DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-538/N-000
Drug Name:	Accretropin™ (Somatropin [rDNA origin] for Injection)
Indication(s):	(A) [redacted] treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone (B) Treatment of short stature associated with Turner Syndrome in pediatric patients whose epiphyses are not closed
Applicant:	Cangene Corporation
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Keywords:	NDA review, clinical studies, historical controls

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from 2 open-label studies have demonstrated that Accretropin was efficacious in increasing height and in stimulating height velocity for children with growth hormone deficiency (GHD) or Turner Syndrome.

1.2 Brief Overview of Clinical Studies

Cangene Corporation has developed Accretropin™, somatropin (rDNA origin) for daily injection, as a new growth hormone drug for human use. The sponsor has submitted the results from 3 completed clinical trials (GA-002, GA-005/5A, and GA-007/7A) to this NDA to support the following proposed indications:

- treatment of pediatric patients who have a growth failure due to an inadequate secretion of normal endogenous growth hormone, and
- Treatment of short stature associated with Turner Syndrome in pediatric patients whose epiphyses are not closed.

Except for GA-002 which was a Phase 1 pharmacokinetic/bioequivalence study, GA-005/5A and GA-007/7A were Phase 3 and 2 studies, respectively, to evaluate the efficacy and safety of Accretropin™. The GA-005/5A study is to seek approval for the growth hormone deficiency (GHD) indication and the GA-007/7A study for the Turner Syndrome indication. The sponsor designed both studies as single-arm, open-label, non-randomized, historically controlled trials, enrolling rhGH treatment naïve prepubertal children with either GHD or Turner Syndrome. The former study was a 4-center study conducted in Poland and Hungary, while the latter one was a 1-center study in Poland. Both studies were designed to be of 6 months of treatment initially, with an additional 30 months of continuous treatment to determine the long-term effect of Accretropin™. Height velocity was the primary efficacy endpoint of interest.

1.3 Statistical Issues and Findings

As mentioned in Section 3.1.1 Study Design and Endpoints, due to the fact that the pre-study height velocity data were not collected in a standardized manner, the sponsor changed the

primary efficacy analysis from analyzing the change from baseline in height velocity (HV) to comparing the on-treatment HV with historical HV obtained using local and international (Tanner et al., 1966) standards. However, as noted in Section 3.1.5 Efficacy Results and Discussion, due to the use of the same reference height data for the age- and gender-matched subjects, the standard deviation of the historical HV data was generally smaller than that of the observed data, which would potentially yield a larger two-sample t-statistic than when using a concurrent control. In other words, neither the original nor the new primary efficacy analysis produced an absolutely reliable outcome in this reviewer's view. Therefore, results from all the primary and secondary analyses were reviewed in its totality so that the final sound conclusion can be drawn. The collective evidence is summarized by indication as follows.

Indication for Children with Growth Hormone Deficiency

The annualized height velocities of children with GHD after treatment with Accretropin were 8.9, 7.6, and 7.0 cm for the 1st, 2nd, and 3rd years, respectively, which were all highly significantly better than that of normal age- and gender-matched children using either local or international (Tanner) standards (Text Table 1).

Text Table 1 – Study GA-005/5A

Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard		International Standard	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	4.1 ± 1.2 (44)	NA	---	5.8 ± 0.9 (44)	---
0 – 12	8.9 ± 2.3 (41)	6.0 ± 1.1 (41)	<0.0001	6.0 ± 1.1 (41)	<0.0001
12 – 24	7.6 ± 1.4 (34)	5.8 ± 1.2 (34)	<0.0001	5.7 ± 1.1 (34)	<0.0001
24 – 36	7.0 ± 1.6 (26)	5.3 ± 1.6 (26)	0.0004	5.6 ± 0.9 (25)[1]	0.0006

[1] Subject 108 was 16.5 years old at 36 months. A standard HV using the international standard could not be calculated since it does not include age 16.5 or older for females.

The mean changes from baseline in height velocity, height velocity SDS (Tanner), and height SDS (local and Tanner) at Month 12 were all highly significantly different from zero in favor of the Accretropin treatment (Text Table 2). Although the height of children with GHD after 12 months of treatment was still below the height of normal children of the same age and gender (HSDS = -2.5 using local and -2.0 using Tanner standards), the mean growth rate at 12 months was improved (HV = 8.9 cm/year) and higher than that of normal age- and gender-matched children (HVSDS = 3.6 using Tanner standard). Similar significant findings were also observed for the 2nd and 3rd years of continuous treatment with Accretropin.

Text Table 2 – Study GA-005/5A: Results for Change from Baseline at Month 12

Efficacy Variable	Month 12 Mean ± SD (N)	Month 0 Mean ± SD (N)	Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
HV (cm/year)	8.9 ± 2.3 (41)	4.1 ± 1.2 (41)	4.76 ± 2.89 (41)	<0.0001	(3.87, 5.64)
HVSDS (Tanner)	3.6 ± 3.6 (41)	-1.8 ± 1.5 (41)	5.42 ± 3.97 (41)	<0.0001	(4.20, 6.63)
HSDS (Local)	-2.5 ± 0.7 (41)	-3.1 ± 0.8 (41)	0.60 ± 0.53 (41)	<0.0001	(0.43, 0.76)
HSDS (Tanner)	-2.0 ± 0.7 (41)	-2.6 ± 0.8 (41)	0.59 ± 0.45 (41)	<0.0001	(0.46, 0.73)

HVSDS = Height velocity standard deviation score; HSDS = Height standard deviation score

Treatment effects on change from baseline in height velocity at Month 12 were consistent across the subgroups defined by age and gender. However, a significant treatment difference was observed between Poland and Hungary (p = 0.0492). According to the sponsor, it was most likely due to the different dosage of Accretropin administered in the 2 countries, where 0.05 mg/kg/day was used in Poland and 0.03 – 0.04 mg/kg/day was used in Hungary. No subgroup analysis for race was performed since all the study subjects were Caucasian.

Indication for Children with Turner Syndrome

The annualized height velocities of children with Turner Syndrome after treatment with Accretropin were 8.6 and 6.9 cm for the 1st and 2nd years, respectively, which were both highly significantly better than that of normal or untreated Turner Syndrome children of the same age using either local or international (Tanner) standards. Although the 3rd year growth rate of Accretropin-treated children (5.8 cm/year) was similar to that of normal children of the same age, it was significantly larger than that of untreated age-matched Polish children with Turner Syndrome (Text Table 3).

Text Table 3 – Study GA-007/7A

Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard **(Normal Children)**		International Standard **(Normal Children)**		Local Standard **(Turner Children)**	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	3.8 ± 1.0 (37)	NA	---	6.1 ± 1.0 (37)	---	NA	---
0 – 12	8.6 ± 1.7 (37)	5.9 ± 0.6 (37)	<0.0001	6.0 ± 0.6 (37)	<0.0001	4.0 ± 0.8 (37)	<0.0001
12 – 24	6.9 ± 1.2 (36)	5.8 ± 2.0 (35)[1]	0.0060	5.8 ± 0.9 (36)	<0.0001	3.7 ± 1.2 (35)[1]	<0.0001
24 – 36	5.8 ± 1.9 (35)	5.2 ± 2.3 (30)[1]	0.2372	5.4 ± 1.8 (35)	0.3412	3.7 ± 1.0 (30)[1]	<0.0001

[1] Excluded standard height velocities with 0 caused by the same age-matched heights from the standard table for the two visits used in the calculation. This occurred when the time elapsed between two visits was less than the age increments in the standard table and the subject's birthday did not occur between the two visits.

The mean changes from baseline in height velocity, height velocity SDS (Tanner), and height SDS (local and Tanner) at Month 12 were all highly significantly different from zero in favor of the Accretropin treatment (Text Table 4). Although the height of children with Turner Syndrome after 12 months of treatment was still below the height of normal children of the same age (HSDS = -2.7 using local and -1.9 using Tanner standards), the mean growth rate at 12 months was improved (HV = 8.6 cm/year) and higher than that of normal age-matched children (HVSDS = 3.1 using Tanner standard). In addition, the height of Accretropin-treated children with Turner Syndrome was larger than that of untreated age-matched children with Turner Syndrome after 12 months (HSDS = 1.0 using local Turner standard). Similar significant findings were also observed for the 2nd and 3rd years of continuous treatment with Accretropin.

Text Table 4 – Study GA-007/7A: Results for Change from Baseline at Month 12

Efficacy Variable	Month 12 Mean ± SD (N)	Month 0 Mean ± SD (N)	Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
HV (cm/year)	8.6 ± 1.7 (37)	3.8 ± 1.0 (37)	4.74 ± 2.00 (37)	<0.0001	(4.09, 5.38)
HVSDS (Tanner)	3.1 ± 2.6 (37)	-2.4 ± 1.5 (37)	5.49 ± 2.78 (37)	<0.0001	(4.60, 6.39)
HSDS (Local – Normal)	-2.7 ± 1.2 (37)	-3.2 ± 0.9 (37)	0.50 ± 0.48 (37)	<0.0001	(0.35, 0.66)
HSDS (Tanner – Normal)	-1.9 ± 1.0 (37)	-2.4 ± 0.8 (37)	0.46 ± 0.35 (37)	<0.0001	(0.35, 0.58)
HSDS (Local – Turner)	1.0 ± 0.9 (37)	0.2 ± 0.7 (37)	0.76 ± 0.33 (37)	<0.0001	(0.66, 0.87)

HVSDS = Height velocity standard deviation score; HSDS = Height standard deviation score

Treatment effect on change from baseline in height velocity at Month 12 was consistent across the subgroups defined by age. No subgroup analyses for gender and race were performed since all the study subjects were female Caucasian.

In general, this reviewer's results for both studies agree with the sponsor's conclusions.

2. INTRODUCTION

2.1 Overview

Accretropin™ (somatropin [rDNA origin]), Cangene's recombinant human growth hormone (rhGH) product, is intended for (1) [redacted] treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and (2) treatment of short stature associated with Turner Syndrome in pediatric patients whose epiphyses are not closed. The clinical development program for Accretropin™ included one pharmacokinetic/bioequivalence study (GA-002) and two long-term (36 months) efficacy and safety studies (GA-005/5A and GA-007/7A).

The sponsor designed the GA-005/5A and GA-007/7A studies as single-arm, open-label, non-randomized, historically controlled trials, enrolling rhGH treatment naïve prepubertal children with growth hormone deficiency (GHD) and Turner Syndrome, respectively. The former study is to seek approval for the GHD indication and the latter study for the Turner Syndrome indication. The primary endpoint in both studies was the annualized height velocity of children with GHD or Turner Syndrome after treatment with Accretropin, which was compared to the historical height velocity of age and gender-matched healthy children using local and international (Tanner et al., 1966) standards. The study highlights are presented below.

Protocol Locations	Study Design (No. Enrolled)	Age/Gender/ Race	Primary Endpoint
GA-005/5A 2 countries 3 centers in Hungary 1 center in Poland	A non-randomized, open-label, single-arm, historical-controlled, 36-month, multi-center, Phase 3 study, conducted in children with **growth hormone deficiency** (44)	4.3 – 14.3 years (Mean = 9.0) Male: 59.1% Female: 40.9% Caucasian: 100%	Height velocity
GA-007/7A 1 country (Poland) 1 center	A non-randomized, open-label, single-arm, historical-controlled, 36-month, single-center, Phase 2 Study, conducted in children with **Turner Syndrome** (37)	5.3 – 12.8 years (Mean = 9.4) Female: 100% Caucasian: 100%	Height velocity

2.2 Data Sources

This NDA is a paper submission in CTD-format. The volumes this reviewer reviewed are 1/51 – 3/51, 32/51 – 34/51, 41/51 – 42/51, and Amendments #7 and #8. The electronic data sets this reviewer used (gvbase.xpt, loceff.xpt, taneff.xpt, and turneff.xpt) are located in the EDR \\Cdsesub1\n21538\N_000\2006-05-09\CRT\DATASETS\GA005_5A and GA007_7A. The data (tangveff.xpt) for height velocity standard deviation score using international (Tanner) standard were submitted to the EDR on 01/26/2007 (\\Cdsesub1\n21538\N_000\2007-01-26\NDA #21538 additional dataset), which also

contained the annualized height velocity from Month 0 (baseline) to Month 24 that was not submitted originally. According to the sponsor's Amendment #7 submission, local height velocity standards were not available at the time of analysis; therefore, no baseline and on-treatment height velocity standard deviation score using local standards were generated and submitted.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study GA-005/5A (06/2000 – 01/2004, Phase 3) and Study GA-007/7A (08/2000 – 03/2004, Phase 2) were 3-year, single-arm, open-label, non-randomized, historically controlled trials, enrolling rhGH treatment naïve prepubertal children with GHD and Turner Syndrome, respectively. The former study was a multi-center study conducted in Poland and Hungary; the latter one was a single-center study conducted in Poland. Each of the 2 studies consisted of 2 parts. The first part was designed to be of 6 months of treatment; the second part was a continuation of the first part and lasted for an additional 30 months. Note that in the GA-005/5A study, the Polish children received a higher dose of Accretropin (0.05 mg/kg/day) than the Hungarian children (0.03 – 0.04 mg/kg/day). In addition, subjects were removed from the study once they reached puberty.

Efficacy assessments in both studies included height velocity (HV), height velocity standard deviation score (HVSDS), height, height standard deviation score (HSDS), body weight, IGF-1, and IGFBP-3. The primary efficacy endpoint in each study was the annualized height velocity following 24 weeks of treatment with Accretropin. According to the protocols, this on-treatment data were to compare with pre-treatment height velocities as the primary analysis. However, the pre-treatment data were not collected in a standardized manner consistent with GCP or per protocol. For example, as stated in the sponsor's clinical reports (page 29 of Vol. 32/51 and page 27 of Vol. 41/51), various physicians collected growth data from subjects' charts at different locations and the heights were not measured during an identical period prior to administration of Accretropin. Therefore, the sponsor's primary analysis became a comparison to historical height velocities of age- and gender-matched normal children using local (Poland [Unknown] and Hungary [Eiben and Panto, 1986]) and international (Tanner et al., 1966) standards. In addition, for Study GA-007/7A, the annualized height velocity was also compared with age-matched untreated Turner Syndrome girls using local (Polish [Wisniewski et al., 2002]) standard.

3.1.2 Statistical Methods

A two-sample t-test was used to compare the 6-month annualized height velocity with the aforementioned historical height velocity (the primary analysis). A paired t-test was

performed to examine if growth rate after 6 months of treatment was significantly improved over that at baseline. According to the sponsor, the paired t-test results were used only for supportive purpose for the reasons mentioned above. Based on the circumstance, both the medical and statistical reviewers found this analysis plan acceptable. The analyses were also done for the 12-, 24-, and 36-month time points. Note that in the sponsor's clinical reports and subsequent amendments, HV and HVSDS at the 6-, 12-, 24-, and 36-month time points were calculated as annualized from Month 0 to Month 6, Month 0 to Month 12, Month 12 to Month 24, and Month 24 to Month 36, respectively. Results from the 12-month time point will be the emphasis in this review since it is the general practice of growth hormone studies.

The primary analysis population for efficacy was the intention-to-treat (ITT) population comprising all subjects who received the study medication. The sponsor did not use any imputation method for dropouts or missing data. This reviewer found it not critical since there were only 3 dropouts in the GA-005/5A study by Month 12 and 0 in the GA-007/7A study. In fact, most dropouts in the GA-005/5A study were due to the start of puberty (see Section 3.1.3) and not related to lack of efficacy or safety issues. In other words, the censoring mechanism did not appear to be drug related. Therefore, all the efficacy analyses here were based on the observed data.

Throughout this report, whenever height velocity is mentioned, it means annualized height velocity. Also, unless otherwise stated, Months 6, 12, 24, and 36 height velocities (and SDS) refer to Months 0-6, 0-12, 0-24, and 0-36 height velocities (and SDS), respectively. Month 0 (baseline) height velocity means the growth rate prior to treatment. In all the tables below, NA results from no data available to this reviewer.

3.1.3 Subject Disposition

Study GA-005/5A (06/2000 – 01/2004)

A total of 44 subjects were enrolled in this study; 42 of them completed the first 24 weeks of treatment (the first part of the study); and 24 of them completed the 3-year trial. The reasons for withdrawal were as follows: non-compliance (2 patients), withdrawn consent (1 patient), death (1 patient), lack of efficacy (1 patient), start of puberty (14 subjects), and hospitalization (1 patient). All 44 subjects were included in the ITT population.

Study GA-007/7A (08/2000 – 03/2004)

A total of 37 subjects were enrolled in this study and 36 of them completed the 3-year trial (1 subject withdrew due to non-compliance after Month 18 visit). All 37 subjects were included in the ITT population.

3.1.4 Demographic and Baseline Characteristics

Study GA-005/5A (06/2000 – 01/2004)

There were 4 centers in this study: 1 in Poland (24 subjects) and 3 in Hungary (20 subjects). Among the 44 enrolled subjects, 26 of them (59%) were males and 18 (41%) were females. All subjects were Caucasian. The mean age at entry was about 9 years and average weight and height were 21.6 kg and 115.3 cm, respectively. The growth rate of those children with short stature and GHD before entering the study, measured by height SDS (mean = -3.0 using local standard) and height velocity SDS (mean = -1.8 using international standard), was lower than that of normal children of the same age and gender. The height velocities at baseline were calculated using heights measured at 0 month and heights measured from approximately 5 to 20 months (median = 9 months) prior to the start of treatment. The resulting mean height velocity at baseline was 4.1 cm/year (Table 1).

Table 1 – Study GA-005/5A: Demographic and Baseline Characteristics of All Enrolled Subjects

	Age (year)	Weight (kg)	Height (cm)	Height SDS (Local)	Height Velocity (cm/year)	Height Velocity SDS (Tanner)
N	44	44	44	44	44	44
Mean ± SD	9.0 ± 2.6	21.6 ± 7.1	115.3 ± 13.4	-3.0 ± 0.8	4.1 ± 1.2	-1.8 ± 1.4
Median	9.3	20.7	116.4	-2.7	4.2	-1.7
Range	4.3 – 14.3	10.2 – 47.0	87.6 – 150.5	-5.1 – -1.9	1.2 – 7.2	-6.3 – 1.3

Study GA-007/7A (08/2000 – 03/2004)

All subjects were female and Caucasian in this study. The mean age at entry was about 9 years and average weight and height were 23.6 kg and 117.8 cm, respectively. The growth rate of those children with short stature and Turner Syndrome before entering the study, measured by height SDS (mean = -3.2 using local standard) and height velocity SDS (mean = -2.4 using international standard), was lower than that of normal children of the same age. The height velocities at baseline were calculated using heights measured at 0 month and heights measured from approximately 6 to 17 months (median = 11 months) prior to the start of treatment. The resulting mean height velocity at baseline was 3.8 cm/year (Table 2).

Table 2 – Study GA-007/7A: Demographic and Baseline Characteristics of All Enrolled Subjects

	Age (year)	Weight (kg)	Height (cm)	Height SDS (Local)	Height Velocity (cm/year)	Height Velocity SDS (Tanner)
N	37	37	37	37	37	37
Mean ± SD	9.4 ± 1.7	23.6 ± 5.2	117.8 ± 7.1	-3.2 ± 0.9	3.8 ± 1.0	-2.4 ± 1.5
Median	9.3	23.7	118.5	-3.0	3.8	-2.1
Range	5.3 – 12.8	13.8 – 33.0	101.5 – 130.8	-5.6 – -1.9	1.8 – 6.5	-5.7 – 1.3

3.1.5 Efficacy Results and Discussion

Study GA-005/5A (06/2000 – 01/2004)

Height Velocity (HV). As Table 3 shows, the mean height velocity of Accretropin-treated children with GHD was increased from 4.1 cm/year at baseline to 9.6 cm/year at Month 6, and then was gradually decreasing throughout the rest of the 3-year trial. The annualized height velocity for the 1st, 2nd, and 3rd years were 8.9, 7.6, and 7.0 cm/year, respectively, which were all highly significantly better than the ones from the normal children of the same age and gender using either local or international (Tanner) standards (Figure 1).

Note that historical growth rates for normal children were based on age and gender category (whole years for Poland and half-years for Hungary). See Appendix I for the sponsor's response regarding how standard height velocity was calculated. In the trial, children of the same age and gender, with different observed height velocities, were mapped to the same historical growth rate, normalized by time on study. As a result of this mapping, the variability of the control HV data was smaller than that of the observed data and probably smaller than what would have been observed in a concurrent control. The comparison with the historical controls therefore yielded a potentially larger two sample t-statistic and more significant result. However, the statistical results were highly significant and clearly would have remained significant even if a much larger control variance had been used.

Table 3 – Study GA-005/5A: Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard		International Standard	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	4.1 ± 1.2 (44)	NA	---	5.8 ± 0.9 (44)	---
0 – 6	9.6 ± 2.4 (42)	6.0 ± 1.1 (42)	<0.0001	6.0 ± 1.1 (42)	<0.0001
0 – 12	8.9 ± 2.3 (41)	6.0 ± 1.1 (41)	<0.0001	6.0 ± 1.1 (41)	<0.0001
0 – 24[2]	8.4 ± 1.7 (34)	NA	---	NA	---
0 – 36[2]	7.9 ± 1.6 (31)	5.6 ± 1.1 (31)	<0.0001	5.8 ± 0.7 (30)[1]	<0.0001
12 – 24	7.6 ± 1.4 (34)	5.8 ± 1.2 (34)	<0.0001	5.7 ± 1.1 (34)	<0.0001
24 – 36	7.0 ± 1.6 (26)	5.3 ± 1.6 (26)	0.0004	5.6 ± 0.9 (25)[1]	0.0006

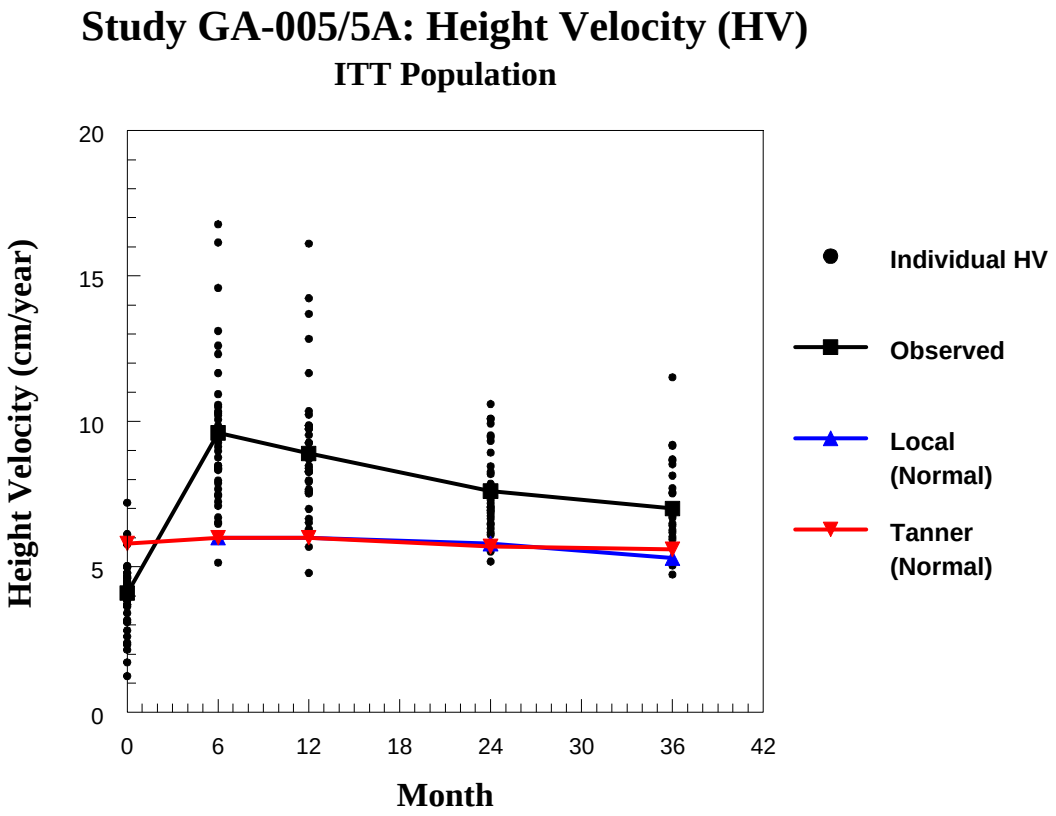
[1] Subject 108 was 16.5 years old at 36 months. A standard HV using the international standard could not be calculated since it does not include age 16.5 or older for females.

[2] The sponsor did not provide the results.

Also note that the standard height velocities at Months 6 and 12 were identical because Month 12 reference data were used for the calculation at Month 6. The sponsor explained that this was done because the Polish standards were provided only in increment of 1 year of age, resulting in many of the Polish subjects with a standard height velocity of 0 cm/year at

Month 6 when a birthday did not occur between baseline and Month 6 (see Appendix I for details).

Figure 1



HV at Month 6 = HV (Months 0 - 6); HV at Month 12 = HV (Months 0 - 12); HV at Month 24 = HV (Months 12 - 24)
HV at Month 36 = HV (Months 24 - 36); No baseline HV of local standard was available.

Table 4 – Study GA-005/5A: Results for Change from Baseline in Height Velocity (cm/year)

HV Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
0 – 6	9.6 ± 2.4 (42)	4.1 ± 1.2 (42)	5.5 ± 3.0 (42)	<0.0001	(4.6, 6.4)
0 – 12	8.9 ± 2.3 (41)	4.1 ± 1.2 (41)	4.8 ± 2.9 (41)	<0.0001	(3.9, 5.6)
0 – 24[1]	8.4 ± 1.7 (34)	4.2 ± 1.2 (34)	4.2 ± 2.3 (34)	<0.0001	(3.4, 5.0)
0 – 36[1]	7.9 ± 1.6 (31)	4.1 ± 1.2 (31)	3.8 ± 2.4 (31)	<0.0001	(2.9, 4.6)
12 – 24	7.6 ± 1.4 (34)	4.2 ± 1.2 (34)	3.5 ± 2.0 (34)	<0.0001	(2.8, 4.1)
24 – 36	7.0 ± 1.6 (26)	4.2 ± 1.3 (26)	2.8 ± 2.5 (26)	<0.0001	(1.8, 3.7)

[1] The sponsor did not provide the results.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height velocities of children with GHD were all significantly increased over that at baseline (Table 4), and also in the 2nd and 3rd years.

There were 40 subjects (98% = 40/41) responding to the Accretropin treatment at the end of 12 months (change from baseline in HV at Month 12 > 0) and also showed more than 1 cm increase from baseline. In addition, among the 41 subjects, 34 of them (83%) had > 2 cm/year increment.

Since the pre-study height velocity data were not reliable, this reviewer also performed a one-sample t-test comparing the height velocity at Month 12 with a referent value of 5 cm/year (Tanner et al., 1966), as done by the sponsor. It was found that the growth of children with GHD after 12 months was significantly higher than 5 cm/year ($p < 0.0001$).

Height Velocity Standard Deviation Score (HVSDS). The mean height velocity standardized score (observed value normalized by historical mean and SD) using international (Tanner) standard was reversed from a negative value at baseline to positive values at all post-treatment time points (Table 5), indicating that under the Accretropin treatment, the rate of growth of children with GHD became higher than that of normal children of the same age and gender. Specifically, the largest standardized difference in height velocity between the Accretropin-treated children and the normal age- and gender-matched children occurred at Month 6.

Table 5 – Study GA-005/5A: Results for Change from Baseline in HVSDS Using International Standard

HV Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
0 – 6	4.4 ± 3.3 (42)	-1.9 ± 1.5 (42)	6.22 ± 3.70 (42)	<0.0001	(5.10, 7.34)
0 – 12	3.6 ± 3.6 (41)	-1.8 ± 1.5 (41)	5.42 ± 3.97 (41)	<0.0001	(4.20, 6.63)
0 – 24[1]	2.9 ± 2.9 (33)	-1.7 ± 1.3 (33)	4.62 ± 3.34 (33)	<0.0001	(3.48, 5.76)
0 – 36[1]	3.0 ± 2.8 (31)	-1.9 ± 1.3 (31)	4.89 ± 3.42 (31)	<0.0001	(3.68, 6.09)
12 – 24	1.9 ± 2.3 (33)	-1.7 ± 1.3 (33)	3.69 ± 2.75 (33)	<0.0001	(2.75, 4.63)
24 – 36	1.8 ± 2.9 (26)	-1.8 ± 1.3 (26)	3.54 ± 3.38 (26)	<0.0001	(2.24, 4.84)

[1] The sponsor did not provide the results.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height velocity standard deviation scores using international (Tanner) standard for children with GHD were all significantly increased over that at baseline (Table 5), and also in the 2nd and 3rd years.

As mentioned in Section 2.2 Data Sources, no baseline and on-treatment height velocity SDS data using local standard were submitted by the sponsor.

Height Standard Deviation Score (HSDS). The mean height SDS using local standard at 0, 6, 12, 24, and 36 months were -3.0, -2.7, -2.5, -2.1, and -1.8, respectively. The decreasing negative scores over time indicate that the heights of children with GHD under the Accretropin treatment were gradually improved and closer to the average height of normal children of the same age and gender over the course of the study.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height standard deviation scores using local standard for children with GHD were all significantly increased over that at baseline (Table 6). There were 37 subjects (90% = 37/41) responding to the Accretropin treatment at the end of 12 months (change from baseline in HSDS at Month 12 > 0) and 28 out of the 41 subjects (68%) showed more than 0.25 standardized score increase from baseline.

Table 6 – Study GA-005/5A: Results for Change from Baseline in HSDS Using Local Standard

Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
6	-2.7 ± 0.8 (42)	-3.0 ± 0.8 (42)	0.32 ± 0.44 (42)	<0.0001	(0.19, 0.46)
12	-2.5 ± 0.7 (41)	-3.1 ± 0.8 (41)	0.60 ± 0.53 (41)	<0.0001	(0.43, 0.76)
24	-2.1 ± 0.8 (34)	-3.1 ± 0.8 (34)	1.03 ± 0.68 (34)	<0.0001	(0.80, 1.26)
36	-1.8 ± 0.8 (31)	-3.1 ± 0.9 (31)	1.34 ± 0.88 (31)	<0.0001	(1.03, 1.65)

The above results are this reviewer's.

As shown in Table 7, the results obtained based on the international (Tanner) standard were similar to the ones based on the local standard.

Table 7 – Study GA-005/5A: Results for Change from Baseline in HSDS Using International Standard

Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
6	-2.3 ± 0.7 (42)	-2.6 ± 0.8 (42)	0.33 ± 0.23 (42)	<0.0001	(0.26, 0.40)
12	-2.0 ± 0.7 (41)	-2.6 ± 0.8 (41)	0.59 ± 0.45 (41)	<0.0001	(0.46, 0.73)
24	-1.6 ± 0.8 (34)	-2.6 ± 0.8 (34)	1.05 ± 0.63 (34)	<0.0001	(0.84, 1.27)
36	-1.4 ± 0.9 (30)	-2.6 ± 0.8 (30)	1.26 ± 0.82 (30)	<0.0001	(0.97, 1.55)

The above results are this reviewer's.

Study GA-007/7A (08/2000 – 03/2004)

Height Velocity (HV). As Table 8 shows, the mean height velocity of Accretropin-treated children with Turner Syndrome was increased from 3.8 cm/year at baseline to 8.8 cm/year at Month 6, and then was gradually decreasing throughout the rest of the 3-year trial. The annualized height velocity for the 1st and 2nd years were 8.6 and 6.9 cm/year, respectively, which were both highly significantly better than the ones from the normal or untreated Turner Syndrome children of the same age using either local or international (Tanner) standards. The 3rd year annualized height velocity of those Accretropin-treated children (5.8 cm/year) was also significantly better than that of untreated Turner Syndrome Polish children, but not statistically when compared to the normal age-matched children using either local or international (Tanner) standards (Figure 2).

Note that SDs of the historical data, particularly during Year 1, were smaller than that of the observed data, which was due to using the same reference height data for the age-matched normal or untreated Turner Syndrome subjects. Also note that the standard height velocities at Months 6 and 12 were identical because Month 12 reference data were used for the calculation at Month 6. The sponsor explained that this was done because the Polish standards were provided only in increment of 1 year of age, resulting in many of the Polish subjects with a standard height velocity of 0 cm/year at Month 6 when a birthday did not occur between baseline and Month 6 (see Appendix I for details).

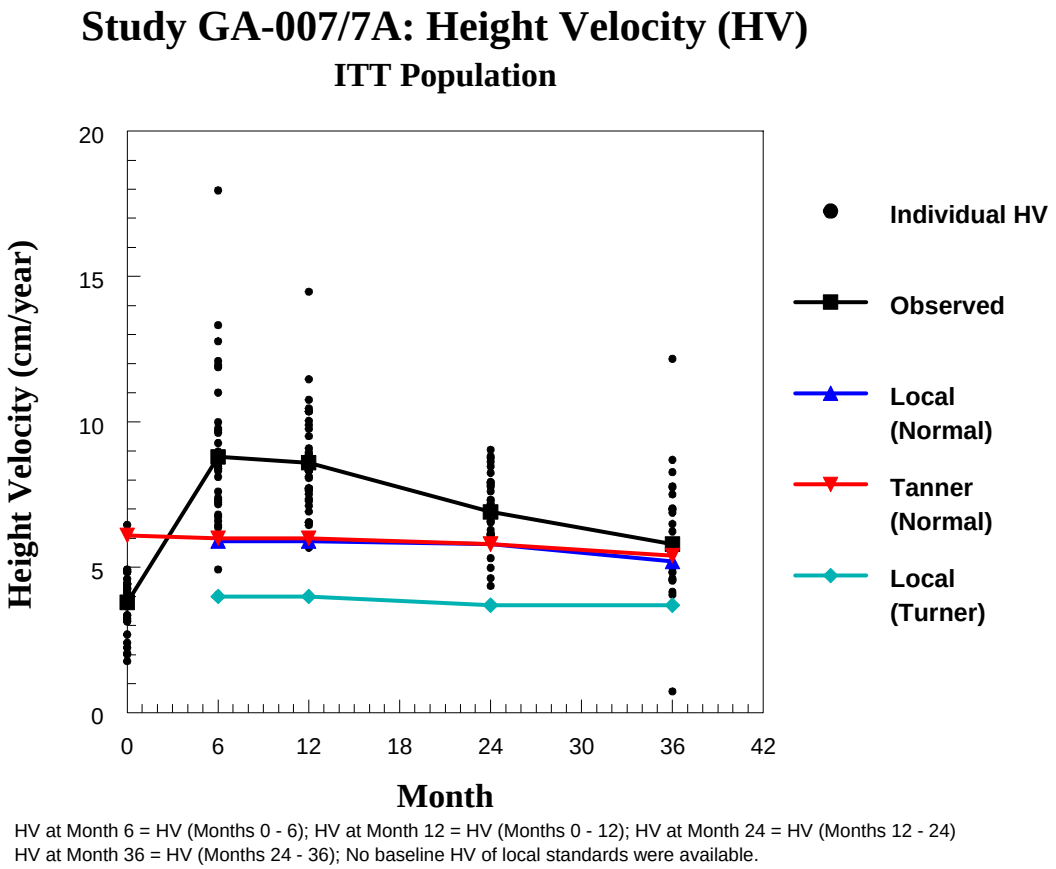
Table 8 – Study GA-007/7A: Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard **(Normal Children)**		International Standard **(Normal Children)**		Local Standard **(Turner Children)**	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	3.8 ± 1.0 (37)	NA	---	6.1 ± 1.0 (37)	---	NA	---
0 – 6	8.8 ± 2.6 (37)	5.9 ± 0.6 (37)	<0.0001	6.0 ± 0.6 (37)	<0.0001	4.0 ± 0.8 (37)	<0.0001
0 – 12	8.6 ± 1.7 (37)	5.9 ± 0.6 (37)	<0.0001	6.0 ± 0.6 (37)	<0.0001	4.0 ± 0.8 (37)	<0.0001
0 – 24[2]	7.7 ± 1.3 (36)	NA	---	NA	---	NA	---
0 – 36[2]	7.1 ± 1.3 (35)	5.4 ± 1.2 (35)	<0.0001	5.7 ± 0.8 (35)	<0.0001	3.6 ± 0.6 (35)	<0.0001
12 – 24	6.9 ± 1.2 (36)	5.8 ± 2.0 (35)[1]	0.0060	5.8 ± 0.9 (36)	<0.0001	3.7 ± 1.2 (35)[1]	<0.0001
24 – 36	5.8 ± 1.9 (35)	5.2 ± 2.3 (30)[1]	0.2372	5.4 ± 1.8 (35)	0.3412	3.7 ± 1.0 (30)[1]	<0.0001

[1] Excluded standard height velocities with 0 caused by the same age-matched heights from the standard table for the two visits used in the calculation. This occurred when the time elapsed between two visits was less than the age increments in the standard table and the subject's birthday did not occur between the two visits.

[2] The sponsor did not provide the results.

Figure 2



HV at Month 6 = HV (Months 0 - 6); HV at Month 12 = HV (Months 0 - 12); HV at Month 24 = HV (Months 12 - 24)
HV at Month 36 = HV (Months 24 - 36); No baseline HV of local standards were available.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height velocities of children with Turner Syndrome were all significantly increased over that at baseline (Table 9), and also in the 2nd and 3rd years.

Table 9 – Study GA-007/7A: Results for Change from Baseline in Height Velocity (cm/year)

HV Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
0 – 6	8.8 ± 2.6 (37)	3.8 ± 1.0 (37)	5.0 ± 2.7 (37)	<0.0001	(4.1, 5.9)
0 – 12	8.6 ± 1.7 (37)	3.8 ± 1.0 (37)	4.7 ± 2.0 (37)	<0.0001	(4.1, 5.4)
0 – 24[1]	7.7 ± 1.3 (36)	3.8 ± 1.0 (36)	3.9 ± 1.6 (36)	<0.0001	(3.4, 4.4)
0 – 36[1]	7.1 ± 1.3 (35)	3.8 ± 1.0 (35)	3.3 ± 1.5 (35)	<0.0001	(2.8, 3.8)
12 – 24	6.9 ± 1.2 (36)	3.8 ± 1.0 (36)	3.0 ± 1.3 (36)	<0.0001	(2.6, 3.5)
24 – 36	5.8 ± 1.9 (35)	3.8 ± 1.0 (35)	2.0 ± 2.0 (35)	<0.0001	(1.4, 2.7)

[1] The sponsor did not provide the results.

All 37 subjects responded to the Accretropin treatment at the end of 12 months (change from baseline in HV at Month 12 > 0) and 36 of them also showed more than 1 cm increase from baseline. In addition, among the 37 subjects, 35 of them (95%) had > 2 cm/year increment.

Since the pre-study height velocity data were not reliable, this reviewer also performed a one-sample t-test comparing the height velocity at Month 12 with a referent value of 5 cm/year (Tanner et al., 1966), as done by the sponsor. It was found that the growth of children with Turner Syndrome after 12 months was significantly higher than 5 cm/year ($p < 0.0001$).

Height Velocity Standard Deviation Score (HVSDS). The mean height velocity standardized score (observed value normalized by historical mean and SD) using international (Tanner) standard was reversed from a negative value at baseline to positive values at all post-treatment time points (Table 10), indicating that under the Accretropin treatment, the rate of growth of children with Turner Syndrome became higher than that of normal children of the same age. Specifically, the largest standardized difference in height velocity between the Accretropin-treated children and the normal age-matched children occurred at Month 6, and then the difference was gradually decreased as the treatment continued throughout the rest of the 3-year trial.

Table 10 – Study GA-007/7A: Results for Change from Baseline in HVSDS Using International Standard

HV Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
0 – 6	3.4 ± 3.9 (37)	-2.4 ± 1.5 (37)	5.79 ± 3.72 (37)	<0.0001	(4.59, 6.99)
0 – 12	3.1 ± 2.6 (37)	-2.4 ± 1.5 (37)	5.49 ± 2.78 (37)	<0.0001	(4.60, 6.39)
0 – 24[1]	2.4 ± 2.2 (36)	-2.4 ± 1.5 (36)	4.87 ± 3.20 (36)	<0.0001	(3.82, 5.91)
0 – 36[1]	1.9 ± 3.6 (33)	-2.3 ± 1.5 (33)	4.25 ± 4.69 (33)	<0.0001	(2.65, 5.85)
12 – 24	1.5 ± 1.9 (36)	-2.4 ± 1.5 (36)	3.94 ± 2.87 (36)	<0.0001	(3.00, 4.88)
24 – 36	0.5 ± 3.3 (33)	-2.3 ± 1.5 (33)	2.81 ± 4.33 (33)	0.0007	(1.33, 4.29)

[1] The sponsor did not provide the results.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height velocity standard deviation scores using international (Tanner) standard for children with Turner Syndrome were all significantly increased over that at baseline (Table 10), and also in the 2nd and 3rd years.

As mentioned in Section 2.2 Data Sources, no baseline and on-treatment height velocity SDS data using local standards (normal and untreated) were submitted by the sponsor.

Height Standard Deviation Score (HSDS). The mean height SDS using local standard of normal children at 0, 6, 12, 24, and 36 months were -3.2, -2.8, -2.7, -2.4, and -2.3, respectively. The decreasing negative scores over time indicate that the heights of children with Turner Syndrome under the Accretropin treatment were gradually improved and closer to the average height of normal Polish children of the same age over the course of the study.

The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height standard deviation scores using local normal standard for children with Turner Syndrome were all significantly increased over that at baseline (Table 11). There were 30 subjects (81% = 30/37) responding to the Accretropin treatment at the end of 12 months (change from baseline in HSDS at Month 12 > 0) and 28 out of the 37 subjects (76%) showed more than 0.1 standardized score increase from baseline.

Table 11 – Study GA-007/7A: Results for Change from Baseline in HSDS Using Local Normal Standard

Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
6	-2.8 ± 1.0 (37)	-3.2 ± 0.9 (37)	0.33 ± 0.46 (37)	<0.0001	(0.19, 0.48)
12	-2.7 ± 1.2 (37)	-3.2 ± 0.9 (37)	0.50 ± 0.48 (37)	<0.0001	(0.35, 0.66)
24	-2.4 ± 1.2 (36)	-3.2 ± 0.9 (36)	0.76 ± 0.65 (36)	<0.0001	(0.55, 0.97)
36	-2.3 ± 1.2 (35)	-3.2 ± 0.9 (35)	0.90 ± 0.67 (35)	<0.0001	(0.68, 1.13)

The above results are this reviewer's.

As shown in Table 12, the results obtained based on the international (Tanner) standard of normal children were similar to the ones based on the local standard of normal children.

Table 12 – Study GA-007/7A: Results for Change from Baseline in HSDS Using International Normal Standard

Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
6	-2.2 ± 0.9 (37)	-2.4 ± 0.8 (37)	0.22 ± 0.22 (37)	<0.0001	(0.15, 0.29)
12	-1.9 ± 1.0 (37)	-2.4 ± 0.8 (37)	0.46 ± 0.35 (37)	<0.0001	(0.35, 0.58)
24	-1.8 ± 1.2 (36)	-2.4 ± 0.8 (36)	0.67 ± 0.56 (36)	<0.0001	(0.48, 0.85)
36	-1.7 ± 1.2 (35)	-2.4 ± 0.8 (35)	0.70 ± 0.62 (35)	<0.0001	(0.49, 0.90)

The above results are this reviewer's.

The mean height SDS using local standard of untreated children with Turner Syndrome at 0, 6, 12, 24, and 36 months were 0.2, 0.6, 1.0, 1.5, and 1.9, respectively. The increasing

positive scores over time indicate that the heights of study children with Turner Syndrome were similar to that of local age-matched children with Turner Syndrome at entry, but following initiation of the Accretropin treatment, the heights of study children outpaced those of local untreated Turner Syndrome children of the same age over the course of the study. The paired t-test results showed that after 6, 12, 24, and 36 months of treatment with Accretropin, the mean height standard deviation scores using local untreated standard for children with Turner Syndrome were all significantly increased over that at baseline (Table 13).

Table 13 – Study GA-007/7A: Results for Change from Baseline in HSDS Using Local Turner Standard

Month	On-treatment Mean ± SD (N)	Baseline Mean ± SD (N)	**Accretropin**: Change from Baseline		
			Mean ± SD (N)	p-value	(LCL, UCL)
6	0.6 ± 0.8 (37)	0.2 ± 0.7 (37)	0.38 ± 0.41 (37)	<0.0001	(0.24, 0.51)
12	1.0 ± 0.9 (37)	0.2 ± 0.7 (37)	0.76 ± 0.33 (37)	<0.0001	(0.66, 0.87)
24	1.5 ± 0.9 (36)	0.2 ± 0.7 (36)	1.29 ± 0.43 (36)	<0.0001	(1.15, 1.44)
36	1.9 ± 1.1 (35)	0.2 ± 0.7 (35)	1.73 ± 0.66 (35)	<0.0001	(1.51, 1.95)

The above results are this reviewer's.

3.3 Evaluation of Safety

In consultation with the reviewing medical officer, there were no aspects of safety that required review by a statistician. See Dr. Dragos Roman's report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Study GA-005/5A (06/2000 – 01/2004)

The mean height velocity at Month 12 was numerically larger in the males (9.0 ± 2.6 (N = 24)) than in the females (8.7 ± 1.9 (N = 17)). However, there was no significant treatment difference in change from baseline in height velocity at Month 12 between the 2 sexes (p = 0.8404). The mean height velocity at Month 12 was also numerically larger in the younger subjects (9.4 ± 2.8 (N = 18)) than in the older ones (8.5 ± 1.8 (N = 23)) as defined by median age at baseline (< 9.25 years and ≥ 9.25 years), but no significant treatment difference in change from baseline in height velocity at Month 12 between the 2 age groups was observed (p = 0.8033). There was no subgroup analysis for race performed since all the study subjects were Caucasian.

Study GA-007/7A (08/2000 – 03/2004)

The mean height velocity at Month 12 was numerically larger in the younger subjects (8.8 ± 2.0 (N = 16)) than in the older ones (8.3 ± 1.4 (N = 21)) as defined by median age at baseline

(< 9.25 years and ≥ 9.25 years), but no significant treatment difference in change from baseline in height velocity at Month 12 between the 2 age groups was observed (p = 0.9359). No subgroup analyses for gender and race were performed since all the study subjects were female Caucasian.

4.2 Other Special/Subgroup Populations

Study GA-005/5A (06/2000 – 01/2004)

The mean height velocity at Month 12 was numerically larger in Poland (9.7 ± 2.4 (N = 22)) than in Hungary (8.0 ± 1.9 (N = 19)). A significant treatment difference in change from baseline in height velocity at Month 12 between the 2 countries was observed (p = 0.0492). In fact, a significant difference was seen for all time points. According to the sponsor, it was most likely due to the different dosage of Accretropin administered in the 2 countries, where 0.05 mg/kg/day was used in Poland and 0.03 – 0.04 mg/kg/day was used in Hungary.

Study GA-007/7A (08/2000 – 03/2004)

There were no other special subgroups analyzed by this reviewer or the sponsor.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As mentioned in Section 3.1.1 Study Design and Endpoints, due to the fact that the pre-study height velocity data were not collected in a standardized manner, the sponsor changed the primary efficacy analysis from analyzing the change from baseline in HV (primary efficacy variable) to comparing the on-treatment HV with historical HV obtained using local and international (Tanner) standards. However, as noted in Section 3.1.5 Efficacy Results and Discussion, due to the use of the same reference height data for the age- and gender-matched subjects, the standard deviation of the historical HV data was generally smaller than that of the observed data, which would potentially yield a larger two-sample t-statistic than when using a concurrent control. In other words, neither the original nor the new primary efficacy analysis produced an absolutely reliable outcome in this reviewer's view. Therefore, results from all the primary and secondary analyses were reviewed in its totality so that the final sound conclusion can be drawn. The collective evidence is summarized by indication as follows.

Indication for Children with Growth Hormone Deficiency

There was only 1 study submitted for the proposed indication. The annualized height velocities of children with GHD after treatment with Accretropin were 8.9, 7.6, and 7.0 cm for the 1st, 2nd, and 3rd years, respectively, which were all highly significantly better than that of normal age- and gender-matched children using either local or international (Tanner) standards (Table 14).

Table 14 – Study GA-005/5A: Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard		International Standard	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	4.1 ± 1.2 (44)	NA	---	5.8 ± 0.9 (44)	---
0 – 12	8.9 ± 2.3 (41)	6.0 ± 1.1 (41)	<0.0001	6.0 ± 1.1 (41)	<0.0001
12 – 24	7.6 ± 1.4 (34)	5.8 ± 1.2 (34)	<0.0001	5.7 ± 1.1 (34)	<0.0001
24 – 36	7.0 ± 1.6 (26)	5.3 ± 1.6 (26)	0.0004	5.6 ± 0.9 (25)[1]	0.0006

[1] Subject 108 was 16.5 years old at 36 months. A standard HV using the international standard could not be calculated since it does not include age 16.5 or older for females.

The mean changes from baseline in height velocity, height velocity SDS (Tanner), and height SDS (local and Tanner) at Month 12 were all highly significantly different from zero in favor of the Accretropin treatment (Table 15). Although the height of children with GHD after 12 months of treatment was still below the height of normal children of the same age and gender (HSDS = -2.5 using local and -2.0 using Tanner standards), the mean growth rate at 12 months was improved (HV = 8.9 cm/year) and higher than that of normal age- and gender-matched children (HVSDS = 3.6 using Tanner standard). Similar significant findings were also observed for the 2nd and 3rd years of continuous treatment with Accretropin.

Table 15 – Study GA-005/5A: Results for Change from Baseline at Month 12

Efficacy Variable	Month 12 Mean ± SD (N)	Month 0 Mean ± SD (N)	Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
HV (cm/year)	8.9 ± 2.3 (41)	4.1 ± 1.2 (41)	4.76 ± 2.89 (41)	<0.0001	(3.87, 5.64)
HVSDS (Tanner)	3.6 ± 3.6 (41)	-1.8 ± 1.5 (41)	5.42 ± 3.97 (41)	<0.0001	(4.20, 6.63)
HSDS (Local)	-2.5 ± 0.7 (41)	-3.1 ± 0.8 (41)	0.60 ± 0.53 (41)	<0.0001	(0.43, 0.76)
HSDS (Tanner)	-2.0 ± 0.7 (41)	-2.6 ± 0.8 (41)	0.59 ± 0.45 (41)	<0.0001	(0.46, 0.73)

Indication for Children with Turner Syndrome

There was only 1 study submitted for the proposed indication. The annualized height velocities of children with Turner Syndrome after treatment with Accretropin were 8.6 and 6.9 cm for the 1st and 2nd years, respectively, which were both highly significantly better than that of normal or untreated Turner Syndrome children of the same age using either local or international (Tanner) standards. Although the 3rd year growth rate of Accretropin-treated children (5.8 cm/year) was similar to that of normal children of the same age, it was significantly larger than that of untreated age-matched Polish children with Turner Syndrome (Table 16).

Table 16 – Study GA-007/7A: Results for Height Velocity (cm/year) Compared to Historical Data (Standards)

HV Month	Accretropin Mean ± SD (N)	Local Standard **(Normal Children)**		International Standard **(Normal Children)**		Local Standard **(Turner Children)**	
		Mean ± SD (N)	p-value	Mean ± SD (N)	p-value	Mean ± SD (N)	p-value
Baseline	3.8 ± 1.0 (37)	NA	---	6.1 ± 1.0 (37)	---	NA	---
0 – 12	8.6 ± 1.7 (37)	5.9 ± 0.6 (37)	<0.0001	6.0 ± 0.6 (37)	<0.0001	4.0 ± 0.8 (37)	<0.0001
12 – 24	6.9 ± 1.2 (36)	5.8 ± 2.0 (35)[1]	0.0060	5.8 ± 0.9 (36)	<0.0001	3.7 ± 1.2 (35)[1]	<0.0001
24 – 36	5.8 ± 1.9 (35)	5.2 ± 2.3 (30)[1]	0.2372	5.4 ± 1.8 (35)	0.3412	3.7 ± 1.0 (30)[1]	<0.0001

[1] Excluded standard height velocities with 0 caused by the same age-matched heights from the standard table for the two visits used in the calculation. This occurred when the time elapsed between two visits was less than the age increments in the standard table and the subject's birthday did not occur between the two visits.

The mean changes from baseline in height velocity, height velocity SDS (Tanner), and height SDS (local and Tanner) at Month 12 were all highly significantly different from zero in favor of the Accretropin treatment (Table 17). Although the height of children with Turner Syndrome after 12 months of treatment was still below the height of normal children of the same age (HSDS = -2.7 using local and -1.9 using Tanner standards), the mean growth rate at 12 months was improved (HV = 8.6 cm/year) and higher than that of normal age-matched children (HVSDS = 3.1 using Tanner standard). In addition, the height of Accretropin-treated children with Turner Syndrome was larger than that of untreated age-matched children with Turner Syndrome after 12 months (HSDS = 1.0 using local Turner standard). Similar significant findings were also observed for the 2nd and 3rd years of continuous treatment with Accretropin.

Table 17 – Study GA-007/7A: Results for Change from Baseline at Month 12

Efficacy Variable	Month 12 Mean ± SD (N)	Month 0 Mean ± SD (N)	Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
HV (cm/year)	8.6 ± 1.7 (37)	3.8 ± 1.0 (37)	4.74 ± 2.00 (37)	<0.0001	(4.09, 5.38)
HVSDS (Tanner)	3.1 ± 2.6 (37)	-2.4 ± 1.5 (37)	5.49 ± 2.78 (37)	<0.0001	(4.60, 6.39)
HSDS (Local – Normal)	-2.7 ± 1.2 (37)	-3.2 ± 0.9 (37)	0.50 ± 0.48 (37)	<0.0001	(0.35, 0.66)
HSDS (Tanner – Normal)	-1.9 ± 1.0 (37)	-2.4 ± 0.8 (37)	0.46 ± 0.35 (37)	<0.0001	(0.35, 0.58)
HSDS (Local – Turner)	1.0 ± 0.9 (37)	0.2 ± 0.7 (37)	0.76 ± 0.33 (37)	<0.0001	(0.66, 0.87)

In general, this reviewer's results for both studies agree with the sponsor's conclusions.

5.2 Conclusions and Recommendations

Data from 2 open-label studies have demonstrated that Accretropin was efficacious in increasing height and in stimulating height velocity for children with growth hormone deficiency (GHD) or Turner Syndrome.

5.3 Labeling Comments

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader

CC: HFD-510/KJohnson, MParks, DRoman
HFD-715/TPermutt, TSahlroot, CLiu
HFD-700/ENevius, LPatrician

6. APPENDIX I

Response to Information Request Letter from Department of Health and Human Services, Food and Drug Administration, dated January 16, 2007

Comments from the FDA are provided in **bold text**, followed by Cangene's response.

1. In both LOCEFF.XPt (local standard) and TANEFF.XPT (Tanner standard) data files, there are SGV_xxx variables for the standard growth velocities. Please give an example to illustrate how they were derived. Also, please explain why the standard growth velocities for Month 6 (SGV_W24) and Month 12 (SGV_M12) are identical.

Cangene's Response:

The local age and gender matched standards for height used for Hungary were provided in half-years while the local standards for Poland were provided in whole years. The result of using standard tables in whole years at the 24 week assessment was that the standard height for baseline and week 24 were the same for all subjects who did not have a birthday between baseline and week 24. The following formula used for calculating standard growth velocity,

$$SGV = \frac{STDHGT_{time2} - STDHGT_{time1}}{(DT_{time2} - DT_{time2})/365}$$

results in a standard growth velocity of 0 cm/year for many of the Polish subjects at week 24. In order to calculate the standard growth velocity at 6 months, the age at 12 months was used, therefore the standard growth velocities at 6 months and 12 months are the same. This approach is the most conservative for efficacy comparisons since the annualized growth velocity is calculated based on the height at 6 months while the standard growth velocity is calculated based on the standard height at 12 months.

Using data from subject GF-501 (study GA-007/7A) the following is an example of the calculation of the variable SGV_W24:

Input data:

- Baseline assessment date: Aug 22, 2000
- Month 12 assessment date: Aug 21, 2001 (note: if the month 12 assessment is missing for a subject, then 365 days were added to the baseline assessment date for the calculation of SGV_W24 despite the fact that SGV_M12 is missing)
- Date of Birth: [redacted]
- Gender: Female

Calculated values:

- Age at Baseline: 12
- Age at Month 12: 13
- Age and gender matched standard height for baseline (Poland): 153
- Age and gender matched standard height for month 12 (Poland): 159.2

$$SGV = \frac{STDHGT_{time2} - STDHGT_{time1}}{(DT_{time2} - DT_{time2})/365}$$

$$SGV = \frac{159.2 - 153}{(21AUG2001 - 22AUG2000)/365} = 6.217 \text{ cm/year}$$

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/s/

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3/6/2007 04:12:13 PM
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3/7/2007 02:09:39 PM
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