from several approved rhGH products and Accretropin in pediatric GHD clinical trials*

rhGH product	Dose and regimen	Baseline HV (cm/yr)	First year HV (cm/yr) on-treatment	References
Humatrope	0.1 IU/kg/day, daily; s.c.	4.0 ± 1.3	9.4 ± 1.9	Shih et al., 1994
Genotropin	0.1 IU/kg/day, daily; s.c.	3.4 ± 0.7	11.3 ± 2.0	Shih et al., 1994
Saizen	0.2 IU/kg/day, daily; s.c.	3.7 ± 1.2	11.1 ± 3.3	Shih et al., 1994
Saizen	0.6 IU/kg/week, 3x/week; s.c.	3.5 ±1.1	10.6 ± 2.7	Stubbe et al., 1992
Saizen	0.45 IU/kg/week, 7x/week; s.c.	3.5 ±1.1	8.6 ± 2.0	Stubbe et al., 1992
Genotropin	0.17 IU/kg/week, 3x/week; i.m.	3.26 ± 0.42	7.1 ± 0.47	Girard and Goulmelen, 1986
Norditropin	0.5 IU/kg/week, 6-7x/week; s.c.	4.0 ± 2.4	9.2 ± 2.9**	Iyoda et al., 1999
Genotropin	0.3 mg/kg/week, daily, s.c.	4.1 ± 1.6	11.4 ± 2.5	MacGillivray et al., 1996
Genotropin	0.5-0.7 IU/kg/week, 6-7x/week; s.c.	3.4 ± 1.4	10.2 ±2.5	Wilton and Gunnarsson, 1988
Accretropin	0.03-0.05 mg/kg/day, 6x/week; s.q.	4.1 ± 1.2	8.8 ± 2.2	Current NDA

Source: Table 7-1. Study Report GA-005/GA-005A.
* The relationship between IU and mg for rhGH is 3:1.
**Annualized 6-month data used. For all other products the results data are annual HV.

GA-007/7A

The applicant provides a tabulated summary of efficacy information obtained with several approved rhGH products in Turner syndrome clinical trials (Table 37). Although different doses and regimens were evaluated in different trials, the results obtained with Accretropin in Study GA-007/7Aare within the range of observations made with other marketed rhGH products when used to treat children with Turner syndrome.

Table 37: First-year height velocity from several approved rhGH products and Accretropin in Turner syndrome clinical trials

rhGH product	Dose and regimen	Baseline HV (cm/yr)	First year HV (cm/yr) on-treatment	References
Humatrope	0.36 mg/kg/week; s.c.	4.0 ± 1.2	6.8 ± 1.1*	Quigley et al., 2002
Saizen	0.21 mg/kg/week; s.c..	4.0 ± 0.8	6.3 ± 1.3	Stahnke et al., 1992
Protropin/ Norditropin	0.33 mg/kg/week; s.c.	4.0 ± 2.3	7.5 ± 2.0	Plotnik et al., 1998
Norditropin	0.32 mg/kg/week;	Approx. 6	Approx. 10	Van Teunenbroek et

	s.c.			al., 1996
Protropin	0.37 mg/kg/week; s.c.	4.5 ± 0.8	6.6 ± 1.2	Rosenfeld et al., 1987
Valtropin	0.053 mg/kg/day, daily; s.c.	3.8 ± 1.8	9.7 ± 1.6	Peterkova et al., 2004
Accretropin	0.06 mg/kg/day, 6x/week; s.q.	3.8 ± 0.9	8.5 ± 1.7	Current NDA

Source: Table 7-1. Study Report GA-007//GA-007A.
*Annualized from 18-month data. For all other products the results are annual HV.
NP=not presented.

Integrated summary of efficacy results across indications

Table 38 summarizes the efficacy results for height velocity and height by year of treatment for Studies GA-005/5A and GA-007/7A. As expected, GHD patients had, descriptively, better efficacy responses than Turner syndrome patients even though the dose of Accretropin given to Turner syndrome patients was higher than that given to GHD patients (0.06 mg/kg/day vs. 0,04-0.05 mg/kg/day).

Table 38: Summary of efficacy results across studies – ITT Populations

Endpoint	**Study GA-005/5A**			**Study GA-007/7A**		
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
HV (cm/yr)						
N	41	34	26	37	36	35
Mean ± SD	8.88 ± 2.2	7.63 ± 1.4	6.97 ± 1.6	8.55 ± 1.7	6.85 ± 1.2	5.84 ± 1.8
Median	8.7	7.4	6.5	8.3	6.6	5.3
Range	4.7 to 16.1	5.1 to 10.5	4.7 to 11.5	5.6 to 14.4	4.3 to 9.0	0.7 to 12.1
HV SDS						
N	41	33	26	37	36	33
Mean ± SD	3.5 (3.5)	1.9 (2.3)	1.7 (2.8)	3.0 (2.5)	1.5 (1.8)	0.4 (3.2)
Median	3.4	2.1	1.1	2.9	1.0	-0.4
Range	-2.8 to 12.8	-2.1 to 6.7	-5.4 to 10.4	-1.6 to 11.2	-1.5 to 7.4	-3.7 to 7.3
Height SDS						
N	41	34	31	37	36	35
Mean ± SD	-2.4 (0.7)	-2.1 (0.8)	-1.77 (0.84)	-2.6 (1.1)	-2.4 (1.2)	-2.2 (1.2)
Median	-2.4	-1.9	-1.7	-2.6	-2.4	-2.4
Range	-4.1 to -1.2	-4.0 to -0.5	-3.4 to - 0.04	-5.9, -0.7	-5.3 to -0.2	-5 to - 0.08
Height SDS change						
N	41	34	26	37	36	35
Mean ± SD	0.59 ± 0.5	0.35 ± 0.2	0.33 ± 0.3	0.5 (0.4)	0.24 (0.4)	0.15 (0.4)
Median	0.50	0.33	0.3	0.64	0.31	0.14
Range	-0.09 to 2.3	-0.08 to 0.9	-0.1 to 1.1	-0.4 to 1.4	-0.8 to 1.1	-0.6 to 0.9

Source: Table 2.7.3.a and efficacy tables from individual study reports.

6.1.5 Clinical Microbiology

Accretropin is not an antimicrobial. Therefore this section of the review template does not apply to this product.

6.1.6 Efficacy Conclusions

In summary, Accretropin, when administered at standard doses, was efficacious in accelerating linear growth over 3 years of continuous treatment in children with severe short stature due to GH deficiency (GHD) and/or Turner syndrome. The efficacy data that supports this conclusion is summarized by study in the following sections.

Study GA-005/5A (GHD indication)

A standard dose of Accretropin[59] given to a cohort of patients with pediatric GHD doubled the mean height velocity (HV) for the first 12 months of treatment relative to baseline (8.8 ± 2.2 cm/year vs. 4.1 ± 1.2 cm/yr). The mean height velocities for the second and the third year of treatment were also above the baseline height velocity (7.6 ± 1.4 cm/year for the 2nd year and 6.9 ± 1.6 cm/year for the 3rd year, respectively). Thus, Accretropin added 4.76 ± 2.89 cm/yr for Months 0-12; 3.45 ±2.02 cm/yr for Months 12- 24; and 2.79 ± 2.48 cm/yr for Months 24-36, respectively, relative to baseline HV. This increment in height velocity is fully consistent with that described for other approved somatropins.

The mean height velocity values observed with Accretropin treatment in this study were higher than the mean height velocity of two reference populations of normally growing children (one Polish and one British); these "historical" comparisons made for the ITT population at Month 6, Month 12, Month 24 and Month 36 timepoints were all statistically significant (primary efficacy analysis). The same analyses conducted in the per protocol population produced concordant results.

Several other efficacy analyses further substantiate and complement the above described observations:

- A comparison of height velocity on Accretropin treatment with a reference values of 5 cm/year (which approximates the mean HV in normally growing prepubertal children) was statistically significant through Month 36.
- The mean height velocity SDS increased from negative values at baseline to values that were above the population mean through Month 36[60].
- Mean height SDS increased from values consistent with severe short stature at baseline (-3.0 ± 0.7) to values in the low normal range at Month 36 (-1.77 ± 0.84); the cumulative change in mean height SDS after 3 years of treatment was approximately 1.27 and was comparable for both genders.

[59] Dose of 0.03-0.05 mg/kg/day (0.18 to 0.3 mg/kg/week) administered as subcutaneous injections 6 days/week.
[60] Baseline HV SDS was -1.85. It increased to 3.5 at Month 12; 1.9 at Month 24 and 1.7 at Month 36.

- Accretropin treatment increased the serum concentration of IGF-1 and IGFBP-3 during the three years of treatment[61]. With respect to IGF-1, it doubled the mean serum IGF-1 concentrations and increased the mean serum IGF-1 SDS from markedly negative values at baseline (-1.47 ± 1.1) to values closer to the population mean (generally between -0.5 and 0) through Month 36.

The above described acceleration in linear growth was not associated with undue acceleration of bone age maturation for the duration of the trial.

Despite methodological limitations for (i.e. shortcomings in the method of collection of baseline height velocity) the totality of the efficacy data clearly confirms the effectiveness of Accretropin treatment in severely short children with GHD.

Finally, although anti-GH antibodies were observed in up to 50% of patients, the mean height velocity for patients who developed anti-GH antibodies on Accretropin treatment was comparable to that of patients who remained antibody-negative. Importantly, there was no convincing clinical evidence to suspect growth attenuation on Accretropin treatment up to 3 years of treatment.

Study GA-007/7A (Turner syndrome indication)

Accretropin treatment of Turner syndrome patients at a standard dose[62] increased more than two fold the height velocity from 3.8 ± 0.9 cm/yr at baseline to 8.5 ± 1.7 cm/yr at Month 12. The mean HV at Month 24 (6.8 ± 1.2 cm/yr) and at Month 36 (5.8 ± 1.8 cm/yr) were also above the baseline HV. This represents an increase in HV of 4.7 ± 2.8 cm/yr for Months 0-12 and 3.4 ± 2.0 cm/yr for Months 12-24 and 2.7 ±2.4 cm/yr for Months 24-36. This increment in HV is consistent with that of other somatropins in similar cohorts of patients with Turner syndrome.

The mean height velocity on Accretropin treatment was higher than the height velocity of two reference populations of normally growing children (one Polish and one British); these "historical" comparisons were statistically significant for the Month 6, Month 12, and Month 24 timepoints but not for the Month 36 timepoint (primary efficacy analysis, ITT population). In general, per protocol and ITT analyses were concordant. A similar comparison of HV on Accretropin treatment with the HV of untreated Turner syndrome children (a more appropriate comparator than normally growing children) was statistically significant at all the timepoints studied up to Month 36.

Several other analyses confirmed the efficacy of Accretropin in children with Turner syndrome:

- A comparison of height velocity on Accretropin treatment with a reference values of 5 cm/year (which approximates the mean HV in normally growing prepubertal children) was also statistically significant through Month 36.

[61] Both IGF-1 and IGFBP-3 are established biomarkers of GH activity.
[62] A dose of 0.06 mg/kg/day (0.36 mg/kg/week) administered 6 days/week.

- The mean height velocity SDS increased from negative values at baseline to values that were above the population mean through Month 36[63].
- The mean height SDS increased from values consistent with severe short stature at baseline (-3.1) to values that were closer to the lower limit of the normal range at Month 36 (-2.2). The cumulative change in mean height SDS after 3 years of treatment was approximately 0.85.
- When mean height SDS on Accretropin treatment was compared with height SD scores derived from girls with Turner syndrome (a more appropriate comparison since Turner syndrome children are shorter than normal growing children), the height SDS on treatment increased from an average height (height SDS of 0.2) to a height in the upper limit of normal for Turner syndrome girls (height SDS of 1.9); the cumulative height SDS increase at 3 years was 1.7.
- Accretropin treatment increased the level of IGF-1 and IGFBP-3. Specifically it resulted in a doubling of the mean serum IGF-1 concentrations and in an increase in mean serum IGF-1 SDS from markedly negative values at baseline (-1.2 ± 0.7) to values slightly above the population mean through Month 6.

The above described acceleration in linear growth was not associated with undue acceleration of bone age maturation for the duration of the trial.

As already mentioned in reference to the GHD cohort, there were some shortcomings relative to the collection of baseline height velocity information. However, the totality of the data clearly confirms the efficacy of Accretropin in severely short children with Turner syndrome.

Although up to 35% of children developed anti-GH antibodies, the mean height velocity for patients who developed anti-GH antibodies on Accretropin treatment was comparable to that of patients who did not develop antibodies through Month 36. There was no compelling clinical evidence to suspect growth attenuation on Accretropin for this duration of treatment.

[63] HV SDS was -2.4 at baseline. It increased to 3.0 at Month 12; 1.5 at Month 24; and 0.4 at Month 36.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Study GA-005/5A

There was one death recorded in this study: subject 205. This 15-year-old male was a participant in this trial for 11 months when he developed fatigue, dyspnea, hypotension, and anuria. The patient was intubated, mechanically ventilated, and admitted to the ICU[64]. He died approximately 24 hours later. An autopsy found macroscopic fatty degeneration of the liver and of the heart. The cause of death was reported to be cardiogenic shock due to fatty change of the heart. The investigator did not deem this adverse event drug related.

Study GA-007/7A

There were no deaths during this study.

7.1.2 Other Serious Adverse Events

Study GA-005/5A

There were 21 serious adverse events (SAEs) reported by 16 subjects (36.4%) in this study. Only one SAE (patient 302, hospitalization for adjustment in insulin dosage) was considered to have a probable, but expected relationship to the study drug[65] while for all other SAEs the relationship to the study drug was considered doubtful.

Several SAEs are worth mentioning. Cardiogenic shock and death have been already described for patient 205 in Section 7.1.1. One patient (213) with a history of atopy developed

[64] The following investigations were reported: normal electrolytes, severe acidosis (pH = 6.8), normal cranial CT, enlarged heart on chest CT scan, right ventricular overload on ECG, leukocytosis (WBC: 22 x 10^9/L) without a clinical site of infection, normal thyroid tests (done at an annual visit two days prior to this event). This patient also carried a diagnosis of hypopituitarism and diabetes mellitus.

[65] Patient 302 had an underlying diagnosis of diabetes mellitus and celiac disease. She was admitted to the hospital for three days for adjustment of her insulin dose. Given that GH has antiinsulinemic effects this event was not unexpected.

angioneurotic edema during the trial which resolved without discontinuation of the study drug and did not recur on treatment. Patient 116 had an SAE of headache and suspected intracranial hypertension; although judged by the investigator as not related to the study drug, intracranial hypertension has been described in association with GH. An additional patient (120) was diagnosed with Fanconi anemia during the trial; this patient, however had laboratory abnormalities at screening/baseline and his enrollment was appropriately judged later as a protocol violation. The SAEs recorded in trial GA-005/5A are listed in Table 39.

Table 39: List of SAEs in clinical trial GA-005/5A

Patient ID	SAE and comments	Relationship with study drug*
102	Abdominal pain	unrelated
102	Abdominal pain, anemia	unrelated
102	Abdominal pain due to nephrolithiasis	unrelated
105	Respiratory tract infection and vomiting	unrelated
109	Surgery for testicular torsion	unrelated
111	Pneumonia and concurrent varicella	unrelated
113	Hospital admission for work up of delayed puberty	unrelated
115	Acute gastritis (vomiting)	unrelated
116	Hepatitis B infection	unrelated
116	Hospital follow-up following surgery for sella turcica	unrelated
116	Suspected benign intracranial hypertension (headache)	unrelated
119	Hypertension (due to hypoplastic right renal artery)/nephrectomy	unrelated
120	Hospital admission for anemia work up (diagnosed with Fanconi anemia, congenital)	unrelated
121	Hospital admission for follow-up MRI	unrelated
205	Cardiogenic shock/death	unrelated
207	CNS trauma (bicycle accident)	unrelated
207	Wound/foreign body removal	unrelated
208	Tympanoplasty following suppurative otitis media	unrelated
210	Adenoidal hypertrophy	unrelated
213	Urticaria/angioedema edema (while treatment with GH continued)	unrelated
302	Insulin adjustment for high blood glucose (history of Type 1 diabetes mellitus)	probably related

Source: Module 5: Clinical Study Report (text) and Summary of Clinical Safety (Table 2.7.4.2.1.8a).
* In the opinion of the investigator. "Unrelated" encompasses both "doubtful" and "conditional".

Study GA-007/7A

There were 10 SAEs reported by 6 subjects. They are summarized in Table 40. None was considered related to the study drug by the investigator.

Table 40: Summary of SAEs in clinical trial GA-007/7A

Patient ID	SAE and comments	Relationship with study drug*
508	Gastroenteritis	unrelated
508	Abdominal pain	unrelated

508	Gastroenteritis (H.pylori)	unrelated
514	Surgical correction of right upper eyelid ptosis (diagnosed in early childhood)	unrelated
518	Acute appendicitis	unrelated
520	Lymphadenitis, body temperature increased.	unrelated
523	Tonsillectomy and adenoidectomy	unrelated
525	Cystitis	unrelated
525	Epilepsy	unrelated
525	Bronchitis	unrelated

Source: Module 5: Clinical Study Report (text) and Summary of Clinical Safety (Table 2.7.4.2.1.8a)..
* In the opinion of the investigator. "Unrelated" encompasses both "doubtful" and "conditional".

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Study GA-005/5A

No subjects discontinued the trial due to an adverse event. One patient who was diagnosed with Fanconi anemia decided to not enroll in the GA-007A extension of Study GA-005.

Study GA-007/7A

No subjects discontinued the trial due to an adverse event.

7.1.3.2 Adverse events associated with dropouts

Study GA-005/5A

Refer to section 7.1.3.1.

Study GA-007/7A

Refer to section 7.1.3.1.

7.1.3.3 Other significant adverse events

Study GA-005/5A

There were no other significant adverse events reported in this study.

Study GA-007/7A

There were no other significant adverse events reported in this study.

7.1.4 Other Search Strategies

Due to the small size of the datasets and the low frequency of the individual adverse events no extensive re-evaluation of the datasets was undertaken (the safety profile of rhGH is, in general, well understood and characterized). Emphasis has been placed on adverse events and laboratory changes that could be seen in association with anti-GH antibodies (see section on immunogenicity).

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The applicant reports that adverse events (AEs) for studies GA-002, GA-005/5A and GA-007/7A were coded using the MedDRA dictionary, and the classification of events by body system was performed using the WHO classification system. The principal investigator was the person responsible for making the determination of causality and severity of all AEs before they were reviewed by the applicant.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events

Study GA-005/5A

Forty-three (98%) of the 44 subjects enrolled experienced at least one adverse event (AE) and reported a total of 543 AEs during the three years of the study[66]. The number and percentage of patients with adverse events > 5% are presented in Table 41. Included is also the number of events for each adverse event. The majority of the treatment-emergent adverse events (TEAEs) represent common pediatric symptoms and conditions (pharyngitis, URIs, headache, bronchitis, fever, cough, vomiting, etc). Injection site reactions such as erythema (38.6%), swelling (20.5%), bruising (11.4%), pain (6.8%) and pruritus (6.8%) were relatively frequent. Several recorded TEAEs that could be mechanistically related to GH are scoliosis (13.6%), arthralgia (11.4%), hypothyroidism (6.8%), and pain in extremity (6.8%). Evaluation of TEAEs by degree

[66] More TEAEs were reported in Hungary relative to Poland. Specifically, in Hungary 20 patients reported 320 TEAEs while in Poland 23 patients reported 223 TEAEs (patients were approximately evenly distributed by country: 24 patients were enrolled at one site in Poland and 22 patients at three sites in Hungary).

of severity indicates that 7 (15.9%) patients experienced severe TEAEs[67], while 26 (59.1%) and 10 (22.7%) patients had moderate and mild TEAEs, respectively.

Table 41: Adverse events with an incidence > 5% - Study GA-005/5A

Adverse event (preferred term)	N (%) of patients with adverse event	Number of adverse events
Pharyngitis	24 (54.5)	57
Upper respiratory tract infection, nonspecific	18 (40.9)	42
Injection site erythema	17 (38.6)	24
Headache	16 (36.4)	64
Bronchitis, nonspecific	10 (22.7)	19
Body temperature increased	10 (22.7)	15
Injection site swelling	9 (20.5)	16
Cough	9 (20.5)	16
Vomiting, nonspecific	7 (15.9)	8
Influenza	7 (15.9)	7
Diarrhea, nonspecific	6 (13.6)	11
Fatigue	6 (13.6)	8
Scoliosis	6 (13.6)	6
Arthralgia	5 (11.4)	13
Injection site bruising	5 (11.4)	11
Dizziness	5 (11.4)	7
Varicella	5 (11.4)	5
Abdominal pain, nonspecific	4 (9.1)	9
Stomach discomfort	4 (9.1)	6
Nausea	4 (9.1)	5
Viral infection, nonspecific	4 (9.1)	4
Aspartate aminotransferase increased	4 (9.1)	4
Seasonal allergy	3 (6.8)	6
Hypothyroidism	3 (6.8)	5
Injection site pain	3 (6.8)	5
Anemia, nonspecific	3 (6.8)	4
Gastritis, nonspecific	3 (6.8)	4
Tonsillitis	3 (6.8)	4
Pneumonia, nonspecific	3 (6.8)	4
Injection site pruritus	3 (6.8)	3
Gastroenteritis, nonspecific	3 (6.8)	3
Parasitic infection, nonspecific	3 (6.8)	3
Alanine aminotransferase increased	3 (6.8)	3
Pain in extremity	3 (6.8)	3
Rhinitis allergic, nonspecific	3 (6.8)	3

Source: Module 5: Clinical Study Report. Tables 12-1.

Table 42 lists the adverse evens that were considered "related" to the study medication. The relationship between TEAEs and the study drug was considered "definite" in 21 (47.7%)

[67] There were 11 severe SAEs (eight were reported in Poland and three in Hungary): anemia NOS, cardiogenic shock, Fanconi syndrome, diarrhea NOS, vomiting NOS, injection site erythema, pneumonia NOS, body temperature increased, testicular torsion, angioneurotic edema, urticaria NOS. Injection site erythema was the only severe AE considered to be related to the study drug (patient 123).

patients[68], "probable" in 4 (9.1%) patients, "possible" in 3 (6.8%) patients, "conditional" in 6 (13.6%) patients, and doubtful in 9 (20.5%) patients.[69] The most common "treatment-related" TEAEs were those related to the injection site (erythema, swelling, pain, pruritus, etc.). Other frequent TEAEs were headache, gastrointestinal symptoms (nausea, abdominal pain) or constitutional symptoms (e.g. fatigue). Adverse events anticipated to be reported in association with rhGH therapy are injection site reactions, occasional headache, scoliosis, hypothyroidism, myalgia, pain in extremity. The adverse event of diabetes was in fact related to insulin adjustment dose in a patient with known type 1 diabetes mellitus.

Four events listed as "related" to the study drug were not expected. The applicant notes that the two unexpected events of paraesthesia[70] occurred in the first week of the study (unclear though whether it was localized and if possibly related to the injection site/technique). The adverse event of vertigo[71] was reported in a patient on the same day as a headache which was characterized as moderate. The adverse event of mild hypocalcemia[72] was an isolated finding at Week 12 and was followed by a normal calcium level at Week 24. The absence of a comparator group limits the ability to draw any firm conclusions regarding these events.

Table 42: Adverse events deemed 'related" to study drug - Study GA-005/5A

Adverse event (preferred term)	N (%) of patients with adverse event	Number of adverse events
All events	28 (63.6%)	121
Injection site erythema	17 (38.6%)	24
Injection site swelling	9 (20.5%)	16
Headache	9 (20.5)	26
Injection site bruising	5 (11.4%)	10
Nausea	3 (6.8%)	4
Fatigue	3 (6.8)	5
Injection site pain	3 (6.8%)	3
Injection site pruritus	3 (6.8%)	3
Abdominal pain NOS	2 (4.5%)	2
Scoliosis	2 (4.5%)	2
Vertigo	1 (2.3%)	1
Hypothyroidism	1 (2.3%)	2
Diarrhea NOS	1 (2.3%)	1
Stomach discomfort	1 (2.3%)	1
Discomfort NOS	1 (2.3%)	1

[68] The applicant states that 'the criteria for a classification of definite relationship [..] were not met in all cases." Indeed, the percentage of adverse events in this category is excessive relative to prior experiences with similar datasets and is not consistent with either the known adverse event profile of GH or other analyses of adverse events from this trial. In the opinion of the applicant these adverse events should be classified as "probable, even though they were classified as definite by the investigator at the site."
[69] Four of the 121 related (i.e. definite, probable, and possible) AEs were unexpected. One patient (203) reported three of them: 2 instances of arm numbness ("paresthesia") during the first week of treatment and one instance of vertigo on the same day of headache. Another patient (208) had mild hypocalcemia at Week 12 with normal subsequent calcium level at Week 24. (
[70]Patient 203.
[71]Patient 203.
[72]Patient 208.

Injection site hemorrhage	1 (2.3%)	1
Injection site edema	1 (2.3%)	2
Injection site rash	1 (2.3%)	1
Diabetes mellitus NOS	1 (2.3%)	1
Hypocalcemia	1 (2.3%)	1
Bone pain	1 (2.3%)	1
Myalgia	1 (2.3%)	5
Pain in extremity	1 (2.3%)	1
Dizziness	1 (2.3%)	1
Paraesthesia	1 (2.3%)	2
Somnolence	1 (2.3%)	1
Rash vesicular	1 (2.3%)	1
Skin discoloration	1 (2.3%)	1
Skin induration	1 (2.3%)	1

Source: Module 5: Clinical Study Report. Table 14-50.

Study GA-007/7A

All patients (100%) reported at least one adverse event for a total of 336 adverse events for the three year duration of the study. Of these 336 AEs, 283 (84%) were reported as mild in intensity and 53 (16%) were reported as moderate; none was reported as severe. Thirteen patients (35.1%) experienced mild AEs and 24 patients (64.9%) experienced moderate AEs. The number and percentage of patients with adverse events > 5% are presented in Table 43 (included is also the number of events for each adverse event). The majority of the treatment-emergent adverse events represent common pediatric symptoms and conditions (URI, pharyngitis, otitis media, rhinitis, diarrhea, etc.). Injection site reactions such as erythema (29.7%), bruising (5.4%), and edema (5.8%) were relatively frequent. Otitis media (35.1%), a frequent pediatric condition, has been described with higher frequency in Turner syndrome patients.

Table 43: Adverse events with an incidence > 5% - Study GA-007/7A

Adverse event (preferred term)	N (%) of patients with adverse event	Number of adverse events
Upper respiratory tract infection NOS	24 (64.9)	54
Pharyngitis	19 (51.4)	42
Otitis media NOS	13 (35.1)	29
Rhinitis NOS	14 (37.8)	19
Injection site erythema	11 (29.7)	12
Diarrhea NOS	7 (18.9)	8
Stomach discomfort	7 (18.9)	9
Vomiting NOS	6 (16.2)	10
Tonsillitis	5 (13.5)	8
UTI	6 (16.2)	7
Bronchitis, nonspecific	6 (16.2)	7
Varicella	5 (13.5)	5
Body temperature increased	5 (13.5)	6
Cough	5 (13.5)	5
Abdominal pain NOS	4 (10.8)	7

Influenza	4 (10.8)	4
Mumps	3 (8.1)	3
Streptococcal infection NOS	3 (8.1)	3
Viral infection NOS	3 (8.1)	3
Headache	3 (8.1)	7
Enuresis	3 (8.1)	4
Ear discomfort	2 (5.4)	2
Ear pain	2 (5.4)	2
Injection site bruising	2 (5.4)	2
Injection site edema	2 (5.4)	2
Peripheral edema	2 (5.4)	2
Dizziness	2 (5.4)	3
Cystitis NOS	2 (5.4)	2
Laryngitis NOS	2 (5.4)	2
Rhinitis allergic NOS	2 (5.4)	3
Tonsillectomy	2 (5.4)	2

Source: Module 5: Clinical Study Report. Tables 14-12.

Table 44 lists the adverse evens that were considered "related" to the study medication. The most common TEAEs were those related to injection site (erythema, edema, pain, and pruritus). Most were mild, some were moderate in intensity; none was severe[73].

Table 44: Adverse events deemed 'related" to study drug - Study GA-007/7A

Adverse event (preferred term)	N (%) of patients with adverse event	Number of adverse events
All events	15 (40.5%)	23
Injection site erythema	11 (29.7%)	12
Injection site edema	2 (5.4%)	2
Eyelid edema	1 (2.7%)	4
Vomiting NOS	1 (2.7%)	1
Injection site pain	1 (2.7%)	1
Injection site pruritus	1 (2.7%)	1
Growing pains	1 (2.7%)	2

Source: Module 5: Clinical Study Report. Table 14-10.

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

Of the TEAEs that were considered treatment-related, injection site reactions were the only adverse events that could be clearly associated with the study drug[74]. The rest of the "treatment-

73 Fourteen patients (37.8) had 19 "mild" events and two patients (5.4%) had 4 "moderate" events.

related" adverse events were mostly adverse events known to occur in association with GH in general[75]. The few TEAEs that did not fall in this category were infrequent and inconsistently seen between the two clinical trials. Absence of a control group and the small size of the datasets limit the ability to draw additional conclusions.

7.1.5.6 Additional analyses and explorations

Due to the small size of the datasets and the known safety profile of rhGH in general, no extensive additional analyses or explorations were done. Emphasis has been placed on safety analyses related to the immunogenicity of Accretropin.

7.1.6 Less Common Adverse Events

Adverse events that occurred in < 5% in studies GA-005/5A and GA-007/7A are listed next.

Study GA-005/5A

Adverse events (by preferred term) that occurred in 2 patients (4.5%) were enteritis, toothache, epidermodysplasia verruciformis, otitis media NOS, sinusitis NOS, streptococcal infection NOS, urinary tract infection NOS, wound NOS, myalgia, rash NOS, and hospitalization NOS[76].

Adverse events (by preferred term) that occurred in 1 patient (2.3%) were lymphadenitis NOS, cardiogenic shock (see SAE Section), congenital atrial septal defect, Fanconi syndrome (see SAE Section), ear pain, vertigo, delayed puberty, secondary hypothyroidism, eyelid edema, hypermetropia, myopia, abdominal discomfort, abdominal pain upper, aphtous stomatitis, dyspepsia, gastrointestinal disorder NOS, chest discomfort, chest pain, discomfort NOS, injection site hemorrhage, injection site edema, injection site rash, cholelithiasis, food allergy, gastroenteritis salmonella, hepatitis B, laryngitis acute NOS, mumps, otitis media acute NOS, otitis media suppurative, parasitic infection intestinal, respiratory tract infection, tonsillitis acute NOS, upper respiratory tract infection viral NOS, arthropod bite, arthropod sting, bite NOS, clavicle fracture, facial bones fracture, hand fracture, head injury, hypothermia, injury, appetite decreased NOS, diabetes mellitus NOS, hypocalcemia, hypoglycemia NOS, iron deficiency, weight loss poor, back pain, bone pain, bone spur, muscle twitching, musculoskeletal pain, osteochondrosis, mycosis fungoides NOS, benign intracranial hypertension, paraesthesia, somnolence, syncope, anxiety, tic, nephrolithiasis, testicular torsion, adenoidal hypertrophy, rhinitis NOS, angioneurotic edema[77], contusion, dermatitis allergic, dermatitis bullous, dry skin,

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[74] In study GA-005/5A they were recorded under several preferred terms with the following incidence rates: injection site erythema (38.6%), swelling (20.5%), bruising (11.4%), pain (6.8%), pruritus (6.8%), hemorrhage (2.3%), edema (2.3%), rash (2.3%). In study GA-007/7A they were recorded under several preferred terms with the following incidence rates: injection site erythema (29.7%), edema (5.4%), pain (2.7%), and pruritus (2.7%).
[75] Preferred terms: headache, scoliosis, hypothyroidism, myalgia, bone pain, growing pains, pain in the extremities, nausea and vomiting and headache (in the context of benign increased intracranial hypertension).
[76] Source: Table 14-45 from Study Report GA-005/5A
[77] According to Table 14-49, angioneurotic edema and urticaria were reported by the same patient; both were judged

itching scar, photosensitivity allergic reaction, rash vesicular, skin discoloration, skin induration, sweating increased, urticaria NOS, vitiligo, asthma exacerbation, mole excision, tooth extraction NOS, and hypertension NOS[78].

Study GA-007/7A

Adverse events (by preferred term) that occurred in 1 patient (2.7%) were anemia NOS, lymphadenitis NOS, congenital renal anomaly NOS, hypoacusis, otorrhea, hypothyroidism, eyelid edema, eyelid ptosis, gastritis NOS, gastroesophagial reflux disease, stomatitis, injection site pain, injection site pruritus, hepatomegaly, adenoiditis, appendicitis, diarrhea infectious, gastroenteritis NOS, herpes simplex, otitis media chronic NOS, otitis media suppurative, parasitic infection NOS, pneumonia NOS, rubella, sinusitis NOS, tracheitis NOS, vulvovaginitis NOS, joint sprain, upper limb fracture NOS, blood growth hormone increased, weight increased, appetite decreased NOS, arthralgia, growing pains, pain in extremity, scoliosis, convulsions NOS, epilepsy NOS, somnolence, insomnia, dermatitis allergic, dermatitis atopic, psoriasis, rash NOS, polypectomy, hypertension NOS, and lymphedema NOS[79].

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Study GA-005/5A

The laboratory assessments included standard hemotology[80] and chemistry[81] analytes, urinalysis, endocrinological assessments[82], anti-E.coli polypeptide (ECP) antibodies and anti-GH antibodies. Standard analytes and endocrinological assessments were evaluated at baseline, weeks 8, 12, and 24; they were not measured beyond 6 months. Antibodies evaluations were done at baseline, weeks 8, 12 and 24, months 6, 9, 12, and every 6 months thereafter up to 36 months.

Study GA-007/7A

Similar to study GA-005/5A described above.

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as unrelated to treatment (Table 15050).
[78] Source: Table 14-45 from Study Report GA-005/5A
[79] Source: Table 14-11 from Study Report GA-007/7A
[80] Complete blood count with differential.
[81] Alkaline phosphatase, ALT, AST, calcium, chloride, creatinine, GGT, glucose, potassium, sodium, total protein, and urea.
[82] LH, FSH, T4, TSH, IGF-I and IGFBP-3 (the latter two were evaluated as secondary efficacy endpoints). LH, FSH, T4, and TSH were evaluated for the first 24 weeks of the study only.

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

There were no controls in any of the two clinical studies included in this submission.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Study GA-005/5A

There were no clinically significant changes in mean values for the analytes evaluated[83]. The mean ± SD alkaline serum concentration increased on treatment from 225.38 ± 48.91 IU to 307.10 ± 84.00 at Week 24, a known pharmacodynamic effect of GH. As expected, the mean serum concentrations of IGF-1 more than doubled on treatment; mean serum IGFBP-3 concentrations also increased in association with Accretropin treatment[84].

Study GA-007/7A

There were no clinically significant changes in mean values for the analytes evaluated[85]. As noted in Study GA-005/5A there was a small increase in the mean ± SD serum concentration for alkaline phosphatase on treatment from 268.80 ± 84.86 IU/L at baseline to 316.17 ± 79.30 IU/L at Week 24, a known pharmacodynamic effect of GH. An increase in the mean serum concentrations of IGF-1 and IGFBP-3 was observed, as expected, in association with Accretropin treatment[86].

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Study GA-005/5A

There were 51 out of range chemistry measurements. The out of range serum chemistry values were as follows[87]:

- ALT (SGPT): 6 measurements in 5 patients (none > 2X ULN)
- AST (SGOT): 12 measurements in 8 patients (none > 2X ULN)
- alkaline phosphtase : 15 measurements in 7 patients (none > 2X ULN)
- GGT: 1 measurement in one patient (below 2X ULN)
- total protein: 6 measurements in 4 patients (all close to the upper limit of normal)
- sodium: 2 measurements in 2 patients (mild variations below and above the normal range)

[83] Source: Table 14-57, Table 14-59, Table 14-61, Table 14-63 from Study Report GA-005/5A.
[84] IGF-1 and IGFBP-3 were also secondary efficacy endpoints (see Efficacy Section for details).
[85] Source: Table 14-15, Table 14-17, Table 14-19 and Table 14-21.
[86] IGF-1 and IGFBP-3 were also secondary efficacy endpoints (see Efficacy Section for details).
[87] Source: Table 14-58 from Study Report GA-005/5A.

- urea: 2 measurements in 1 patient (mild reductions)
- calcium: 2 measurements in 2 patients (mild reductions[88])
- glucose: 5 measurements in 4 patients: one was slightly below the lower limit, two were low and associated with "technical problems" and two were elevated and clinically significant[89].

Table 45 summarizes the GGT, AST and/or ALT measurements that were above the upper limit of normal. One patient (109) had mild elevation of GGT at baseline. Another patient (205) had both ALT and AST elevations at baseline (both mild) but the AST elevation was in excess to the ALT increase suggesting a muscle origin for the two enzymes; for this patient AST elevations persisted throughout the trial while the ALT increase resolved by Week 12. All other patients had occasional AST elevations with only occasional ALT elevations accompanying them.

Table 45: Abnormal LFTs in study GA-005/5A

Patient ID	Time of assessment on trial	Analyte	Test Result	Normal range
GD105	Baseline	AST (SGOT)	81	20-60 IU/L
	Week 8	AST (SGOT)	84	20-60 IU/L
	Week 12	AST (SGOT)	87	20-60 IU/L
	Week 24	AST (SGOT)	92	20-60 IU/L
GD109	Baseline	GGT	84	2-49 IU/L
GD110	Week 24	ALT (SGPT)	60	5-45 IU/L
	Week 24	AST (SGOT)	96	20-60 IU/L
GD116	Week 24	ALT (SGPT)	46	5-45 IU/L
	Week 24	AST (SGOT)	71	20-60 IU/L
GD124	Week 12	AST (SGOT)	57	15-45 IU/L
	Week 24	AST (SGOT)	59	15-45 IU/L
GD204	Week 24	AST (SGOT)	56	15-45 IU/L
GD205	Baseline	ALT (SGPT)	64	5-45 IU/L
	Week 8	ALT (SGPT)	53	5-45 IU/L
	Baseline	AST (SGOT)	77	15-45 IU/L
	Week 8	AST (SGOT)	82	15-45 IU/L
	Week 12	AST (SGOT)	47	15-45 IU/L
	Week 24	AST (SGOT)	56	15-45 IU/L
GD215	Week 12	AST (SGOT)	61	20-60 IU/L

Source: Table 14-58 Study Report GA-005/5A.

There were 105 out of range hematology measurements, the vast majority of no clinical significance[90]. One patient (GD 120) who was diagnosed with Fanconi anemia on trial had 25

[88] Patients 208 and 215 had each of them a serum calcium of 2.18 at Week 12 and Week 8, respectively (normal range of 2.2-2.7 mmol/L).
[89] They were both in patient GD 302 (who had a diagnosis of diabetes mellitus prior to enrollment) one at baseline (20 mmmol/L) and the other one at Week 12 (17.2 mmol/L); the normal range for these measurements was 3.8 to 9.4 mmol/L. Measurements at Weeks 8 and Week 24 were normal (8.9 mmol/L at each time point).

markedly abnormal measurements related to anemia, neutropenia and thrombocytopenia, all findings consistent with this condition (see also the SAE section of this review)[91]. Several out of range hemoglobin values were reported; most were mild reductions of no clinical significance (the lowest was 10.3 g/dl). In one patient (GD 102) hemoglobin reductions were associated with a diagnosis of anemia. None of the platelet count abnormalities were clinically significant (the lowest was 110,000/mm^3)[92]. Mild neutropenia or leukocytosis was occasionally reported (of no clinical consequence). Four patients had eosinophilia (two at baseline, one at Week 8 and one at Week 24; none was ≥ 2 ULN)[93].

The urinalysis results were, in general, normal. A few isolated deviations from the normal were occasionally reported (e.g. patient 302 who was diagnosed with diabetes and celiac disease prior to trial initiation had two measurements of glycosuria (at baseline and Week 12)[94].

Several patients had abnormalities in thyroid hormone measurements (TSH and/or T4). Excluding patients with known conditions that may affect thyroid hormone levels (multiple pituitary hormone deficiency[95] and celiac disease[96]), two patients (105 and 107) displayed "clinically significant" TSH abnormalities, three patients (105, 115, and 214) had "clinically significant" T4 measurements, and one patient (202) had abnormal T4 levels that were deemed "not clinically significant". Abnormalities of thyroid hormone measurements (a downshift in T4 and TSH serum levels) are known to be associated with rhGH treatment, as is unmasking of hypothyroidism.

Serum IGF-1 concentrations above the upper limit of the normal range were reported in only two patients: patient 111 (at Week 12) and patient 117 (Weeks 12, 24 and Month 24)[97].

Study GA-007/7A

There were 85 out of range chemistry measurements. There were three isolated AST (SGOT) elevations in three patients and four ALT (SGPT) elevations in three patients, none was > 2X ULN (Table 46). There were two isolated total bilirubin concentrations slightly over the upper limit of normal in two patients[98]; none of the measurements was associated with liver enzyme

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[90] Source: Table 14-60 from Study Report GA-005/5A.
[91] This patient had thrombocytopenia (38,000/mm^3) and neutropenia (2,800/mm^3) at baseline and anemia by Week 8; baseline hemoglobin was at about the lower limit of normal.
[92] Excepting Patient GD120 with Fanconi anemia.
[93] The two patients with eosinophilia on treatment were: GD122 (1.31 at Week 8 with normal range of 0-0.7 X10E9/L; this patient was judged non-compliant and was discontinued; also had an elevated antibody titer at week 12) and GD114 (0.61 at Week 24 with normal range of 0 to 0.56 X10E9/L; was antibody posiyive by week 12).
[94] Source: Tables 14-61 and 14-62 Study Report GA-005/5A.
[95] Patients 116 and 205.
[96] Patient 302.
[97] The IGF-1 levels recorded were 675 µg/mL for patient GD111 (normal range: 88-274 µg/mL) at Week 12 and 829 µg/mL, 994 µg/mL, and 1051 µg/mL, for patient GD117 at weeks 12, 24 and Month 24 respectively (normal range 117-771 µg/mL).
[98] Patient GF527 had a total bilirubin of 22 µmol/L at Week 24 (normal range: 3-21 µmol/L). Patient GF523 had a total bilirubin of 24 µmol/L at Week 24 (normal range: 3-21 µmol/L.)

elevation. Three patients had one measurement each of serum calcium slightly above (1 patient[99]) or below (2 patients[100]) the normal range. There were 8 minor elevations in uric acid in three patients and one mild reduction in another patient. There were multiple clinically insignificant borderline elevations in serum albumin or total protein in several patients. One patient had a borderline low glucose measurement. As expected from the on-treatment change in mean serum alkaline phosphatase concentrations, several patients exhibited borderline or mild elevations in isolated or multiple measurements of this analyte.

Table 46: Abnormal LFTs in study GA-007/A

Patient ID	Time of assessment on trial	Analyte	Test Result	Normal range
GF501	Week 24	AST (SGOT)	70	15-45 IU/L
GF508	Week 12	AST (SGOT)	47	15-45 IU/L
GF514	Week 8	ALT (SGPT)	55	5-45 IU/L
	Week 12	ALT (SGPT)	82	5-45 IU/L
	Week 12	AST (SGOT)	69	20-60 IU/L
GF521	Baseline	ALT (SGPT)	48	5-45 IU/L
GD528	Baseline	ALT (SGPT)	47	5-45 IU/L

Source: Table 14-16 Study Report GA-007/7A.

There were 80 out of range hematology values. Twelve out of range hemoglobin values were recorded in seven patients; two measurements in one patient were consistent with anemia[101], while all others were minimal elevations above the upper limit of normal of no clinical significance. There were four reports of abnormal platelet counts in three patients, all of no clinical importance (the lowest platelet count was 121,000/mm^3). Eight out of range white counts were recorded in six patients; one was a case of mild leukocytosis while all other were cases of mild neutropenia (except one measurement of 3300WBCs/ mm^3 which was associated with a viral infection). Five reports of eosinophilia in 3 patients were all small or minimal increases above the upper limit of normal[102].

A total of 31 abnormal urinalysis values were reported. There were no cases of glycosuria. The proportion of patients with hematuria and proteinuria was not elevated on treatment relative to baseline.

Fifteen out of range TSH values were recorded in 8 patients. Two such measurements were observed only at baseline. Most other measurements above the upper of limit were isolated small elevations; a few were observed at repeated visits. Importantly, there were no abnormalities in the T4 levels during the whole trial.

[99] Patient GF524 had a serum calcium of 2.73 mmol/L at baseline (normal range 2.20-2.70 mmol/L).
[100] Patient GF503 had a serum calcium of 2.18 mmol/L at Week 8 (normal range 2.20-2.70 mmol/L). Patient GF520 had a serum calcium of 2.03 mmol/L at baseline (normal range 2.20-2.70 mmol/L).
[101] Patient GF 534 had Hb measurements of 99 and 88 g/L at Weeks 8 and 24, respectively (normal range for age: 116-162 g/L).
[102] Patient GF501 had Week 8 and Week 12 eosinophils of 0.57 and 0.61 X10E9/L, respectively (normal range: 0-0.56 X10E9/L). Patient GF529 had a baseline eosinophil count of 0.77 (normal range: 0.0 to 0.7 X10E9/L). Patient GF534 had Week 8 and Week 8 eosinophil counts of 0.6 and 0.59 (normal range of 0-0.56 X10E9/L).

Above normal serum IGF-I concentrations were reported in only two patients: GF535 (at Week 24) and GF537 (at Week 24)[103].

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Study GA-005/5A

There were no marked outliers in laboratory values and there were no patients who were reported to drop out of the trial because of an abnormality in laboratory measurements. The few clinically significant out of normal range analytes (such as the neutropenia and thrombocytopenia in one patient diagnosed with Fanconi syndrome) had clear non-drug related explanations.

Study GA-007/7A

There were no marked outliers in laboratory values and there were no patients who were reported to drop out of the trial because of an abnormality in laboratory measurements. The few clinically significant out of normal range analytes (such as neutropenia associated with a viral infection) had clear non-drug related explanations.

7.1.7.4 Additional analyses and explorations

The main analyses and explorations of laboratory findings were purely descriptive. Tables summarizing and describing the absolute measurements of abnormal laboratory values at different time points were visually inspected, and a judgment was made as to the presence or absence of a trend. It is important to recognize that the laboratory profile associated with GH treatment has been well characterized in multiple clinical trials in relatively diverse patient populations over the last 40 years. No unusual or new trends were observed in trials GA-005/5A and GA-007/7A.

[103]Patients GF535 and GF537 had IGF-1 levels of 932 ng/ml ant 933 ng/ml, respectively,/at Week 24 (normal range 88-474 ng/ml).

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured at baseline, Week 8, Week 12, Week 24 Month 9, Month 12 and every 6 months through Month 36. They included body temperature, pulse, systolic and diastolic blood pressure, height and weight.

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

There were no control groups in Studies GA-005/5A and GA-007/7A.

7.1.8.3 Standard analyses and explorations of vital signs data

Analysis of vital signs consisted in an inspection of the descriptive statistics for each of the parameters evaluated in the clinical trial.

7.1.8.3.1 Analyses focused on measures of central tendencies

Study GA-005/5A

There were no significant changes in mean values other than those expected due to physiological growth (e.g. weight changes). There were no outlier values reported.

Study GA-007/7A

There were no significant changes in mean values other than those expected due to physiological growth. There were no outlier values reported.

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 were done.

7.1.9 Electrocardiograms (ECGs)

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

ECG testing was not done in this clinical trial (there are no known ECG abnormalities described in association with appropriate rhGH use to date).

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

Refer to Section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to Section 7.1.9.1.

7.1.9.3.1 Analyses focused on measures of central tendency

Refer to Section 7.1.9.1.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to Section 7.1.9.1.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Refer to Section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

Limited safety information was provided from Study GA-002, which was conducted in healthy adult volunteers, a patient population different from that intended for Accretropin use. No patients died and no patients experienced serious adverse events in this study. For additional details see a summary of the study in the Appendix.

7.1.10 Immunogenicity

Immunogenicity data are provided for 81 patients (44 with GHD and 37 with Turner syndrome) followed for up to 36 months.

Study GA-005/5A

Table 47 summarizes the number and percentage of patients who developed anti-GH and anti-E. coli polypeptide (ECP) antibodies; it also includes descriptive statistics of the antibody titers in

study GA-005/5A. All the patients enrolled were naïve to rhGH therapy and none of them had anti-GH antibodies at baseline. At the end of the study (Month 36) 11/31 of the evaluable patients (35%) and approximately 50% of patients in an LOCF analysis were positive for anti-GH antibodies. Anti-GH antibody titers were detected at Week 8 (first on-treatment evaluation) in 16% of patients. The mean titers peaked at Month 12 and declined slightly through Month 24 and further at Month 36 (at Month 36 about ¼ of patients did not have antibody evaluations). The applicant points out that the highest individual antibody concentration found at any measured time point was 0.663 mg/L, below what has been traditionally regarded as an anti-GH antibody level above which growth attenuation may be seen (1 mg/L to 2 mg/L)[104].

Anti-ECP antibodies were present at baseline in 35/44 or 79.5% patients and in up to 90-100% .thereafter. An actual increase in anti-ECP antibody titers was noted in 35/42 (83.3%) at Month 6, 37/41 (90.2%) at Month 12, 31/34 (91.1%) at Month 24, and 27/31 (87%) at Month 36. The mean increase in anti-ECP titers peaked by Month 12 and remained about the same by Month 36.

Table 47: Summary of anti GH and anti-E.coli polypeptide antibodies – Study GA-005/5A

Statistics	Baseline	Week 8	Week 12	Week 24	Month 12	Month 24	Month 36
Patients with anti-GH antibodies							
n/N	0/44	7/44	15/44	16/42	19/41	14/34	11/31
%	0	15.9	34.0	38.0	46.3	41.1*	35.4**
Anti-GH antibodies (mg/L)							
N	44	44	44	42	41	34	31
Mean (SD)	0.000 (0.000)	0.027 (0.087)	0.045 (0.120)	0.044 (0.078)	0.059 (0.088)	0.043 (0.065)	0.025 (0.041)
Range	0.000 to 0.000	0.000 to 0.436	0.000 to 0.663	0.000 to 0.357	0.000 to 0.399	0.000 to 0.242	0.000 to 0.152
Patients with anti-ECP antibodies							
n/N	35/44	40/44	41/44	41/42	41/41	34/34	30/31
%	79.5%	90.9%	93.1%	97.6%	100%	100%	96.7%
Anti-ECP antibody titers (Z-score)							
N	44	44	44	42	41	34	31
Mean (SD)	0.338 (0.311)	0.407 (0.326)	0.410 (0.295)	0.464 (0.300)	0.538 (0.321)	0.522 (0.308)	0.536 (0.281)
Range	0.000 to 1.461	0.000 to 1.471	0.000 to 1.478	0.000 to 1.487	0.202 to 1.614	0.213 to 1.565	0.000 to 1.315

Source: Tables 12-5, 12-1208, 14--41 and text.
N = total number of subjects evaluated for the time point.
*LOCF: 50 %
**LOCF: 48.3%.

Importantly, accounting for the natural slowdown in height velocity seen with GH beyond the first year of treatment, none of the nine patients who did not have anti-ECP antibodies at baseline and developed them on trial, had growth attenuation (Table 48). Similarly, none of the 22 patients who developed anti-GH antibodies during Accretropin treatment provides clear evidence of growth attenuation[105].

[104] Okada et al., 1987 and Pirazzoli et al., 1995.
[105] Several patients (e.g. 109 and 201) were withdrawn from the study because of onset of puberty and did not have evaluations at Month 24 and/or Month 36 (this was done according to the protocol). Both also had high antibody

Table 48: Individual annualized height velocities for patients who became antibody positive during Accretropin treatment

Patient ID	Annualized height velocity (cm/year)			
	Baseline	Month 12	Month 24	Month 36
Patients with anti-E-coli antibodies				
109	2.61	6.65	6.65	NA
114	5.03	8.26	10.6	NA
115	4.38	12.84	9.93	9.19
116	2.15	16.11	10.09	9.16
203	2.81	10.36	NA	NA
208	3.41	4.79	6.10	5.61
209	4.61	6.30	6.49	4.73
213	3.89	NA	NA	NA
402	4.42	9.27	5.92	5.05
Patients with anti-GH antibodies				
101	7.2	8.89	7.30	5.55
103	5.98	8.97	7.05	6.69
106	4.09	7.52	6.45	6.48
107	2.39	8.48	6.32	7.52
108	2.32	8.26	7.85	8.13
109	2.61	6.65	6.65	NA
111	3.84	8.91	9.52	6.18
112	3.63	10.23	6.18	8.66
114	5.03	8.26	10.60	NA
115	4.38	12.84	9.93	9.19
117	4.35	8.76	7.62	NA
118	4.14	9.86	7.59	6.26
119	4.61	8.69	8.46	NA
121	3.91	9.00	8.19	11.52
201	3.71	5.96	NA	NA
202	4.10	9.26	NA	NA
205	1.72	7.60	NA	NA
211	5.00	6.52	6.85	6.75
213	3.89	NA	NA	NA
302	3.69	9.75	8.26	NA
401	4.98	9.74	7.62	7.55
402	4.42	9.27	5.92	5.05

Source: Tables 12-7 and 12-10 and 14-36 in Clinical Study Report for Study GA-005/5A.
Highlighted are HV values for patients who had at least one anti-GH titer >0.100 mg/dL while on Accretropin treatment.

At the request of this reviewer the applicant provided in the "Amendment # 8" submission (Table 16) descriptive statistics for absolute eosinophil counts in anti-GH antibody positive and negative patients. Such assessments were completed at baseline, Week 8, Week 12 and Month 6. The mean levels and the mean change in absolute eosinophil counts were similar for both

titers at Week 8 (0.346 mg/mL and 0.436 mg/mL, respectively) and Month 12 (0.441 mg/mL and 0.663 mg/mL, respectively) followed by a reduction till the end of the study. The applicant points out that three subjects with relatively low height velocities at Month 36 (patients 101, 211 and 402) had low antibody titers (<0.1).

subgroups (and comparable to baseline counts). Importantly, the maximum eosinophil counts were also comparable.

Study GA-007/7A

Table 49 summarizes the number and percentage of patients who developed anti-GH and anti-E. coli polypeptide antibodies; it also includes descriptive statistics of the antibody titers in study GA-007/7A. There were no patients with who had anti-GH antibodies at baseline. By Week eight, 16% of all patients developed anti-GH antibodies. The percentage of antibody positive patients increased steadily and peaked at Month 12; at Month 24 it included 33% patients (35% in a LOCF analysis) and at Month 36 it included 19% patients (26% in a LOCF analysis). The mean anti-GH antibody titers peaked at Months 12-24 and appear to decline thereafter (however, almost ¼ of patients do not have assessments for the Month 36 timepoint). During the whole study, the highest individual antibody concentration at any time point was 0.243 mg/L at Month 24; this is below the 1-2 mg/L level above which a risk of growth attenuation had been described.

The mean anti-ECP titers (Z-score) increased over time. It seems to level off by Month 12 with only minimally increased at Months 24 and 36.

Table 49: Summary of anti GH and anti-E.coli polypeptide antibodies – Study GA-007/7A

Statistics	Baseline	Week 8	Week 12	Week 24	Month 12	Month 24	Month 36
Patients with anti-GH antibodies							
n/N	0/37	6/37	11/37	12/37	14/37	12/36	6/31
%	0	16.2	29.7	32.4	37.8	33.3%*	19.3**
Anti-GH antibody titers(mg/L)							
N	37	37	37	37	37	36	31
Mean (SD)	0.000 (0.000)	0.019 (0.048)	0.028 (0.053)	0.035 (0.060)	0.036 (0.057)	0.034 (0.062)	0.015 (0.035)
Range	0.000 to 0.000	0.000 to 0.189	0.000 to 0.200	0.000 to 0.219	0.000 to 0.190	0.000 to 0.243	0.000 to 0.156
Patients with anti-ECP antibodies							
n/N	28/37	29/37	28/37	32/37	35/37	35/36	30/31
%	75.7	78.4	75.7	86.5	94.6	97.2	96.8
Anti-ECP antibody titers (Z-score)							
N	37	37	37	37	37	36	31
Mean (SD)	0.384 (0.333)	0.410 (0.328)	0.413 (0.310)	0.493 (0.289)	0.513 (0.271)	0.528 (0.301)	0.538 (0.229)
Range	0.000 to 1.448	0.000 to 1.302	0.000 to 1.181	0.000 to 1.157	0.000 to 1.209	0.000 to 1.722	0.000 to 0.952

Source: Tables 12-3, 12-06, and 14-5.
n= subject with abnormal finding;
N = total number of subjects evaluated for the time point.
*LOCF: 35.1 %
**LOCF: 25.8%.

Individual height velocities for antibody positive patients are displayed in Table 50. Eight patients had an undetectable anti-ECP antibody at baseline which become positive on Accretropin treatment (for most patients this occurred by Months 6-12). Nineteen patients developed anti-GH antibodies. One needs to recognize that there is a natural slowdown in height velocity that is to be seen with GH beyond the first year of treatment. Patient 525 is the only patient with a marked decline in annualized height velocity at Month 36 (0.74 cm/yr). This patient had a negative anti-GH titer at baseline, Week 8, Week 12 and Month 36 and a low titer at Week 24 and Months12 and 24[106]. This same patient had anti-ECP antibodies at various timepoints but the titer peaked by Month 6 and declined to subsequent timepoints[107]. Another patient whose height velocity declined at Month 36 relative to previous assessments (albeit not to the same degree) was patient 528 who had only low anti-GH antibodies at multiple timepoints but not at Month 36. Similarly, patient 526 who had a relatively low HV at Month 36 did not have any anti-GH antibodies up to Month 36 and a very low titer at this timepoint. Patient 533, who had the highest titer on trial at Week 25 (0.216 mg/L) had steadily declining titers through Month 36.

Table 50: Annualized height velocity for patients who became antibody positive during Accretropin treatment

Patient ID	Annualized height velocity (cm/year)		
	Month 12	Month 24	Month 36
Patients with anti-E-coli antibodies			
506	7.72	7.82	5.15
513	9.51	4.62	6.49
514	7.35	5.95	5.37
515	7.72	6.16	5.14
518	5.67	6.13	4.16
522	10.76	6.08	5.77
525	6.45	4.98	0.74
536	8.82	6.72	6.99
Patients with anti-GH antibodies			
502	8.40	7.61	5.81
505	10.04	7.15	7.02
506	7.72	7.82	5.15
508	8.07	6.29	5.29
509	7.12	6.54	4.82
514	7.35	5.95	5.37
517	11.46	8.82	8.27
519	8.31	7.94	7.02
520	8.76	7.77	7.79
524	9.09	8.25	5.70
525	6.45	4.98	0.74
526	7.52	5.72	4.06
528	10.36	7.30	3.71
529	10.46	8.63	4.99

[106] Anti-GH antibody "values" at Week 24, Month 12 and Month 24 were 0.060 mg/L, 0.047 mg/L and 0.097 mg/L, respectively.
[107] The anti-ECP titers (Z-score) were 0.191 at Week 8, 0.321 at Week 24, 0.203 at Month 12, 0.214 at Month 24, and).253 at Month 36. No titers were detected at baseline and Week 12.

530	7.64	NA	NA
531	8.59	7.92	6.88
532	9.76	7.19	5.23
533	8.32	5.94	5.08
534	6.92	5.31	5.12

Source: Tables 12-5 and 12-8 in Clinical Study Report for Study GA-007/7A.
Highlighted are HV values for patients who had at least one anti-GH titer >0.100 mg/dL while on Accretropin treatment.

At the request of this reviewer the applicant provided in the "Amendment # 8" submission descriptive statistics for absolute eosinophil counts in anti-GH antibody positive and negative patients. Such assessments were completed at baseline, Week 8, Week 12 and Month 6. The mean levels and the mean change in absolute eosinophil counts were similar for both subgroups (and comparable to baseline counts). Importantly, the maximum eosinophil counts were also comparable.

The immunogenicity of Accretropin is somewhat higher then that of currently marketed immediate-release rhGH products. As illustrated in Table 51, the incidence of immunogenicity in immediate-release rhGH products is in general below 12-23% while depot preparations have higher immunogenicity. With Accretropin, the incidence of patients who became anti-GH antibody positive reached 35-50%. Importantly, the binding capacities are not in the neutralizing range and there is no evidence of growth attenuation on Accretropin over 3 years of treatment.

Table 51: Between-product comparison of anti-rhGH immunogenicity data

Product	N (%) of patients with anti GH antibodies	Source or reference
Accretropin	**50 %** and **35%**	Current NDA
Genotropin	10/378 (**2.6%**)	Wilton and Gunnarsson, 1988
Saizen	13/218 (**6.0%**)	Lutz and von Petrykowski, 1992
Norditropin	13/111 (**12%**)	Cohen et al., 2002
Nutropin	19/84 (**23%**)	Fine et al. 1994
Humatrope	304 (**2%**)	NDA 19-640
Omnitrope	0/51 (**0%**)	NDA 21-426
Nutropin Depot*	16/36 (**44%**)	Reiter et al., 2001
Nutropin Depot*	26/38 (**68%**)	Reiter et al., 2001

Source: Expanded applicant's Table 2.3.3.10a.
*The only non-immediate release product in the table. No longer marketed.

7.1.11 Human Carcinogenicity

There were no malignancies reported in the clinical trials. Although IGF-1 (the main mediator of GH activity) is a known mitogen and high IGF-1 serum levels have been associated with an increased risk of several cancers in adults in epidemiological studies, the analyses conducted to date from accumulated safety data in postmarketing surveillance studies over several decades do not indicate a risk of malignancies except for patients with predisposing conditions. During the Accretropin clinical trials IGF-1 serum levels were maintained, in general, in the normal range.

7.1.12 Special Safety Studies

The applicant did not conduct any safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The clinical experience accumulated with GH in approximately 200,000 patients over four decades does not contain any evidence suggestive of withdrawal phenomena.

The off-label use (and abuse) of GH in athletes and or aging individuals for its anabolic effect is a documented social phenomenon.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported in the clinical trial.

7.1.15 Assessment of Effect on Growth

Linear growth was an efficacy endpoint in both study GA-005/5A and GA007/7A (see Section 6.1.4).

7.1.16 Overdose Experience

There are no reported cases of acute or chronic GH overdosing in clinical trials GA-005/5A and GA007/7A. Chronic overdosing was avoided by monitoring serum IGF-I concentrations. The potential effects of chronic exposure to excessive GH doses are well characterized in both children (gigantism) and adults (acromegaly).

7.1.17 Postmarketing Experience

Accretropin is not currently licensed in any country. Therefore there are no postmarketing data.

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 6.13.

7.2.1.2 Demographics

Refer to Section 6.14.

7.2.1.3 Extent of exposure (dose/duration)

Applicant's Table 2.7.4.1.2.a summarizes the extent of exposure to Accretropin in the three clinical studies submitted. In addition to the 81 children treated in studies GA-005/5A and GA-007/7A 23 healthy adults were exposed to a single 4 mg dose of Accretropin in Study GA-002. The total patient exposure was 243 patient years.

Table 2.7.4.1.2a Extent of Exposure to NP-004

Study	Number of subjects and duration of exposure*							
	1 day	≤ 12 weeks	≤ 6 months	≤ 12 months	≤ 18 months	≤ 24 months	≤ 30 months	≤ 36 months
GA-002	23							
GA-005/5A		2	1	1	1	8	6	25
GA-007/7A					1			36

* The duration of exposure refers to the length of the clinical studies, not the number of days of administration. In studies GA-005/5A and GA-007/7A, NP-004 was administered six days out of every seven for the duration of the study.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

There is no postmarketing experience accumulated with Accretropin since it is not an approved drug product.

7.2.2.3 Literature

The literature search provided by the applicant contained helpful and extensive information which applied directly to the issues that were specific to this submission.

7.2.3 Adequacy of Overall Clinical Experience

The two datasets provided (44 patients enrolled in trial GA-005/5A which lasted for 3 years and 37 patients enrolled in trials GA-007/7A treated for the same length of time for a cumulative exposure of 243 patient-years) is adequate for both indications proposed, given the prevalence of these conditions[108] and the large body of knowledge accumulated over 4 decades of GH treatment mostly in children.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See the preclinical pharmacology and toxicology review. Since the toxicity of GH has been well characterized in animal studies and it is well characterized in humans due to conditions of GH excess (e.g. acromegaly and gigantism) no extensive animal studies are necessary to characterize GH toxicity.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical and laboratory testing in trials GA-005/5A and GA-007/7A is adequate and, in general, consistent with that of other clinical trials that evaluate GH treatment of short stature.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetics of GH in general and the mechanisms of absorption, distribution, metabolism and excretion of GH are well known. The applicant did not conduct any additional studies beyond a single pharmacokinetic study, the results of which are consistent with the general characteristics of GH.

[108] The estimated prevalence for classic GH deficiency: 1 in 3500 pediatric patients; for Turner syndrome: 1 in 2500 girls or 1 in 5000 pediatric patients.

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

The applicant's evaluation of adverse events is adequate.

7.2.8 Assessment of Quality and Completeness of Data

The efficacy and safety data provided for both indications are, in general, adequate.

7.2.9 Additional Submissions, Including Safety Update

At the request of this reviewer the applicant provided additional clinical data analyses in two submissions (Amendment # 8 and # 10). The results of these analyses have been incorporated in the body of this review.

In response to a request for a safety update the applicant stated that

> Since the filing of the NDA for Accretropin™ on May 9, 2006, there have been no on-going or additional studies and as it is not a marketed product, there are no updates to the safety information of the drug product.

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

In general, the pattern of treatment-emergent adverse events observed in patients with GHD and Turner syndrome in the Accretropin Phase III clinical program is descriptively similar to that observed in published literature and in datasets reviewed by this Division. There were no new safety signals identified in these 81 children with severe short stature treated continuously for three years at standard GH doses. It is important to recognize that safety profile of GH is well known and characterized in children.

Of the TEAEs that were considered treatment-related, injection site reactions were the only adverse events that could be clearly associated with the study drug[109]. The rest of the "treatment-related" adverse events were mostly adverse events known to occur in association with GH in general[110]. The few TEAEs that did not fall in this category were infrequent and inconsistently seen between the two clinical trials. Absence of a control group and the small size of the datasets limit the ability to draw additional conclusions.

[109] In study GA-005/5A they were recorded under several preferred terms with the following incidence rates: injection site erythema (38.6%), swelling (20.5%), bruising (11.4%), pain (6.8%), pruritus (6.8%), hemorrhage (2.3%), edema (2.3%), rash (2.3%). In study GA-007/7A they were recorded under several preferred terms with the following incidence rates: injection site erythema (29.7%), edema (5.4%), pain (2.7%), and pruritus (2.7%).
[110] Preferred terms: headache, scoliosis, hypothyroidism, myalgia, bone pain, growing pains, pain in the extremities, nausea and vomiting and headache (in the context of benign increased intracranial hypertension).

The percentage of patients who developed anti-GH antibodies during Accretropin treatment is greater than that observed with other approved immediate-release somatropins. Specifically, as many as 50% of patients in Study GA-005/5A and as many as 35% of girls in Study GA-007/7A developed anti-GH antibodies in LOCF analyses[111]. This compares unfavorably with other marketed immediate-release somatropins for which studies indicate that development of anti-GH antibodies occurs in <12% of patients and only occasionally in 20% of patients evaluated. Importantly, however, the anti-GH antibody binding activity was relatively small and certainly below 1-2 mg/L, which is the "threshold value" under which neutralizing antibodies to GH have not been described with rhGH therapy.[112] In Study GA-005/5A the mean anti-GH antibody binding activity peaked by Months 12, declined somewhat by Month 24 and appeared to further decline by Month 36. The maximum individual antibody binding activity was 0.665 mg/L (at Week 12 and declined steadily thereafter)[113]. In Study GA-007/7A the mean anti-GH binding activity peaked by Month 12, remained relatively stable through Year 1 and 2, respectively and decreased at Month 36. The maximum individual antibody binding activity was 0.219 mg/L at Month 6[114].

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

Although the applicant provided pool data across the clinical trials, such data are not particularly informative due to the fact that the patient populations in each of the three Phase II-III trials were quite distinct (healthy adult volunteers in Study GA-002, children with GHD in Study GA-005/5A and Turner syndrome patients in Study GA0007/7A). Therefore, the safety data were presented separately by indication in this review.

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[111] In study GA005/5A anti-GH antibodies were seen as early as 8 weeks in15.9 % of all patients and further increased to 34% at Week 12, 38% at Week 24, 46.3% at Month12, 41.1% (50% in LOFC analysis) at Month 24 and 35.4% (48.3% in LOFC analysis) at Month 36. In study GA007/7A anti-GH antibodies were seen as early as 8 weeks in 16% of patients; it increased further to 29.7% patients at Week 12, 32.4% at Week 24 37.8% at Month 12. At the end of the second year 33.3% (35% in LOCF analysis) were antibody positive and after 3 years 19.3% (25.8% in LOFC analysis) were antibody positive.

[112] Ohada et al.: A case report of growth attenuation during methionyl human growth hormone treatment. Endocrinol. Japan. 34 (4), 621-626 (1987),
Pirazzoli P et al.: Follow-up of antibodies to growth hormone in 210 growth hormone-deficient children treated with different commercial preparations. Acta Paediatri 84; 1233-6, 1995.
Kaplan SL et al. Antibodies to human growth hormone arising in patients treated with human growth hormone: incidence, characteristics and effects on growth. In: *Advances in human growth hormone research: a symposium.* Washington: US Department of Health Education and Welfare, publication no NIH 74-612, 1974; 725-47.

[113] 0.357 mg/L at Week 24; 0.399 mg/L at Month 12, 0.242 mg/L at Month 24 and 0.152 mg/L Month 36 .

[114] 0.190 mg/L at Months 12 and 0.243 mg/L at Month 24 and 0.156 mg/L at Month 36.

7.4.1.2 Combining data

Refer to comments in section 7.4.1.1.

7.4.2 Explorations for Predictive Factors

The dataset was too small to conduct additional analyses.

7.4.2.1 Explorations for dose dependency for adverse findings

Due to the small size of the dataset no dose dependency analyses were done.

7.4.2.2 Explorations for time dependency for adverse findings

Due to the small size of the dataset no time dependency analyses were done.

7.4.2.3 Explorations for drug-demographic interactions

Due to the small size of the dataset no analyses exploring drug-demographic interactions were done.

7.4.2.4 Explorations for drug-disease interactions

Due to the small size of the dataset no analyses exploring drug-disease interactions were done.

7.4.2.5 Explorations for drug-drug interactions

Due to the small size of the dataset no drug-drug interaction analyses were done.

7.4.3 Causality Determination

Due to the small size of the dataset and the absence of a control group, causality of any specific adverse event, other than injection site reactions, is difficult to establish. It is important to recognize that the vast experience with GH across different products and pediatric indications has resulted in a good understanding of what adverse events are associated with GH therapy (see Precautions and Warning Sections in the Accretropin label).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Indication specific regimens of GH have been established over the last 20 years of recombinant human GH use. The dose regimens used in pediatric GHD patients[115] and Turner syndrome patients[116] used in the Accretropin clinical program are standard for each indication[117].

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

8.3 Special Populations

This application does not include any formal studies that evaluate the effect of gender, age, race, or co-morbid states (such as renal or hepatic failure) on the efficacy and safety of Accretropin. Efficacy analyses by gender indicated similar responses for the primary efficacy variable in boys and girls in Study GA-005/5A.

8.4 Pediatrics

Both indications sought under this submission are pediatric indications.

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting related to this application.

8.6 Literature Review

There is a vast literature published with GH for the last half century. Summarizing it is not relevant to this review. The GH labels and position statements issued periodically by

[115] For Study GA-005/5A: 0.03 to 0.05 mg/kg/day once daily 6 times per week (0.18-0.30 mg/kg/week) for GHD and 0.06 mg/kg/day once daily 6 times per week for Turner syndrome.
[116] For Study GA-007/7A: 0.06 mg/kg/day once daily 6 times per week for Turner syndrome.
[117] Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone Deficiency in children. GH Research Society, 2000).
Tanaka T et. al: Diagnosis and management of growth hormone deficiency in childhood and adolescence – Part 2: growth hormone treatment in growth hormone deficient children. Growth Hormone & IGF Research 12, 323-41 (2002).
[118] Although the youngest patients enrolled were 4 years old in Study GA-005/5A and 5 years old, respectively in Study GA-007/7A, it is expected that children between ages 2 -5 years will not behave differently from an efficacy and safety standpoint.

professional societies (see Reference Section) reflect the current knowledge of the efficacy and safety as it relates to this family of drug products.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan was not located in the submission. In the Filing Letter (dated July 12, 2006) the applicant was asked to supply one.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

Accretropin, when administered at standard doses, was efficacious in accelerating linear growth over 3 years of continuous treatment in children with severe short stature due to GH deficiency and/or Turner syndrome. In both patient populations Accretropin doubled the mean height velocity for the first 12 months of treatment relative to baseline and maintained height velocities during the 2nd and 3rd year of treatment that were above those recorded at baseline. The increase in height velocity observed on Accretropin is fully consistent with that described by other approved somatropins. Despite methodological limitations (i.e. shortcomings in the method of collection of baseline height velocity) the totality of the efficacy data clearly confirms the effectiveness of Accretropin treatment in severely short children with GHD and Turner syndrome. Finally, although anti-GH antibodies were observed in up to 35-50% of patients, the mean height velocity for patients who developed anti-GH antibodies on Accretropin treatment was comparable to that of patients who remained antibody-negative. Importantly, there was no convincing clinical evidence to suspect growth attenuation on Accretropin treatment up to 3 years of treatment.

Safety

Except for a somewhat different immunogenicity profile, the safety profile of Accretropin was similar to that observed for other rhGH products currently marketed. There were no new safety signals identified in this combined dataset of 81 patients (44 with GHD and 37 with Turner syndrome) treated for up to three years[119].

[119] 243 patient years of exposure, comparable per indication to other recently approved GH products.

The percentage of patients who developed anti-GH antibodies during Accretropin treatment is greater than that observed with other approved immediate-release somatropins. Specifically, as many as 50% of patients in Study GA-005/5A and as many as 35% of girls in Study GA-007/7A developed anti-GH antibodies in LOCF analyses[120]. This compares unfavorably with other marketed immediate-release somatropins for which studies indicate that development of anti-GH antibodies occurs in <12% of patients and only occasionally in 20% of the patients evaluated. Importantly, however, the anti-GH antibody binding activity was relatively small and certainly below 1-2 mg/L, which is the "threshold value" under which neutralizing antibodies to GH have not been described with rhGH therapy.[121] Very importantly, the mean height velocities in anti-GH antibody positive and anti-GH antibody negative patients were comparable through Month 36. There were no clinical signs/symptoms suggestive of allergy, no differences in absolute eosinophil counts in patients with or without antibodies and no growth attenuation[122]. It is not clear why a larger percentage of patients appear to develop low titers relative to other somatropins. The chemistry review indicates that Accretropin has acceptable levels of impurities.

9.2 Recommendation on Regulatory Action

Given that Accretropin is efficacious in improving linear growth in children with short stature due to either growth hormone deficiency or Turner syndrome, while having a safety profile similar to that of other approved recombinant human growth hormone products, it should be approved for both above mentioned indications.

[120] In study GA005/5A anti-GH antibodies were seen as early as 8 weeks in15.9 % of all patients and further increased to 34% at Week 12, 38% at Week 24, 46.3% at Month12, 41.1% (50% in LOFC analysis) at Month 24 and 35.4% (48.3% in LOFC analysis) at Month 36. In study GA007/7A anti-GH antibodies were seen as early as 8 weeks in 16% of patients; it increased further to 29.7% patients at Week 12, 32.4% at Week 24 37.8% at Month 12. At the end of the second year 33.3% (35% in LOCF analysis) were antibody positive and after 3 years 19.3% (25.8% in LOFC analysis) were antibody positive.

[121] Ohada et al.: A case report of growth attenuation during methionyl human growth hormone treatment. Endocrinol. Japan. 34 (4), 621-626 (1987),
Pirazzoli P et al.: Follow-up of antibodies to growth hormone in 210 growth hormone-deficient children treated with different commercial preparations. Acta Paediatri 84; 1233-6, 1995.
Kaplan SL et al. Antibodies to human growth hormone arising in patients treated with human growth hormone: incidence, characteristics and effects on growth. In: *Advances in human growth hormone research: a symposium.* Washington: US Department of Health Education and Welfare, publication no NIH 74-612, 1974; 725-47.

[122] The mean levels and the mean change in absolute eosinophil counts (through Month 6) were similar for anti-GH positive and negative patients (and comparable to baseline counts). Importantly, the maximum eosinophil counts were also comparable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant is encouraged to develop 1) a postmarketing surveillance study similar to those conducted by other manufacturers (e.g.,) with the goal of enhancing the long-term understanding and knowledge of Accretropin's safety profile and 2) tools and means that will evaluate and control the distribution process of Accretropin to ensure that it is prescribed by pediatric endocrinologists or physicians with expertise in pediatric growth disorders to the rightful recipients.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The applicant's proposed label is, in general acceptable. Modifications should be made, however, to ensure consistency with the recently implemented class labeling changes for all somatropins. In addition several changes to the Clinical Studies and Adverse Events sections are also recommended in order to enhance clarity (see attached label).

9.5 Comments to Applicant

In addition to those related to labeling and approval recommendations, the applicant is advised to develop and implement an assay that can evaluate for the presence or absence of neutralizing anti-GH antibodies.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Studies GA-005/5A and GA-007/7A

The two clinical studies (GA-005/5A and GA-007/7A) were reviewed individually in the body of this review.

10.1.2 Study GA-002

The safety information from Study GA-002 (a single-dose bioequivalence study conducted in 20 healthy adults is briefly summarized. There were no deaths, no serious or other significant adverse events reported. There were forty-five adverse events involving 14 subjects. Only one AE was reported as severe (abdominal pain); 9 AEs were moderate and 35 were mild. The applicant reports that "none of the adverse events had a definite association with the test or reference drugs"; 10/45 AEs had a "probable" association with the test or reference drug; 18/45 AEs had a "possible" association; 12/45 had a "conditional" association and 5/45 had a "doubtful" association. Ten adverse events were considered "related" to Accretropin. They were: three reports of vomiting (one mild, two moderate), two reports of abdominal pain (one moderate, one severe), one report of back pain (moderate), one report of nausea (mild), one report of sweating (moderate), one report of "belching" (mild), and one report of anorexia (mild). Three adverse events were considered "related" to Humatrope administration; they were: one report of abdominal pain (mild), one report of diarrhea (mild), and one report of headache (mild). The incidence of patients with adverse events was comparable between Accretropin- and Humatrope-treated subjects (21.7% vs. 20%). The incidence of subjects with adverse events that were "definitely" related to study medication was slightly higher in the Accretropin-treated subjects relative to the Humatrope-treated subjects (8.7% vs. 5%).

Due to the small size of the dataset and limited exposure (single dose) the ability to draw firm conclusions is very limited. The Phase III clinical trials GA-005/5A and GA-007/7A, which were conducted in the patients for which Accretropin is intended for use, provide a more meaningful set of safety data for the indications sought by the applicant.

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Additional references are imbedded in footnotes of the review.

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