CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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:	21-905/N-000
Drug Name:	Valtropin® (Somatropin (rDNA origin) for Injection)
Indication(s):	[redacted] b(4)
Applicant:	LG Life Sciences, Ltd.
Date(s):	Received 11/30/05; user fee (10 months) 10/01/06
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
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Keywords:	NDA review, clinical studies, non-inferiority

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

After 12 months of treatment with Eutropin, the height, growth rate, and related standardized scores in the BP-EU-003 (for Indication A), BP-EU-002 (for Indication B), and TS-KOR-06102005 (for Indication B) studies were all highly significantly improved over that at baseline. The difference in height between the Eutropin-treated children and the normal age- and gender-matched children was gradually decreased as the treatment continued. Also, the rate of growth was reversed from slower than that of normal children of the same age and gender to faster than that of normal ones during the course of the studies (especially in the early stage of the treatment phase). In other words, under the Eutropin treatment, the children with growth hormone deficiency (GHD) or Turner Syndrome grew faster than before.

In the BP-EU-003 study, Eutropin was shown to be non-inferior to Humatrope in promoting growth effect for children with GHD. The 2 study groups also showed comparable results in height velocity SDS, height SDS, and predicted adult height.

In conclusion, the data from the 3 children studies have demonstrated that Eutropin was efficacious in increasing height and in stimulating height velocity for children with GHD (Indication A) or Turner Syndrome (Indication B).

1.2 Brief Overview of Clinical Studies

LG Life Sciences, Ltd. has developed Valtropin®, somatropin (rDNA origin) for daily injection, as a new growth hormone drug for human use. It was registered in the USA in October 2005, but was described as Eutropin™ throughout the dossier. According to the sponsor, Eutropin™ INJ (a 1.33 mg / 4 IU formulation of somatropin initially approved for marketing in Korea) has gained regulatory approval in 12 countries worldwide (Brazil, Chile, Colombia, Egypt, India, Indonesia, Iraq, Korea, Pakistan, Syria, Thailand, and Venezuela) and is marketed in all of them. From 1992-2004, an estimated [redacted] vials have been sold, providing approximately 12 years of human exposure. b(4)

The sponsor has submitted the results from 5 completed clinical trials (BP-EU-003, BP-EU-002, TS-KOR-06102005, HGCL-001, and BP-EU-001) to this NDA to support the following proposed indications:

(A) [redacted] b(4)

(B) [redacted]

(C) [redacted]

b(4)

Except for BP-EU-001 which was a Phase I bioavailability study, all others were Phase III studies to evaluate the efficacy and safety of Eutropin™. The BP-EU-003 study is to seek approval for Indication A, the BP-EU-002 and TS-KOR-06102005 studies for Indication B, and the HGCL-001 study for Indication C. The BP-EU-003 study was a Phase III, randomized, double-blind, multi-center, non-inferiority study (using Humatrope® as the active comparator) conducted in children with short stature and GHD. The BP-EU-002 and TS-KOR-06102005 studies were Phase III, open, uncontrolled, single-arm studies conducted in children with Turner Syndrome. The former study was a single-center study in Moscow, Russia, while the latter one was a multi-center study in Korea. All 3 children studies (for Indications A and B) were designed to be of 12 months of treatment, with height velocity as the primary efficacy variable of interest. They were reviewed in this report. Another FDA statistician, Jim Gebert, reviewed the adult study, HGCL-001 for Indication C.

1.3 Statistical Issues and Findings

There were no serious statistical issues noted by this reviewer in this submission. In general, this reviewer's results for the 3 children studies agree with the sponsor's conclusions. The collective evidence was summarized by indication as follows.

Indication A – Children with Growth Hormone Deficiency

There was only 1 study submitted for Indication A. The mean changes from baseline in height velocity, height velocity SDS, height SDS for chronological age, predicted adult height, and predicted adult height SDS at Month 12 were all highly significantly different from zero in the Eutropin group (Text Table 1). Specifically, the mean height velocity was increased from 3.50 cm/year at baseline to 11.36 cm/year at Month 12. Although the mean height of children with short stature and growth hormone deficiency (GHD) after 12 months of treatment with Eutropin (height SDS CA = -2.33) was still below the average height of normal children of the same age and gender, the rate of growth of those Eutropin-treated children was improved after 12 months (height velocity SDS = 5.71) and higher than that of normal age- and gender-matched children. In addition, the mean predicted adult height of those GHD children was increased from 162.27 cm at screening to 165.77 cm at Month 12 based on the Bayley and Pinneau method.

All the 88 ITT subjects in the Eutropin group responded to the treatment at the end of the 12-month trial (change from baseline in HV and HSDS CA at Month 12 > 0). Among them, 95.5% (= 84/88) showed more than 2 cm/year increase in HV from baseline and 97.7% (= 86/88) showed more than 0.25 height standard deviation score increase from baseline.

Text Table 1 – Collective Evidence for Indication A Using ITT Population with LOCF

Study BP-EU-003 Efficacy Variable	**Eutropin**: Mean ± SD (N)		Mean Change from Baseline	(95% C.I.)
	Month 0	Month 12		
Height Velocity (cm/year)	3.50 ± 1.45 (88)	11.36 ± 2.92 (88)	7.8656 *	(7.18, 8.55)
Height Velocity SDS	-2.34 ± 1.78 (88)	5.71 ± 3.44 (88)	8.0464 *	(7.16, 8.94)
Height SDS for Chronological Age	-3.54 ± 1.24 (88)	-2.33 ± 1.01 (88)	1.2091 *	(1.08, 1.34)
Height SDS for Bone Age	-0.16 ± 1.47 (86)	-0.003 ± 1.82 (86)	0.1604	(-0.12, 0.44)
Bone Maturation	NA	1.53 ± 0.89 (86)	NA	NA
Predicted Adult Height (BP)	162.27 ± 9.67 (32)	165.77 ± 10.0 (32)	3.5055 *	(1.57, 5.44)
Predicted Adult Height SDS (BP)	-1.71 ± 1.10 (32)	-1.22 ± 1.08 (32)	0.4895 *	(0.22, 0.76)

Except for HSDS for bone age where p = 0.2642, all p-values for the mean changes from screening or baseline at Month 12 based on the paired t-test were < 0.01 (*).

Bone maturation was calculated as ratio of change from screening in bone age at Month 12 to change from screening in chronological age at Month 12.

Within either sex or any of the age subgroups as follows: age ≤ 4, 4 < age ≤ 8, 8 < age ≤ 12, age > 12, the mean height velocity, height velocity SDS, and height SDS for chronological age after 12 months of treatment with Eutropin were all significantly improved over that at baseline (all $p < 0.01$). In addition, it was shown that subjects who were younger at entry, had smaller log maximum GH level after stimulation, or had lower baseline height SDS for chronological age, tended to have greater height velocity after 12 months of treatment with Eutropin. The negative relationship was particularly significant in the cases of log maximum GH level and baseline height SDS for chronological age.

The observed treatment difference in height velocity between the Eutropin and Humatrope groups was 0.21 cm/year in favor of Eutropin. The associated 95% confidence interval was (-0.48, 0.90), which lied entirely within the margin of ±2 cm/year (the sponsor defined), indicating that Eutropin was non-inferior to Humatrope in improving growth for children with short stature and GHD. The 2 study groups also showed comparable results in height velocity SDS, height SDS for chronological age, height SDS for bone age, bone maturation, predicted adult height, and predicted adult height SDS.

Indication B – Children with Turner Syndrome

Since inclusion/exclusion criteria (particular in age at entry), study location (Russia vs. Korea), height velocity calculation method (see Appendices I and II), study period (TS-KOR-06102005 was an older study) etc., are somewhat different between the BP-EU-002 and TS-KOR-06102005 studies, this reviewer thinks that the data from the 2 clinical trials should not be combined for overall treatment estimate.

As for the findings observed in the BP-EU-003 study for Indication A, the mean changes from baseline in height velocity, height velocity SDS, height SDS for chronological age and bone age, predicted adult height, and HA/BA at Month 12, where applicable, were all highly significantly different from zero in the Eutropin group of the BP-EU-002 and TS-KOR-06102005 studies for Indication B (Text Table 2). Specifically, the mean height velocity was increased from 3.75 cm/year at baseline to 9.73 cm/year at Month 12 for the former study and from 3.48 cm/year to 6.97 cm/year for the latter study. Although the mean heights of children with Turner Syndrome after 12 months of treatment with Eutropin (height SDS CA = -1.54 and -2.67, respectively) were still below the average heights of normal children of the same age, the rates of growth of those Eutropin-treated children were improved after 12 months (height velocity SDS = 3.82 for the BP-EU-002 study) and higher than that of normal age-matched children. In addition, the mean predicted adult height of those Turner Syndrome children in the BP-EU-002 study was increased from 152.0 cm at baseline to 156.0 cm at Month 12 based on the Bayley and Pinneau method.

Text Table 2 – Collective Evidence for Indication B Using ITT Population with LOCF

Efficacy Variable	Study	Mean ± SD (N)		Mean Change from Baseline	(95% C.I.)
		Month 0	Month 12		
Height Velocity (cm/year)	BP-EU-002	3.75 ± 1.76 (30)	9.73 ± 1.55 (30)	5.9798 *	(5.20, 6.76)
	TS-KOR-06102005	3.48 ± 1.40 (58)	6.97 ± 1.84 (58)	3.4858 *	(2.94, 4.03)
Height Velocity SDS	BP-EU-002	-2.39 ± 1.90 (30)	3.82 ± 1.95 (30)	6.2157 *	(5.22, 7.21)
	TS-KOR-06102005	NA	NA	NA	NA
Height SDS for CA	BP-EU-002	-2.42 ± 0.91 (30)	-1.54 ± 0.94 (30)	0.8768 *	(0.78, 0.98)
	TS-KOR-06102005	-3.02 ± 0.96 (58)	-2.67 ± 0.99 (58)	0.3464 *	(0.23, 0.46)
Height SDS for BA	BP-EU-002	0.09 ± 1.52 (29)	0.50 ± 1.23 (29)	0.4159 *	(0.20, 0.63)
	TS-KOR-06102005	NA	NA	NA	NA
Bone Maturation	BP-EU-002	NA	1.02 ± 0.35 (29)	NA	NA
	TS-KOR-06102005	NA	NA	NA	NA
Predicted Adult Height (BP)	BP-EU-002	152.0 ± 5.23 (14)	156.0 ± 4.21 (14)	4.0376 *	(2.89, 5.19)
	TS-KOR-06102005	NA	NA	NA	NA
HA/BA	BP-EU-002	NA	NA	NA	NA
	TS-KOR-06102005	0.85 ± 0.15 (58)	0.88 ± 0.12 (58)	0.0257 *	(0.00, 0.05)

P < 0.05 (*) for all mean changes from screening or baseline at Month 12 based on the paired t-test.

CA = Chronological Age; BA = Bone Age; HA = Height Age

Bone maturation was calculated as ratio of change from screening in bone age at Month 12 to change from screening in chronological age at Month 12.

The majority of ITT subjects in the 2 Turner Syndrome studies responded to the Eutropin treatment at the end of the 12-month trial (change from baseline in HV and HSDS CA at Month 12 > 0) and also showed more than 1 cm/year increase in HV from baseline and 0.1 height standard deviation score increase from baseline (Text Table 3).

Text Table 3 – Responder Rate for Change from Baseline at Month 12 for Indication B

Study	Height Velocity (cm/year)		Height SDS	
	>0	>1	>0	>0.1
BP-EU-002	30/30 (100%)	30/30 (100%)	30/30 (100%)	30/30 (100%)
TS-KOR-06102005	57/60 (95%)	49/60 (81.7%)	48/60 (80%)	44/60 (73.3%)

Except for the subgroup of ≤ 4 years in the BP-EU-002 study that did not have any significant finding (n = 4, small sample size, p = 0.1250 based on Wilcoxon signed rank test), within any of the age subgroups as follows: age ≤ 4, 4 < age ≤ 8, 8 < age ≤ 12, age > 12, the mean height velocity and mean height SDS for chronological age after 12 months of treatment with Eutropin were all significantly improved over that at baseline (all $p < 0.05$). In addition, there was a significant treatment difference in change from baseline in height velocity at 12 months among the subgroups of age in the TS-KOR-06102005 study ($p = 0.0092$), but not in the BP-EU-002 study ($p = 0.2977$). It was found that the mean change from baseline in height velocity of the subjects >12 years old in the TS-KOR-06102005 study was significantly smaller than that of the subjects ≤12 years old. No treatment difference in change from baseline in height SDS for chronological age at 12 months was observed among the subgroups of age in either of the 2 Turner Syndrome studies ($p > 0.10$ for both cases).

2. INTRODUCTION

2.1 Overview

Valtropin®, somatropin (rDNA origin) for daily injection, is proposed for the [redacted] b(4)

[redacted] It was registered in the USA in October 2005, but was described as Eutropin™ throughout the dossier.

According to the sponsor, Eutropin™ INJ (a 1.33 mg / 4 IU formulation of somatropin initially approved for marketing in Korea) has gained regulatory approval in 12 countries worldwide (Brazil, Chile, Colombia, Egypt, India, Indonesia, Iraq, Korea, Pakistan, Syria, Thailand, and Venezuela) and is marketed in all of them. From 1992-2004, an estimated [redacted] b(4) vials have been sold, providing approximately 12 years of human exposure.

This NDA includes data from 5 completed clinical trials (BP-EU-003, BP-EU-002, TS-KOR-06102005, HGCL-001, and BP-EU-001) to support the proposed labeling for Valtropin®. Except for BP-EU-001 which was a Phase I bioavailability study, all others were Phase III studies to evaluate the efficacy and safety of Eutropin™. The BP-EU-003 study is to seek approval for Indication A, the BP-EU-002 and TS-KOR-06102005 studies for Indication B, and the HGCL-001 study for Indication C. The 3 studies for Indications A and B were the children studies and were reviewed in this report (see the designs highlighted below). Another FDA statistician, Jim Gebert, reviewed the adult study, HGCL-001 for Indication C.

Protocol (Indication) Locations	Study Design (No. Randomized)	Age/Gender/ Race	Primary Endpoint
BP-EU-003 (A) 11 countries 23 centers European sites: 98.66% USA sites: 1.34%	A randomized, double-blind, active-controlled (Humatrope), 12-month, multicenter, Phase III non-inferiority study, conducted in children with short stature and growth hormone deficiency (149)	3.20 – 11.99 years (Mean = 8.22) Male: 67.79% Female: 32.21% Caucasian: 94.6% Others: 5.4%	Height velocity at Month 12
BP-EU-002 (B) 1 center (in Moscow)	An uncontrolled, open, single-arm, 12-month, single-center (in Russia), Phase III study, conducted in children with Turner Syndrome (30)	2.53 – 9.83 years (Mean = 6.93) Female: 100% Caucasian: 100%	Change from baseline in height velocity at Month 12
TS-KOR-06102005 (B) 4 centers	An uncontrolled, open, single-arm, 12-month, multi-center (in Korea), Phase III study, conducted in children with Turner Syndrome (60)	1.70 – 16.40 years (Mean = 11.00) Female: 100% Asian: 100%	Change from baseline in height velocity at Month 12

2.2 Data Sources

All the raw and derived data sets are in the EDR \\Cdsesub1\n21905\N_000\2005-10-30\crt\datasets. There were no data definition files (define.pdf) in this submission and a lot of redundant or unnecessary information were included in the data files. In addition, for the BP-EU-003 study, there was revision of data not incorporated in the data sets submitted. In response to this reviewer's request, a data definition file and a concise efficacy file for the BP-EU-003 study were received on 06/27/2006 via e-mail. However, the quality of the concise data set was still not satisfactory. The study reports this reviewer reviewed are under Indication A, Indication B, and Indication C folders of \\Cdsesub1\n21905\N_000\2005-10-30\clinstat.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy for Indication A: Children with Growth Hormone Deficiency

3.1.1 Study Design and Endpoints

Protocol BP-EU-003 (10/2001 – 12/2003) was a Phase III, 1-year, randomized, double-blind, 2-parallel-group, active-controlled, multi-center, international study, conducted in children aged 3 to 11 years with short stature and growth hormone deficiency (GHD). Patients were stratified by pre-treatment status (treatment naïve or treatment free at least 2 years), and then were randomized in a 2:1 ratio to receive either Eutropin™ or Humatrope® (the active comparator).

The primary objective was to demonstrate that the mean height velocity observed after 12 months of treatment with Eutropin™ was non-inferior to that seen after 12 months of treatment with Humatrope®. Efficacy assessments included height velocity (HV), height velocity standard deviation score for chronological age (HVSDS CA), height, height standard deviation score for chronological age (HSDS CA), height standard deviation score for bone age (HSDS BA), predicted adult height SDS, ratio of change in bone age to change in chronological age, body weight, IGF-1, and IGFBP-3. According to Amendment No. 2 of the sponsor's statistical analysis plan, the height velocity standard deviation score was calculated based on the reference data of Prader et al. and the height standard deviation score was calculated based on growth charts of the Center for Disease Control (CDC).

The primary efficacy variable was height velocity (HV) at 12 months. The pre-treatment and Month 12 height velocities of each patient were calculated using separate linear regressions of height against time based on the exact dates at which heights were recorded (see Appendix I for examples given by the sponsor). Although observed data, i.e., ((post-treatment height – Month 0 height)/(post-treatment visit date – Month 0 visit date)) × 365.25, are not reported, means were similar to regression-based estimates. The pre-treatment heights included all

measurements taken during the pre-screening period, at Visit 1 (screening), and at Visit 2 (baseline). The on-treatment heights were collected at Months 3, 6, 9, and 12 time points.

Accounting for 20% of randomized subjects not available for the per-protocol analysis set, using a 2 cm/year non-inferiority margin (the sponsor defined) and a 2.5 SD for a 1-sided 2.5% significance level test, 111 randomized subjects (74 Eutropin™ and 37 Humatrope®) was expected to provide at least 90% power for the study.

3.1.2 Statistical Methods

The mean HV at Month 12 was analyzed by ANCOVA techniques using treatment and country as the main factors and chronological age, pre-treatment HV, and log maximum GH level after stimulation as the covariates (the sponsor's model). Since there were very few patients in the USA and Latvia sites, the subjects from these 2 countries were grouped together for analyses. Also, since there were only 3 patients in the Eutropin group and 0 in the Humatrope group receiving rhGH treatment prior entering the study, the stratifying factor (pre-treatment status: treatment naïve or treatment free at least 2 years) was not included in the model. Based on the medical reviewer's request, an additional analysis including baseline height SDS in the ANCOVA model was also conducted. The non-inferiority of Eutropin™ to Humatrope® was determined if the lower bound of the 95% confidence interval of the treatment difference (Eutropin – Humatrope) was > -2 cm/year. A paired t-test was performed for the Eutropin group to examine if growth rate after 12 months of treatment was significantly improved over that at baseline.

The sponsor defined the full analysis set (intention-to-treat) population as all randomized subjects who received at least 1 dose of trial medication and had at least 1 follow-up data for the primary efficacy variable, and defined the per-protocol (PP) population as all full analysis set subjects with no major protocol violations, incomplete documentation, and/or premature termination not related to study medication. Last-observation-carried-forward (LOCF) approach was used for subjects who withdrew early. The sponsor's primary analysis population was the PP population for the reason that the use of a full analysis set for demonstrating non-inferiority is considered by many to be not conservative. Based on our past experience with no consistent evidence of ITT (intention-to-treat) analysis showing less conservative results than PP analysis, the ITT population (which best preserves the randomization) was then chosen to be the primary analysis population in this review.

3.1.3 Subject Disposition

A total of 149 subjects were randomized: 99 and 50 subjects for the Eutropin and Humatrope groups, respectively. The overall withdrawal rate by Month 12 was 6.7% (= 10/149, Table 1). Withdrawn consent was the most common recorded reason for withdrawal in this trial.

Of the 149 randomized subjects, 86.6% (= 129/146) of them were included in the ITT population: 88 and 41 for the Eutropin and Humatrope groups, respectively. Patients who did not have height measured with a wall-mounted stadiometer, did not have valid or complete previous height velocity data, and/or did not reach at least Visit 4 (Month 6) were excluded from the ITT population.

Table 1 – Study BP-EU-003: Subject Disposition

	Eutropin	Humatrope	Total
Number of randomized subjects	99	50	149
Number of completers at Month 12	93 (93.9%)	46 (92.0%)	139 (93.3%)
Number of withdrawals by Month 12	6 (6.1%)	4 (8.0%)	10 (6.7%)
Intolerable adverse events	2	1	3
Lack of compliance	2	2	4
Withdrawn consent	3	3	6
Violation of exclusion criterion	1	0	1

Note: Multiple reasons for withdrawal were found in some subjects.

3.1.4 Demographic and Baseline Characteristics

No statistically significant differences in age, weight, height, height SDS for chronological age, height velocity, height velocity SDS for chronological age, and predicted adult height at screening or Month 0 (baseline) were observed between the Eutropin and Humatrope groups (Table 2). Subject distributions in gender, race, and country were also similar between the 2 study groups.

The mean age at entry was approximately 8 years. The number of male subjects was about twice as many as the number of female subjects in each group. The majority of subjects were Caucasian (95%). The growth rate of those children with short stature and GHD before entering the study, measured by height SDS for chronological age (mean = -3.43) and height velocity SDS (mean = -2.52), was lower than that of normal children of the same age and gender. The mean height velocity at baseline was 3.34 cm/year.

Table 2 – Study BP-EU-003: Demographic and Baseline Characteristics of All Randomized Subjects

Characteristic		Eutropin	Humatrope	Total
Age (year):	Mean ± SD	8.10 ± 2.08 (98)	8.45 ± 1.99 (49)	8.22 ± 2.05 (147)
	Median	8.36	8.28	8.28
	Range	3.97 – 11.67	3.20 – 11.99	3.20 – 11.99
Gender:	Male (%)	69 (69.70)	31 (62.00)	101 (67.79)
	Female (%)	30 (30.30)	19 (38.00)	48 (32.21)
Race:	Asian (%)	2 (2.02)	1 (2.0)	3 (2.01)
	Caucasian (%)	94 (94.95)	47 (94.0)	141 (94.63)

	Negroid (%)	2 (2.02)	0 (0.0)	2 (1.34)
	Other (%)	1 (1.01)	2 (4.0)	3 (2.01)
Weight (kg):	Mean ± SD	18.64 ± 5.18 (99)	19.85 ± 4.82 (50)	19.04 ± 5.08 (149)
	Median	18.5	19.35	18.5
	Range	10.0 – 37.8	9.8 – 34.2	9.8 – 37.8
Height (cm):	Mean ± SD	107.28 ± 11.80 (99)	110.63 ± 10.94 (50)	108.41 ± 11.6 (149)
	Median	106.7	111.5	109.1
	Range	79.2 – 127.1	81.6 – 133.13	79.2 – 133.13
Height SDS for Chronological Age:				
	Mean ± SD	-3.52 ± 1.25 (99)	-3.24 ± 1.03 (50)	-3.43 ± 1.19 (149)
	Median	-3.26	-3.01	-3.16
	Range	-8.07 – -2.07	-6.95 – -1.77	-8.07 – -1.77
Height Velocity (cm/year):				
	Mean ± SD	3.40 ± 1.52 (98)	3.23 ± 1.19 (49)	3.34 ± 1.42 (147)
	Median	3.42	3.31	3.32
	Range	0.17 – 8.94	0 – 5.74	0 – 8.94
Height Velocity for Chronological Age:				
	Mean ± SD	-2.49 ± 1.93 (98)	-2.57 ± 1.46 (49)	-2.52 ± 1.78 (147)
	Median	-2.06	-2.29	-2.12
	Range	-6.89 – 3.18	-5.97 – -0.19	-6.89 – 3.18
Predicted Adult Height 1:				
	Mean ± SD	162.03 ± 9.50 (34)	160.14 ± 8.06 (21)	161.31 ± 8.95 (55)
	Median	162.46	162.94	162.86
	Range	144.58 – 184.12	143.04 – 169.55	143.04 – 184.12
Predicted Adult Height 2:				
	Mean ± SD	158.53 ± 6.84 (99)	159.85 ± 7.16 (50)	158.97 ± 6.95 (149)
	Median	159.23	161.56	159.74
	Range	137.90 – 169.39	139.20 – 171.50	137.90 – 171.50
Country:	Belorussia (%)	6 (6.06)	3 (6.0)	9 (6.04)
	Morocco (%)	6 (6.06)	5 (10.0)	11 (7.38)
	Poland (%)	8 (8.08)	4 (8.0)	12 (8.05)
	Russia (%)	23 (23.23)	10 (20.0)	33 (22.15)
	Serbia (%)	9 (9.09)	4 (8.0)	13 (8.72)
	Slovakia (%)	5 (5.05)	1 (2.0)	6 (4.03)
	South Africa (%)	5 (5.05)	2 (4.0)	7 (4.70)
	Turkey (%)	21 (21.21)	11 (22.0)	32 (21.48)
	USA (%)	0 (0.0)	2 (4.0)	2 (1.34)
	Latvia (%)	2 (2.02)	1 (2.0)	3 (2.01)
	Ukraine (%)	14 (14.14)	7 (14.0)	21 (14.09)

Age, height, height SDS for chronological age (CA), weight, and predicted adult heights here were from the screening visit (Visit 1). Height velocity and its SDS here were from the baseline visit (Visit 2, Month 0).

Predicted adult height 1 was calculated based on Bayley and Pinneau method. Predicted adult height 2 was calculated based on Roche, Wainer, and Thissen method.

3.1.5 Efficacy Results and Discussion

Height Velocity (HV). As Table 3 shows, the mean height velocity in both the Eutropin and Humatrope groups were increased from approximately 3 cm/year at baseline to 11 cm/year at Month 12. The least-squares means (adjusted for country, baseline HV, chronological age, and log maximum GH level) at Month 12 were 11.21 and 11.00 cm/year for the Eutropin and Humatrope groups, respectively, with a treatment difference of 0.21 cm/year in favor of Eutropin. According to the lower limit of the 95% confidence interval of the treatment difference, Eutropin was shown to be non-inferior to Humatrope since -0.48 cm/year was greater than -2 cm/year (the non-inferiority margin). In fact, Eutropin was also shown to be equivalent to Humatrope in promoting the growth effect since the whole 95% confidence interval, (-0.48, 0.90), was lying entirely within the margin of ±2 cm/year. Similar findings were also observed when baseline height SDS was included in the statistical model as the 4th covariate. Appendix IV shows the distribution of Month 12 height velocity in each group.

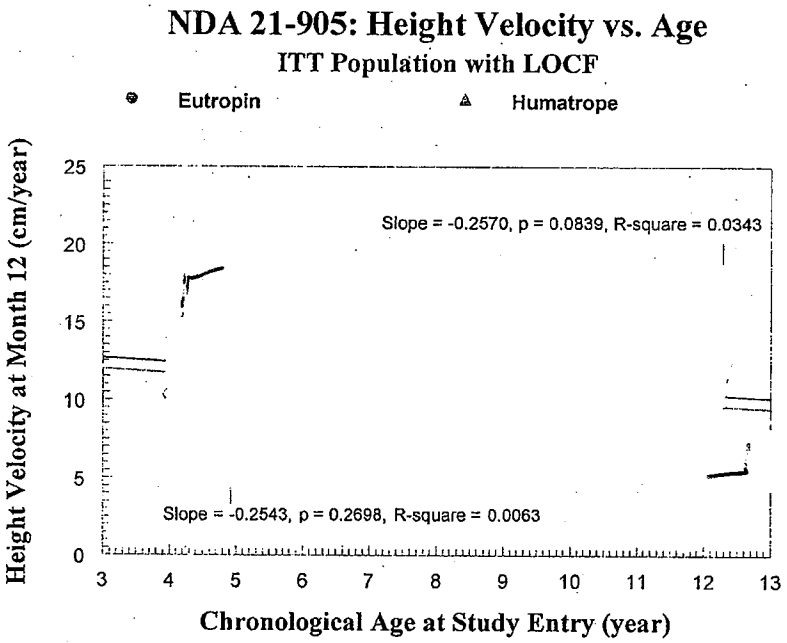
Table 3 – Study BP-EU-003: Results for Height Velocity (cm/year)

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
0	3.4958 ± 1.4501 (88)	3.3867 ± 1.0183 (41)			
12 LOCF	11.3614 ± 2.922 (88)	10.5381 ± 2.606 (41)	7.8656 ± 3.2847 (88)	<0.0001	(7.1793, 8.5519)
Eutropin vs. Humatrope: Least-squares mean height velocity ± standard error (N) using the sponsor's model					
12 LOCF	11.2098 ± 0.231 (88)	10.9982 ± 0.315 (41)	Treatment Difference = 0.2116 ± 0.3468	0.5430	(-0.4754, 0.8985)
Eutropin vs. Humatrope: Least-squares mean height velocity ± standard error (N) using the sponsor's model + baseline height SDS as the 4th covariate					
12 LOCF	11.1736 ± 0.228 (88)	10.9606 ± 0.310 (41)	Treatment Difference = 0.2130 ± 0.3412	0.5337	(-0.4629, 0.8890)

Note: Pre-treatment and Month 12 height velocities of each patient were calculated using separate linear regressions of height against time based on the exact dates at which heights were recorded.

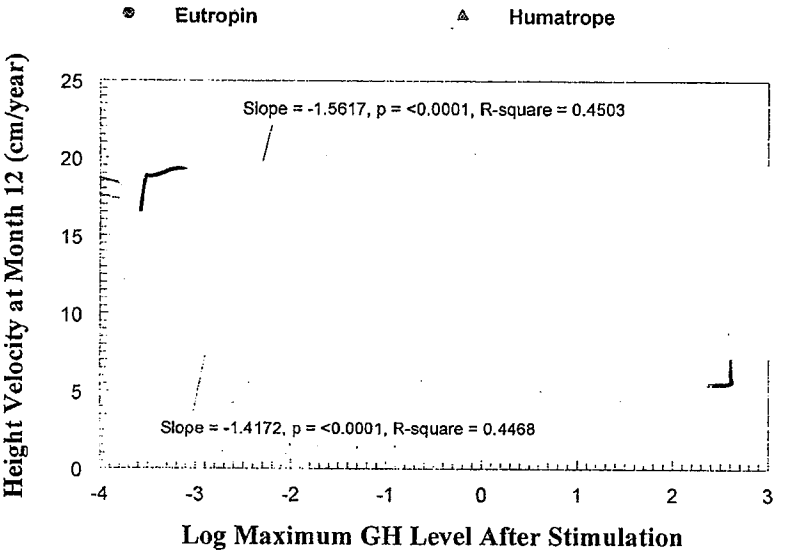
Figures 1, 2, and 3 present fitted regression lines of height velocity at Month 12 (at y-axis) against chronological age at study entry, log maximum GH level after stimulation, and baseline height SDS (at x-axis), respectively. In those graphs, negative correlations between the Month 12 HV data and covariates were seen. In other words, subjects who were younger at entry, had smaller log maximum GH level after stimulation, or had lower baseline height SDS, tended to have greater height velocity after 12 months of growth hormone treatment. Particularly, the negative relationship was statistically significant in the cases of log maximum GH level and baseline height SDS.

Figure 1



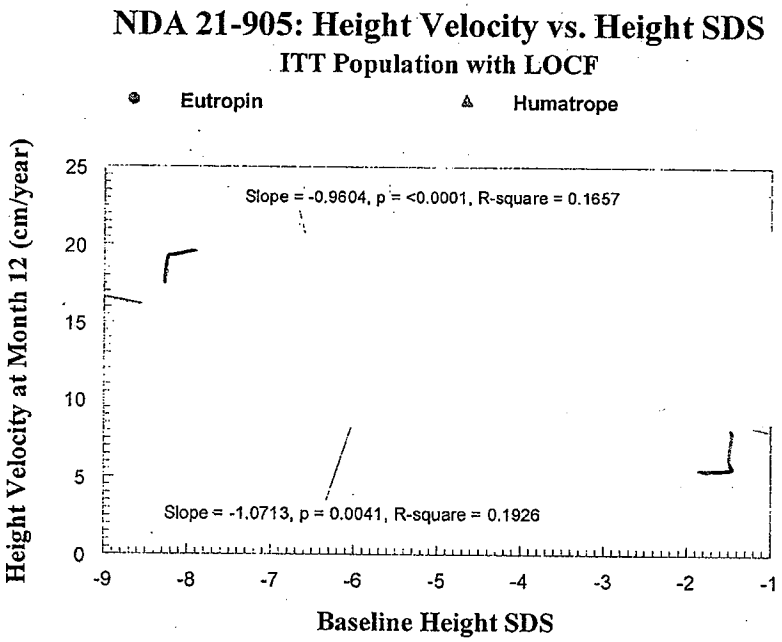
b(4)

Figure 2



b(4)

Figure 3



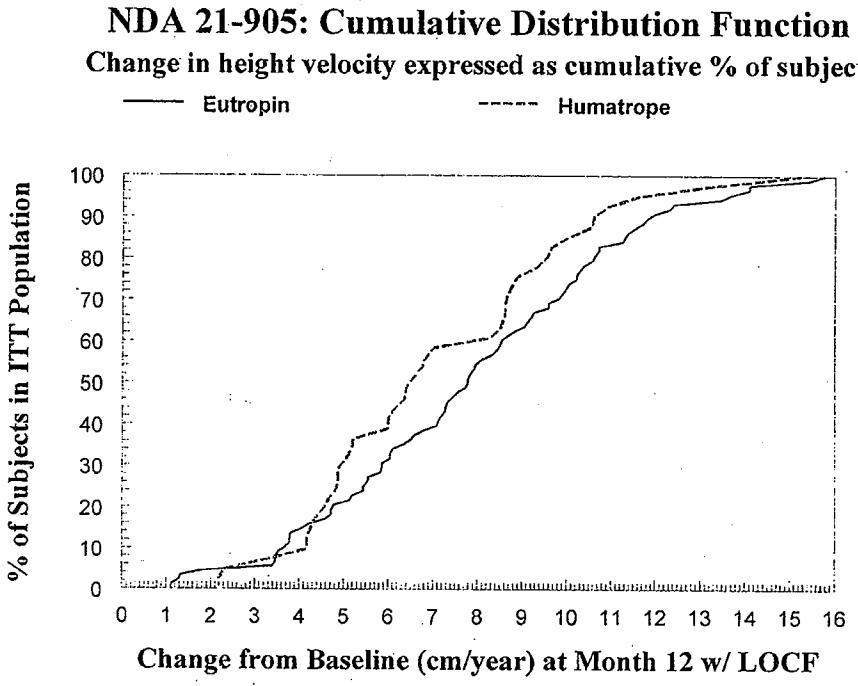
b(4)

The paired t-test result (Table 3) showed that after 12 months of treatment with Eutropin, the mean height velocity (11.36 cm/year, LOCF) of children with short stature and GHD was significantly increased over that at baseline (3.50 cm/year, N = 88).

As depicted in Figure 4, all the 88 ITT subjects in the Eutropin group responded to the treatment at the end of the 12-month trial (change from baseline in HV at Month 12 > 0) and also showed more than 1 cm increase from baseline. In addition, 84 of them (95.5% = 84/88) had >2 cm/year increment. The figure also presents that the Eutropin curve showed more efficacy than the Humatrope one for almost any percentage of subjects, even though the 2 curves had similar profiles. Note that one can easily obtain the % of subjects achieving a given level of response for any definition of responders from Figure 4.

The analyses based on the PP population and completers revealed similar findings to the ones based on the ITT population.

Figure 4



Height Velocity Standard Deviation Score for Chronological Age (HVSDS CA). The mean height velocity standardized scores in both the Eutropin and Humatrope groups were reversed from negative values at baseline to positive values at all post-treatment time points (Table 4), indicating that under the growth hormone treatments, the rates of growth of children with short stature and GHD became higher than that of normal children of the same age and gender. In the Eutropin group, the largest standardized difference in height velocity between the growth hormone treated children and the normal age- and gender-matched children occurred at Month 3, and then the differences were gradually decreased as the treatment continued throughout the rest of the 12-month treatment trial.

No significant difference in the adjusted mean HVSDS at Month 12 was observed between the Eutropin and Humatrope groups, indicating that the growth rates of the 2 study groups, relative to that of the normal children of the same age and gender, may be comparable over a 12-month treatment period. However, it is worth noting that the adjusted mean HVSDS at Month 12 in the Eutropin group was slightly smaller than that in the Humatrope group (treatment difference -0.2913), and it could be smaller by as much as 1.1884 according to the 95% lower confidence limit.

Table 4 – Study BP-EU-003: Results for Height Velocity Standard Deviation Score for Chronological Age

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
0	-2.3387 ± 1.783 (88)	-2.4081 ± 1.304 (41)			
3	6.2381 ± 3.4845 (88)	5.3580 ± 3.3806 (41)	8.5768 ± 4.2792 (88)	<0.0001	(7.6827, 9.4709)
6	6.0487 ± 3.4355 (88)	5.4227 ± 3.5042 (41)	8.3875 ± 4.2746 (88)	<0.0001	(7.4944, 9.2806)
9	5.8985 ± 3.4451 (86)	5.2271 ± 3.4691 (41)	8.2665 ± 4.2788 (86)	<0.0001	(7.3622, 9.1708)
12	5.7386 ± 3.4649 (86)	5.2290 ± 3.6407 (41)	8.1066 ± 4.2946 (86)	<0.0001	(7.1989, 9.0143)
12 LOCF	5.7077 ± 3.4397 (88)	5.2290 ± 3.6407 (41)	8.0464 ± 4.2658 (88)	<0.0001	(7.1551, 8.9377)
Eutropin vs. Humatrope: Least-squares mean height velocity SDS ± standard error (N) using the sponsor's model					
12 LOCF	5.5864 ± 0.3009 (88)	5.8777 ± 0.4106 (41)	Treatment Difference = -0.2913 ± 0.4529	0.5213	(-1.1884, 0.6057)

The paired t-test results showed that after 12 months of treatment with Eutropin, the mean height velocity SDS (5.71, LOCF) of children with short stature and GHD was significantly increased over that at baseline (-2.34, N = 88).

Height Standard Deviation Score for Chronological Age (HSDS CA). The decreasing negative scores over time in both the Eutropin and Humatrope groups (Table 5) indicate that the standardized differences in height between the growth hormone treated children and the normal age- and gender-matched children were decreased over time. In other words, the heights of children with short stature and GHD under either growth hormone 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.

No significant difference in the adjusted mean HSDS for chronological age at Month 12 was observed between the Eutropin and Humatrope groups, indicating that the 2 study groups, relative to the normal children of the same age and gender, may be comparable in inducing growth over a 12-month treatment period. Although the adjusted mean HSDS for chronological age at Month 12 in the Eutropin group was slightly larger than that in the Humatrope group (treatment difference 0.0236), it could actually be smaller by as much as 0.1124 according to the 95% lower confidence limit.

The paired t-test results showed that after 12 months of treatment with Eutropin, the mean height SDS for chronological age (-2.33, LOCF) of children with short stature and GHD was significantly increased over that at baseline (-3.54, N = 88). All the 88 ITT subjects in the

Eutropin group responded to the treatment at the end of the 12-month trial (change from baseline in HSDS CA at Month 12 > 0) and 86 of them (97.7% = 86/88) showed more than 0.25 standardized score increase from baseline.

Table 5 – Study BP-EU-003: Results for Height Standard Deviation Score for Chronological Age

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Baseline (Month 0)		
			Mean ± SD (N)	p-value	(LCL, UCL)
0	-3.5361 ± 1.238 (88)	-3.3458 ± 1.068 (41)			
3	-3.1085 ± 1.128 (88)	-2.9704 ± 1.038 (41)	0.4276 ± 0.2428 (88)	<0.0001	(0.3769, 0.4783)
6	-2.7857 ± 1.068 (88)	-2.6860 ± 0.928 (41)	0.7504 ± 0.3907 (88)	<0.0001	(0.6688, 0.8320)
9	-2.5381 ± 1.045 (86)	-2.4569 ± 0.888 (41)	1.0214 ± 0.5060 (86)	<0.0001	(0.9145, 1.1283)
12	-2.3340 ± 1.022 (86)	-2.2974 ± 0.859 (41)	1.2255 ± 0.6318 (86)	<0.0001	(1.0920, 1.3590)
12 LOCF	-2.3270 ± 1.013 (88)	-2.2974 ± 0.859 (41)	1.2091 ± 0.6340 (88)	<0.0001	(1.0766, 1.3416)
Eutropin vs. Humatrope: Least-squares mean height SDS for CA ± standard error (N) using the sponsor's model					
12 LOCF	-2.3082 ± 0.046 (88)	-2.3318 ± 0.062 (41)	Treatment Difference = 0.0236 ± 0.0686	0.7319	(-0.1124, 0.1595)

Height Standard Deviation Score for Bone Age (HSDS BA). After 12 months of treatment with Eutropin, the mean height SDS for bone age (-0.0033) of children with short stature and GHD was increased, but not significantly based on the paired t-test, over that at screening (-0.1637, N = 86). Similar findings were also observed for the Humatrope group.

No significant difference in the adjusted mean HSDS for bone age at Month 12 was observed between the Eutropin and Humatrope groups (Table 6).

Table 6 – Study BP-EU-003: Results for Height Standard Deviation Score for Bone Age

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Screening		
			Mean ± SD (N)	p-value	(LCL, UCL)
Screen	-0.1850 ± 1.460 (88)	-0.1907 ± 1.373 (41)			
12	-0.0033 ± 1.816 (86)	-0.0531 ± 1.326 (41)	0.1604 ± 1.3234 (86)	0.2642	(-0.1193, 0.4401)
Eutropin vs. Humatrope: Least-squares mean height SDS for BA ± standard error (N) using the sponsor's model					
12	-0.0828 ± 0.154 (86)	-0.0584 ± 0.208 (41)	Treatment Difference = -0.0244 ± 0.2297	0.9156	(-0.4795, 0.4307)

Bone Maturation. Bone maturation during the 12 months of treatment was calculated as ratio of change from screening in bone age to change from screening in chronological age. The mean ratios of children with short stature and GHD were 1.5329 and 1.4717 for the Eutropin and Humatrope groups, respectively. As Table 7 shows, no significant difference in the adjusted mean ratio of change in bone age to change in chronological age at Month 12 was observed between the 2 study groups.

Table 7 – Study BP-EU-003: Results for Bone Maturation

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	Treatment Difference Mean ± SE	p-value	(LCL, UCL)
12	1.5329 ± 0.8933 (86)	1.4717 ± 0.7162 (41)			
Eutropin vs. Humatrope: Least-squares mean bone maturation ± standard error (N) using the sponsor's model					
12	1.5143 ± 0.1088 (86)	1.4917 ± 0.1467 (41)	0.0227 ± 0.1621	0.8891	(-0.2984, 0.3437)

Predicted Adult Height. After 12 months of treatment with Eutropin, the mean predicted adult height, calculated by using the tables of Bayley and Pinneau, was significantly increased over that at screening (mean change = 3.5055 cm, N = 32). As Table 8 shows, no significant difference in the adjusted mean predicted adult height at Month 12 was observed between the Eutropin and Humatrope groups, indicating that the 2 study groups may be comparable in stimulating growth over a 12-month treatment period.

Table 8 – Study BP-EU-003: Results for Predicted Adult Height (Bayley and Pinneau Method)

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Screening		
			Mean ± SD (N)	p-value	(LCL, UCL)
Screen	162.00 ± 9.6418 (33)	160.64 ± 8.2813 (15)			
12	163.74 ± 12.676 (58)	163.83 ± 11.640 (31)	3.5055 ± 5.5946 (32)	0.0013	(1.5671, 5.4439)
Eutropin vs. Humatrope: Least-squares mean predicted adult height ± standard error (N) using the sponsor's model					
12	165.59 ± 1.1404 (32)	166.07 ± 1.6504 (15)	Treatment Difference = -0.4830 ± 1.8343	0.7939	(-4.2109, 3.2448)

In the Eutropin group, Months 0 and 12 mean ± SD for N = 32 were 162.27 ± 9.6746 and 165.77 ± 10.0039, respectively.

Predicted Adult Height SDS. After 12 months of treatment with Eutropin, the mean predicted adult height SDS, calculated by using the tables of Bayley and Pinneau, was significantly increased over that at screening (mean change = 0.4895, N = 32). As Table 9 shows, no significant difference in the adjusted mean predicted adult height SDS at Month 12 was observed between the Eutropin and Humatrope groups.

Table 9 – Study BP-EU-003: Results for Predicted Adult Height SDS (Bayley and Pinneau Method)

ITT Month	Eutropin Mean ± SD (N)	Humatrope Mean ± SD (N)	**Eutropin**: Change from Screening		
			Mean ± SD (N)	p-value	(LCL, UCL)
Screen	-1.7025 ± 1.079 (33)	-1.8083 ± 0.676 (15)			
12	-1.3493 ± 1.460 (58)	-1.2101 ± 1.046 (31)	0.4895 ± 0.7822 (32)	0.0013	(0.2185, 0.7605)
Eutropin vs. Humatrope: Least-squares mean predicted adult height SDS ± standard error (N) using the sponsor's model					
12	-1.2446 ± 0.148 (32)	-1.1474 ± 0.215 (15)	Treatment Difference = -0.0972 ± 0.2368	0.6840	(-0.5785, 0.3841)

In the Eutropin group, Months 0 and 12 mean ± SD for N = 32 were -1.7087 ± 1.096 and -1.2192 ± 1.079, respectively.

For all efficacy variables discussed above, the least-squares mean changes from baseline or screening at Month 12 were tabulated in the Appendix III, as requested by the reviewing medical officer.

3.2 Evaluation of Efficacy for Indication B: Children with Turner Syndrome

3.2.1 Study Design and Endpoints

Protocol BP-EU-002 (11/2001 – 11/2003)

This study was a Phase III, 1-year, open-label, single-arm, single-center (in Moscow, Russia) trial to evaluate the efficacy and safety of Eutropin™ in girls aged 2 to 9 years with short stature associated with Turner Syndrome. Efficacy assessments included height velocity (HV), height velocity standard deviation score for chronological age (HVSDS CA), height, height standard deviation score for chronological age (HSDS CA), height standard deviation score for bone age (HSDS BA), predicted adult height, ratio of change in bone age to change in chronological age, body weight, IGF-1, and IGFBP-3. According to Amendment No. 2 of the sponsor's statistical analysis plan, the height velocity standard deviation score was calculated based on the reference data of Prader et al. and the height standard deviation score was calculated based on growth charts of the Center for Disease Control (CDC).

The primary efficacy variable was height velocity (HV) at 12 months compared to the pre-treatment period, which included all measurements taken during the pre-screening period, at Visit 1 (screening), and at Visit 2 (baseline). The pre-treatment and Month 12 height velocities of each patient were calculated using separate linear regressions of height against time based on the exact dates at which heights were recorded (see Appendix I for examples given by the sponsor). Although observed data, i.e., ((post-treatment height – Month 0 height)/(post-treatment visit date – Month 0 visit date)) × 365.25, are not reported, means

were similar to regression-based estimates. The on-treatment heights were collected at Months 3, 6, and 12 time points.

Protocol TS-KOR-06102005 (01/1995 – 07/1997)

This study was a Phase III, 1-year, open-label, single-arm, multi-center (in Korea) trial to evaluate the efficacy and safety of Eutropin™ in girls aged below 14 years with short stature associated with Turner Syndrome. Efficacy assessments included height velocity (HV), height standard deviation score (HSDS), ratio of height age to bone age, weight SDS for chronological age, weight SDS for height, and IGF-1. The height standard deviation score was calculated based on the Korean Pediatric Society height standards. The on-treatment heights were collected at Months 3, 6, 9, and 12 time points. All height-related endpoints were calculated directly from the observed data. Appendix II gives clarification regarding how pre-treatment height velocity was calculated.

3.2.2 Statistical Methods

Protocol BP-EU-002 (11/2001 – 11/2003)

Since the sample size was small, a paired t-test (parametric method) and a Wilcoxon signed rank test (non-parametric method) were performed to examine if growth rate after 12 months of treatment was significantly improved over that at baseline. The primary analysis population for efficacy was the full analysis set (intention-to-treat) population comprising all subjects who received at least 1 dose of trial medication and had follow-up data for at least 1 efficacy variable. Last-observation-carried-forward (LOCF) approach was used for subjects who withdrew early.

Protocol TS-KOR-06102005 (01/1995 – 07/1997)

The sponsor's efficacy analysis was performed on the per-protocol (PP) population. This review used the intention-to-treat (ITT) population that comprised all subjects who received at least 1 dose of trial medication as the primary analysis set. As for the BP-EU-002 study, a paired t-test (parametric method) and a Wilcoxon signed rank test (non-parametric method) were performed to examine if growth rate after 12 months of treatment was significantly improved over that at baseline. Last-observation-carried-forward (LOCF) approach was used for subjects who withdrew early.

3.2.3 Subject Disposition

Protocol BP-EU-002 (11/2001 – 11/2003)

A total of 30 subjects were enrolled in this study and 29 of them completed the 12-month trial (1 subject withdrew her consent at Month 6 visit). All 30 subjects were included in the ITT population.

Protocol TS-KOR-06102005 (01/1995 – 07/1997)

A total of 60 subjects were enrolled in this study and 50 of them completed the 12-month trial. The reasons for withdrawal were as follows: inclusion criteria violation (2 patients), lost to follow-up (6 patients), poor compliance (1 patient), and early discontinuation by sponsor (1 patient). All 60 subjects were included in the ITT population.

3.2.4 Demographic and Baseline Characteristics

Protocol BP-EU-002 (11/2001 – 11/2003)

All subjects were female and Caucasian in this study. The mean age at entry was about 7 years and average height was 107.5 cm. The growth rate of those Turner Syndrome girls before entering the study, measured by height SDS for chronological age (mean = -2.34) and height velocity SDS (mean = -2.39), was lower than that of normal children of the same age. The mean height velocity at baseline was 3.75 cm/year.

Table 10 – Study BP-EU-002: Demographic and Baseline Characteristics of All Subjects

	Age (year)	Height (cm)	Height SDS for CA	Weight (kg)	Bone Age (year)	Height Velocity (cm/year)	Height Velocity SDS CA	Predicted Adult Height 1	Predicted Adult Height 2
N	30	30	30	30	30	30	30	14	30
Mean	6.9304	107.5133	-2.3443	19.1867	5.05	3.7503	-2.3938	151.97	158.23
Std	2.1863	10.8726	0.9148	4.9894	2.1774	1.7595	1.8979	5.23	3.52
Min	2.5270	84.50	-4.9755	11.50	1.50	1.4440	-5.5360	142.25	149.49
Median	6.9843	109.55	-2.2399	19.30	5.25	3.4034	-2.6565	152.19	157.79
Max	9.8261	123.65	-1.0914	29.50	7.83	8.6443	2.0081	162.70	167.00

Age, height, height SDS for chronological age (CA), weight, bone age, and predicted adult heights here were from the screening visit (Visit 1). Height velocity and its SDS here were from the baseline visit (Visit 2, Month 0).

Predicted adult height 1 was calculated based on Bayley and Pinneau method. Predicted adult height 2 was calculated based on Roche, Wainer, and Thissen method.

Protocol TS-KOR-06102005 (01/1995 – 07/1997)

There were 4 centers in this study. All subjects were female and Korean. The mean age at entry was 11 years and average height was about 122 cm. The height of those Turner Syndrome girls before entering the study, measured by height SDS (mean = -2.99), was lower than that of normal children of the same age. The mean height velocity at baseline was 3.48 cm/year. There was no height velocity SDS computed for this study.

Table 11 – Study TS-KOR-06102005: Demographic and Baseline Characteristics of All Subjects

	Age (year)	Height (cm)	Height SDS	Height Velocity (cm/year)	Weight (kg)	Bone Age (year)
N	60	60	60	58	59	59
Mean	11.0083	122.3533	-2.9924	3.4808	31.4220	9.3726
Std	3.1477	15.2213	0.9538	1.3982	9.9803	2.9036
Min	1.70	71.40	-5.1192	0.3400	13.00	3.00
Median	11.85	126.65	-2.9171	3.6000	33.00	10.00
Max	16.40	151.20	-0.8306	6.3273	62.00	14.50

3.2.5 Efficacy Results and Discussion

Protocol BP-EU-002 (11/2001 – 11/2003)

Height Velocity (HV). Both the paired t-test and Wilcoxon signed rank test results (Table 12) showed that after 12 months of treatment with Eutropin, the mean height velocity (9.73 cm/year, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (3.75 cm/year, N = 30).

Table 12 – Study BP-EU-002: Results for Height Velocity (cm/year)

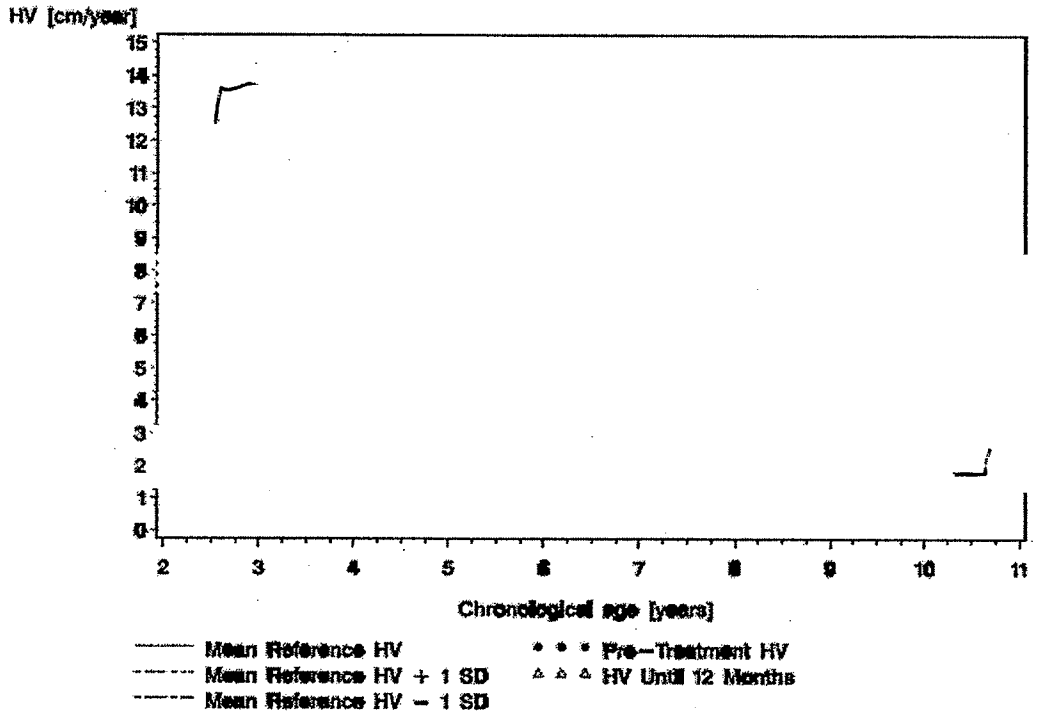
ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	3.7503 ± 1.7595 (30) Median = 3.4034			
Month 12	9.7413 ± 1.5797 (29) Median = 9.8795	5.9698 ± 2.2058 (29) Median = 6.4101	<0.0001 <0.0001	(5.1670, 6.7726)
Month 12 (LOCF)	9.7301 ± 1.5534 (30) Median = 9.8076	5.9798 ± 2.1681 (30) Median = 6.3389	<0.0001 <0.0001	(5.2040, 6.7556)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Note: Pre-treatment and Month 12 height velocities of each patient were calculated using separate linear regressions of height against time based on the exact dates at which heights were recorded.

All 30 subjects responded to the Eutropin treatment at the end of the 12-month trial (change from baseline in HV at Month 12 > 0) and also showed more than 1 cm increase from baseline. In addition, 28 of them (93.3% = 28/30) had >2 cm/year increment.

The following figure (copied from page 44 of the sponsor's clinical study report) clearly shows that all 30 subjects' height velocities at Month 12 were higher than their pre-treatment values as well as the mean reference height velocity by age complied by Prader et al.



b(4)

Height Velocity Standard Deviation Score for Chronological Age (HVSDS CA). The mean height velocity standardized score was reversed from a negative value at baseline to positive values at all post-treatment time points (Table 13), indicating that under the Eutropin treatment, the rate of growth of the Turner Syndrome girls became higher than that of normal children of the same age. Specifically, the largest standardized difference in height velocity between the Eutropin-treated children and the normal age-matched children occurred at Month 3.

Both the paired t-test and Wilcoxon signed rank test results showed that after 12 months of treatment with Eutropin, the mean height velocity SDS (3.82, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (-2.39, N = 30).

Table 13 – Study BP-EU-002: Results for Height Velocity Standard Deviation Score for Chronological Age

ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	-2.3938 ± 1.8979 (30) Median = -2.6565			
Month 3	3.9760 ± 1.7098 (30) Median = 3.9347	6.3698 ± 2.4954 (30) Median = 6.2401	<0.0001 <0.0001	(5.4768, 7.2628)
Month 6	3.7410 ± 1.7719 (30) Median = 3.2130	6.1348 ± 2.6330 (30) Median = 5.8348	<0.0001 <0.0001	(5.1926, 7.0770)
Month 12	3.8725 ± 1.9643 (29) Median = 3.3447	6.1916 ± 2.8383 (29) Median = 6.0067	<0.0001 <0.0001	(5.1586, 7.2246)
Month 12 (LOCF)	3.8219 ± 1.9500 (30) Median = 3.3149	6.2157 ± 2.7921 (30) Median = 6.0270	<0.0001 <0.0001	(5.2166, 7.2148)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Height Standard Deviation Score for Chronological Age (HSDS CA). The mean standardized difference in height between the Turner Syndrome girls treated with Eutropin and the normal age-matched children was gradually decreased over the 12-month treatment trial (Table 14). It means that the heights of those Turner Syndrome girls treated with Eutropin were gradually improved and closer to the average height of normal children of the same age over the course of the study.

Table 14 – Study BP-EU-002: Results for Height Standard Deviation Score for Chronological Age

ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	-2.4188 ± 0.9128 (30) Median = -2.3391			
Month 3	-2.0896 ± 0.9397 (30) Median = -2.0414	0.3293 ± 0.1637 (30) Median = 0.3162	<0.0001 <0.0001	(0.2707, 0.3879)
Month 6	-1.8620 ± 0.9510 (30) Median = -1.8229	0.5568 ± 0.2058 (30) Median = 0.5127	<0.0001 <0.0001	(0.4832, 0.6304)
Month 12	-1.5258 ± 0.9530 (29) Median = -1.4229	0.8948 ± 0.2670 (29) Median = 0.8877	<0.0001 <0.0001	(0.7976, 0.9920)
Month 12 (LOCF)	-1.5421 ± 0.9406 (30) Median = -1.5067	0.8768 ± 0.2804 (30) Median = 0.8834	<0.0001 <0.0001	(0.7765, 0.9771)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Both the paired t-test and Wilcoxon signed rank test results showed that after 12 months of treatment with Eutropin, the mean height SDS for chronological age (-1.54, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (-2.42, N = 30). All 30 subjects responded to the Eutropin treatment at the end of the 12-month trial (change from baseline in HSDS CA at Month 12 > 0) and also showed more than 0.1 standardized score increase from baseline.

Height Standard Deviation Score for Bone Age (HSDS BA). As shown in Table 15, after 12 months of treatment with Eutropin, the mean height SDS for bone age (0.5041) of those Turner Syndrome girls was significantly increased over that at screening (0.0882, N = 29).

Table 15 – Study BP-EU-002: Results for Height Standard Deviation Score for Bone Age

ITT	Mean ± SD (N)	Change from Screening		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Screening	0.1206 ± 1.5025 (30) Median = 0.0812			
Month 12	0.5041 ± 1.2271 (29) Median = 0.2438	0.4159 ± 0.5924 (29) Median = 0.5757	0.0008 0.0002	(0.2003, 0.6315)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Bone Maturation. Bone maturation during the 12 months of treatment was calculated as ratio of change from screening in bone age to change from screening in chronological age. The mean ratio ± SD (N) of children with Turner Syndrome was 1.0204 ± 0.3533 (29) with a median = 0.9177.

Predicted Adult Height. As shown in Table 16, after 12 months of treatment with Eutropin, the mean predicted adult height, calculated by using the tables of Bayley and Pinneau, was significantly increased over that at screening (mean change = 4.0376 cm, N = 14).

Table 16 – Study BP-EU-002: Results for Predicted Adult Height (Bayley and Pinneau Method)

ITT	Mean ± SD (N)	Change from Screening		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Screening	151.97 ± 5.2348 (14) Median = 152.19			
Month 12	157.23 ± 4.7176 (17) Median = 157.11	4.0376 ± 2.1976 (14) Median = 4.1342	<0.0001 0.0002	(2.8864, 5.1888)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Month 12 mean ± SD for N = 14 was 156.01 ± 4.2131.

Protocol TS-KOR-06102005 (01/1995 – 07/1997)

Height Velocity (HV). As Table 17 shows, the mean height velocity of the Turner Syndrome girls was increased from 3.48 cm/year at baseline to almost 8 cm/year at Month 3, and then was gradually decreased throughout the rest of the 12-month trial. Both the paired t-test and Wilcoxon signed rank test results showed that after 12 months of treatment with Eutropin, the mean height velocity (6.97 cm/year, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (3.48 cm/year, N = 58).

Table 17 – Study TS-KOR-06102005: Results for Height Velocity (cm/year)

ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	3.4808 ± 1.3982 (58) Median = 3.60			
Month 3	7.9793 ± 3.0806 (58) Median = 7.60	4.4985 ± 3.3936 (58) Median = 4.4500	<0.0001 <0.0001	(3.6251, 5.3719)
Month 6	7.8345 ± 2.4590 (58) Median = 7.30	4.4020 ± 2.7254 (57) Median = 4.5838	<0.0001 <0.0001	(3.6945, 5.1095)
Month 9	7.4222 ± 1.9226 (54) Median = 7.27	3.9695 ± 2.2582 (54) Median = 4.0919	<0.0001 <0.0001	(3.3672, 4.5718)
Month 12	7.0423 ± 1.8812 (52) Median = 7.05	3.6222 ± 2.1083 (52) Median = 3.9364	<0.0001 <0.0001	(3.0492, 4.1952)
Month 12 (LOCF)	6.9667 ± 1.8381 (58) Median = 6.85	3.4858 ± 2.1177 (58) Median = 3.4318	<0.0001 <0.0001	(2.9408, 4.0308)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

There were 57 (95% = 57/60) subjects responding to the Eutropin treatment at the end of the 12-month trial (change from baseline in HV at Month 12 > 0) and 49 subjects (81.7% = 49/60) showed more than 1 cm increase from baseline. In addition, 40 subjects (66.7% = 40/60) had >2 cm/year increment.

Height Standard Deviation Score (HSDS). As Table 18 shows, the mean standardized difference in height between the Turner Syndrome girls treated with Eutropin and the normal age-matched children was gradually decreased over the 12-month treatment trial. It means that the heights of those Turner Syndrome girls treated with Eutropin were gradually improved and closer to the average height of normal children of the same age over the course of the study.

Both the paired t-test and Wilcoxon signed rank test results showed that after 12 months of treatment with Eutropin, the mean height SDS (-2.67, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (-3.02, N = 58).

There were 48 subjects (80% = 48/60) responding to the Eutropin treatment at the end of the 12-month trial (change from baseline in HSDS at Month 12 > 0) and 44 subjects (73.3% = 44/60) showed more than 0.1 standardized score increase from baseline.

Table 18 – Study TS-KOR-06102005: Results for Height Standard Deviation Score

ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	-2.9924 ± 0.9538 (60) Median = -2.9171			
Month 3	-2.9600 ± 0.9158 (50) Median = -2.8000	0.1184 ± 0.2186 (50) Median = 0.1127	0.0004 <0.0001	(0.0578, 0.1790)
Month 6	-2.8236 ± 1.0064 (58) Median = -2.7765	0.1967 ± 0.3736 (58) Median = 0.1747	0.0002 <0.0001	(0.1006, 0.2928)
Month 9	-2.7440 ± 0.9170 (50) Median = -2.7000	0.3344 ± 0.3320 (50) Median = 0.2975	<0.0001 <0.0001	(0.2424, 0.4264)
Month 12	-2.6087 ± 1.0002 (52) Median = -2.6390	0.3891 ± 0.3912 (52) Median = 0.4254	<0.0001 <0.0001	(0.2828, 0.4954)
Month 12 (LOCF)	-2.6739 ± 0.9860 (58) Median = -2.7669	0.3464 ± 0.4383 (58) Median = 0.4146	<0.0001 <0.0001	(0.2336, 0.4592)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

Height Age/Bone Age (HA/BA). As Table 19 shows, the mean ratio of height age to bone age of the Turner Syndrome girls treated with Eutropin was gradually increased over the 12-month period. Both the paired t-test and Wilcoxon signed rank test results showed that after 12 months of treatment with Eutropin, the mean HA/BA (0.8769, LOCF) of those Turner Syndrome girls was significantly increased over that at baseline (0.8512, N = 58).

Table 19 – Study TS-KOR-06102005: Results for Height Age/Bone Age

ITT	Mean ± SD (N)	Change from Baseline (Month 0)		
		Mean ± SD (N)	p-value	95% (LCL, UCL)
Month 0	0.8528 ± 0.1452 (59) Median = 0.8250			
Month 6	0.8718 ± 0.1228 (58) Median = 0.8647	0.0206 ± 0.0768 (58) Median = 0.0277	0.0459 0.0071	(0.0008, 0.0404)
Month 12	0.8790 ± 0.1237 (52) Median = 0.8584	0.0296 ± 0.1012 (52) Median = 0.0414	0.0400 0.0070	(0.0021, 0.0571)
Month 12 (LOCF)	0.8769 ± 0.1207 (58) Median = 0.8587	0.0257 ± 0.0972 (58) Median = 0.0379	0.0491 0.0091	(0.0007, 0.0507)

The first p-value is from paired t-test and the second p-value is from Wilcoxon signed rank test.

3.3 Evaluation of Safety for Indications A and B

Safety is not the focus of this review. See Dr. Rob Perlstein's review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Indication A – Children with Growth Hormone Deficiency

No subgroup analysis for race was performed since almost 95% of the randomized subjects in the BP-EU-003 study were Caucasian.

Treatment effects on change from baseline in height velocity, height velocity SDS, and height SDS for chronological age at 12 months were consistent across the subgroups of age, as no significant treatment-by-age interactions were seen ($p > 0.10$ for all cases). Also, within the same age category, no statistical difference between the Eutropin and Humatrope groups was observed.

However, treatment effects on change from baseline in height velocity, height velocity SDS, and height SDS for chronological age at 12 months were significantly different between the males and females (treatment-by-sex interaction $p < 0.10$ for all cases). For example, as shown in Table 20, the female Eutropin-treated subjects grew significantly more rapidly than the Eutropin-treated males and Humatrope-treated females at the end of the 12-month trial.

Within either sex or any of the age subgroups shown below, the mean height velocity, height velocity SDS, and height SDS for chronological age after 12 months of Eutropin or Humatrope treatment were all significantly improved over that at baseline (all $p < 0.01$).

Table 20 – Indication A: Subgroup Analysis for Age and Sex Using ITT Population with LOCF

Study	Subgroup	Mean Change from Baseline at Month 12 ± SD (N)	
		Eutropin	Humatrope
Height Velocity	Age ≤ 4	5.5349 ± NA (1)	NA
	4 < Age ≤ 8	7.8595 ± 3.7209 (36)	6.7371 ± 3.4147 (15)
	8 < Age ≤ 12	7.9157 ± 2.9951 (51)	7.3904 ± 2.6624 (26)
	Male	7.6604 ± 3.2609 (61)	7.4643 ± 2.9121 (27)
	Female	8.3293 ± 3.3530 (27)	6.5479 ± 2.9907 (14)
Height Velocity SDS	Age ≤ 4	6.7984 ± NA (1)	NA
	4 < Age ≤ 8	9.7222 ± 4.4907 (36)	8.7612 ± 4.3593 (15)
	8 < Age ≤ 12	6.8880 ± 3.7582 (51)	6.9887 ± 4.3993 (26)
	Male	7.8217 ± 4.2107 (61)	8.0490 ± 4.8599 (27)
	Female	8.5541 ± 4.4260 (27)	6.8428 ± 3.4225 (14)
Height SDS CA	Age ≤ 4	1.2618 ± NA (1)	NA
	4 < Age ≤ 8	1.3464 ± 0.7518 (36)	1.0292 ± 0.5368 (15)
	8 < Age ≤ 12	1.1111 ± 0.5294 (51)	1.0594 ± 0.5038 (26)
	Male	1.0796 ± 0.4711 (61)	1.0553 ± 0.4806 (27)
	Female	1.5015 ± 0.8394 (27)	1.0349 ± 0.5804 (14)

Indication B – Children with Turner Syndrome

No subgroup analyses for gender and race were performed since all the study subjects were either female Caucasian (BP-EU-002 study) or female Korean (TS-KOR-06102005 study).

There was no treatment difference in change from baseline in height velocity at 12 months among the subgroups of age in the BP-EU-002 study ($p = 0.2977$), but not in the TS-KOR-06102005 study ($p = 0.0092$). As shown in Table 21, the mean change from baseline in height velocity of the subjects >12 years old in the TS-KOR-06102005 study was significantly smaller than that of the subjects ≤12 years old. No treatment difference in change from baseline in height SDS for chronological age at 12 months was observed among the subgroups of age in either of the 2 Turner Syndrome studies ($p > 0.10$ for both cases).

Except for the subgroup of ≤ 4 years in the BP-EU-002 study that did not have any significant finding ($n = 4$, small sample size, $p = 0.1250$ based on Wilcoxon signed rank test), the mean height velocity and mean height SDS for chronological age after 12 months of Eutropin treatment in any of the age subgroups shown below (Table 21) were all significantly improved over that at baseline (all $p < 0.05$).

Table 21 – Indication B: Subgroup Analysis for Age Using ITT Population with LOCF

Study	Subgroup	Mean Change from Baseline at Month 12 ± SD (N)	
		Height Velocity	Height SDS CA
BP-EU-002	Age ≤ 4	4.8826 ± 2.7506 (4)	0.6782 ± 0.4216 (4)
	4 < Age ≤ 8	6.5986 ± 2.0324 (14)	0.9762 ± 0.2914 (14)
	8 < Age ≤ 12	5.6235 ± 2.0937 (12)	0.8269 ± 0.1697 (12)
TS-KOR-06102005	4 < Age ≤ 8	4.0061 ± 1.7934 (11)	0.5798 ± 0.3600 (11)
	8 < Age ≤ 12	4.3024 ± 2.1044 (22)	0.3026 ± 0.5389 (22)
	Age > 12	2.5383 ± 1.9404 (25)	0.2823 ± 0.3424 (25)

4.2 Other Special/Subgroup Populations

Indication A – Children with Growth Hormone Deficiency

Treatment effect on height velocity at Month 12 was consistent across the subgroups of country, as no significant treatment-by-country interaction was observed (p = 0.3733).

Indication B – Children with Turner Syndrome

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

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no serious statistical issues noted by this reviewer in this submission. The collective evidence was summarized by indication as follows.

Indication A – Children with Growth Hormone Deficiency

There was only 1 study submitted for Indication A. The mean changes from baseline in height velocity, height velocity SDS, height SDS for chronological age, predicted adult height, and predicted adult height SDS at Month 12 were all highly significantly different from zero in the Eutropin group (Table 22). Specifically, the mean height velocity was increased from 3.50 cm/year at baseline to 11.36 cm/year at Month 12. Although the mean height of children with short stature and growth hormone deficiency (GHD) after 12 months of treatment with Eutropin (height SDS CA = -2.33) was still below the average height of normal children of the same age and gender, the rate of growth of those Eutropin-treated children was improved after 12 months (height velocity SDS = 5.71) and higher than that of normal age- and gender-matched children. In addition, the mean predicted adult height of those GHD children was increased from 162.27 cm at screening to 165.77 cm at Month 12 based on the Bayley and Pinneau method.

Table 22 – Collective Evidence for Indication A Using ITT Population with LOCF

Study BP-EU-003 Efficacy Variable	**Eutropin**: Mean ± SD (N)		Mean Change from Baseline	(95% C.I.)
	Month 0	Month 12		
Height Velocity (cm/year)	3.50 ± 1.45 (88)	11.36 ± 2.92 (88)	7.8656 *	(7.18, 8.55)
Height Velocity SDS	-2.34 ± 1.78 (88)	5.71 ± 3.44 (88)	8.0464 *	(7.16, 8.94)
Height SDS for Chronological Age	-3.54 ± 1.24 (88)	-2.33 ± 1.01 (88)	1.2091 *	(1.08, 1.34)
Height SDS for Bone Age	-0.16 ± 1.47 (86)	-0.003 ± 1.82 (86)	0.1604	(-0.12, 0.44)
Bone Maturation	NA	1.53 ± 0.89 (86)	NA	NA
Predicted Adult Height (BP)	162.27 ± 9.67 (32)	165.77 ± 10.0 (32)	3.5055 *	(1.57, 5.44)
Predicted Adult Height SDS (BP)	-1.71 ± 1.10 (32)	-1.22 ± 1.08 (32)	0.4895 *	(0.22, 0.76)

Except for HSDS for bone age where p = 0.2642, all p-values for the mean changes from screening or baseline at Month 12 based on the paired t-test were < 0.01 (*).

Bone maturation was calculated as ratio of change from screening in bone age at Month 12 to change from screening in chronological age at Month 12.

All the 88 ITT subjects in the Eutropin group responded to the treatment at the end of the 12-month trial (change from baseline in HV and HSDS CA at Month 12 > 0). Among them, 95.5% (= 84/88) showed more than 2 cm/year increase in HV from baseline and 97.7% (= 86/88) showed more than 0.25 height standard deviation score increase from baseline.

The observed treatment difference in height velocity between the Eutropin and Humatrope groups was 0.21 cm/year in favor of Eutropin. The associated 95% confidence interval was (-0.48, 0.90), which lied entirely within the margin of ±2 cm/year (the sponsor defined), indicating that Eutropin was non-inferior to Humatrope in improving growth for children with short stature and GHD. The 2 study groups also showed comparable results in height velocity SDS, height SDS for chronological age, height SDS for bone age, bone maturation, predicted adult height, and predicted adult height SDS.

In general, this reviewer's results based on the ITT population agree with the sponsor's conclusions based on the PP population.

Indication B – Children with Turner Syndrome

Since inclusion/exclusion criteria (particular in age at entry), study location (Russia vs. Korea), height velocity calculation method (see Appendices I and II), study period (TS-KOR-06102005 was an older study) etc., are somewhat different between the BP-EU-002 and TS-KOR-06102005 studies, this reviewer thinks that the data from the 2 clinical trials should not be combined for overall treatment estimate.

As for the findings observed in the BP-EU-003 study for Indication A, the mean changes from baseline in height velocity, height velocity SDS, height SDS for chronological age and bone age, predicted adult height, and HA/BA at Month 12, where applicable, were all highly significantly different from zero in the Eutropin group of the BP-EU-002 and TS-KOR-06102005 studies for Indication B (Table 23). Specifically, the mean height velocity was increased from 3.75 cm/year at baseline to 9.73 cm/year at Month 12 for the former study and from 3.48 cm/year to 6.97 cm/year for the latter study. Although the mean heights of children with Turner Syndrome after 12 months of treatment with Eutropin (height SDS CA = -1.54 and -2.67, respectively) were still below the average heights of normal children of the same age, the rates of growth of those Eutropin-treated children were improved after 12 months (height velocity SDS = 3.82 for the BP-EU-002 study) and higher than that of normal age-matched children. In addition, the mean predicted adult height of those Turner Syndrome children in the BP-EU-002 study was increased from 152.0 cm at baseline to 156.0 cm at Month 12 based on the Bayley and Pinneau method.

Table 23 – Collective Evidence for Indication B Using ITT Population with LOCF

Efficacy Variable	Study	Mean ± SD (N)		Mean Change from Baseline	(95% C.I.)
		Month 0	Month 12		
Height Velocity (cm/year)	BP-EU-002	3.75 ± 1.76 (30)	9.73 ± 1.55 (30)	5.9798 *	(5.20, 6.76)
	TS-KOR-06102005	3.48 ± 1.40 (58)	6.97 ± 1.84 (58)	3.4858 *	(2.94, 4.03)
Height Velocity SDS	BP-EU-002	-2.39 ± 1.90 (30)	3.82 ± 1.95 (30)	6.2157 *	(5.22, 7.21)
	TS-KOR-06102005	NA	NA	NA	NA
Height SDS for CA	BP-EU-002	-2.42 ± 0.91 (30)	-1.54 ± 0.94 (30)	0.8768 *	(0.78, 0.98)
	TS-KOR-06102005	-3.02 ± 0.96 (58)	-2.67 ± 0.99 (58)	0.3464 *	(0.23, 0.46)
Height SDS for BA	BP-EU-002	0.09 ± 1.52 (29)	0.50 ± 1.23 (29)	0.4159 *	(0.20, 0.63)
	TS-KOR-06102005	NA	NA	NA	NA
Bone Maturation	BP-EU-002	NA	1.02 ± 0.35 (29)	NA	NA
	TS-KOR-06102005	NA	NA	NA	NA
Predicted Adult Height (BP)	BP-EU-002	152.0 ± 5.23 (14)	156.0 ± 4.21 (14)	4.0376 *	(2.89, 5.19)
	TS-KOR-06102005	NA	NA	NA	NA
HA/BA	BP-EU-002	NA	NA	NA	NA
	TS-KOR-06102005	0.85 ± 0.15 (58)	0.88 ± 0.12 (58)	0.0257 *	(0.00, 0.05)

P < 0.05 (*) for all mean changes from screening or baseline at Month 12 based on the paired t-test.

CA = Chronological Age; BA = Bone Age; HA = Height Age

Bone maturation was calculated as ratio of change from screening in bone age at Month 12 to change from screening in chronological age at Month 12.

The majority of ITT subjects in the 2 Turner Syndrome studies responded to the Eutropin treatment at the end of the 12-month trial (change from baseline in HV and HSDS CA at Month 12 > 0) and also showed more than 1 cm/year increase in HV from baseline and 0.1 height standard deviation score increase from baseline (Table 24).

Table 24 – Responder Rate for Change from Baseline at Month 12 for Indication B

Study	Height Velocity (cm/year)		Height SDS	
	>0	>1	>0	>0.1
BP-EU-002	30/30 (100%)	30/30 (100%)	30/30 (100%)	30/30 (100%)
TS-KOR-06102005	57/60 (95%)	49/60 (81.7%)	48/60 (80%)	44/60 (73.3%)

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

5.2 Conclusions and Recommendations

After 12 months of treatment with Eutropin, the height, growth rate, and related standardized scores in the BP-EU-003 (for Indication A), BP-EU-002 (for Indication B), and TS-KOR-06102005 (for Indication B) studies were all highly significantly improved over that at baseline. The difference in height between the Eutropin-treated children and the normal age- and gender-matched children was gradually decreased as the treatment continued. Also, the rate of growth was reversed from slower than that of normal children of the same age and gender to faster than that of normal ones during the course of the studies (especially in the early stage of the treatment phase). In other words, under the Eutropin treatment, the children with growth hormone deficiency (GHD) or Turner Syndrome grew faster than before.

In the BP-EU-003 study, Eutropin was shown to be non-inferior to Humatrope in promoting growth effect for children with GHD. The 2 study groups also showed comparable results in height velocity SDS, height SDS, and predicted adult height.

In conclusion, the data from the 3 children studies have demonstrated that Eutropin was efficacious in increasing height and in stimulating height velocity for children with GHD (Indication A) or Turner Syndrome (Indication B).

Primary Statistical Reviewer: Cynthia Liu, MA
Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader
CC: HFD-510/JWeber, MParks, RPerlstein
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HFD-700/ENevius, LPatrician

6. APPENDIX I

The e-mail below was from the sponsor's representative, Dr. Ray Lamy, on 06/30/2006 in responding this reviewer's questions.

First question from June 27 (e-mail to Dr. Babbitt)

Q: "Could you please ask the sponsor to clarify and also give some examples regarding how the pre-treatment height velocity for BP-EU-003, EP-EU-002, and TS-KOR-01602005 studies were calculated."

A: Please be informed that this information is available for each study in the NDA submitted.

For BP-EU-003, in Appendix 16.1.9 Statistical Analysis Plan Amendment 1 of NDA/CTD section 5.3.5.A.1.1.
For BP-EU-002, in Appendix 6.1.9 Statistical Analysis Plan Amendment 2 of NDA/CTD section 5.3.5.B.2.1.

For both studies, the same principle was followed. Take the previous and additional old height measurements, the screening and baseline(mean) height measurements, the corresponding dates of measurement and perform a linear regression of height against visit dates. The corresponding estimate for the slope parameter is used as the value for pre-treatment height velocity. The rules for selecting evaluable old measurements are given in the SAP. The computation of pre-treatment height velocity was done with the SAS procedure **proc reg**. Since there is a simple formula for the slope parameter in linear regression, it is possible to compute phv manually by plugging in the corresponding height measurements and dates.

For example, consider e.g. pt=44001 with

1.) baseline date 30DEC02 (SAS date=15704), average baseline height (mean of all measurements taken at that time) of 122.55 cm,
2.) screening date 29OCT02 (SAS date=15642) and average screening height of 121.65 cm,
3.) previous height measurement date 15JUL02 (SAS date=15536) and previous height of 120.60 cm,
4.) additional previous height measurement date 06MAR00 (SAS date=14675) and additional height of 114.00 cm, the rules in the SAP force us to discard the old additional height measurement, since it is 967 days earlier than screening, where a maximum of 730 days of distance is allowed. The previous height measurement was 106 days before screening, which is well between 84 days (12 weeks) and 730 days; so this measurement is included in the calculation of the height velocity.

Proc reg applied to these data yields a height velocity in terms of cm/day. Multiplication by 365.25 yields the values listed in the analysis, which is phv=4.17257 cm/year for this patient.

On the other hand, inserting the previous, screening and baseline measurements into the slope formula, which is:

sum(of (time_i - meantime)*(height_i - meanheight)) / sum(of (time_i - meantime)**2) and multiplying the result by 365.25 verifies the value obtained from proc reg.

As for TS-KOR-01602005 study, this is still in preparation and will be forwarded shortly.

Also please refer to the above mentioned Amendment 2 in understanding your request (see "second question" below) about M3 & M6 HV variables for BP-EU-002 study.

Second question from June 27 (e-mail to Ray Lamy)

Q: "One more thing..... I was trying to create the height velocity data for EP-EU-002 today, but found the data listing containing only pre-treatment value and Month 12 value. I couldn't locate Month 3 and Month 6 height velocities anywhere in the data listing. Please advice me where to look for them in the report or in the electronic submitted data file. If they have never been reported, please have the sponsor calculate the Months 3 and 6 height velocities."

A: There is no data listing for Month 3 and Month 6 height velocities for BP-EU-002 (Turner Syndrome) because these variables (M3 & M6) were not the planned variables nor are they part of the Statistical Analysis Plan. So, data listings were not created for those specified time points. The primary endpoint, height velocity of 12 months was computed by linear regression for visits and mean height mean height measurements if available. However, the height velocity of Korean T-S study was not calculated in the same way. The primary endpoint was just calculated only with 'baseline date and the measured height' and 'final 12months visit date and the measured height'. The linear regression for computed height velocity was not considered, so the height velocities for 3, 6, & 9 months were calculated and shown at the CSR.

7. APPENDIX II

The e-mail below was from the sponsor's representative, Dr. Ray Lamy, on 07/05/2006 in responding this reviewer's question.

Q: "Could you please ask the sponsor to clarify and also give some examples regarding how the pre-treatment height velocity for BP-EU-003, EP-EU-002, and **TS-KOR-01602005** studies were calculated."

A: The pre-treatment height velocities were calculated as follows:
1. In a naive patient, more than two Pre-Treatment Heights were measured and recorded in the CRF.
2. Of these values, the day(value) closest to 12M from screening visit was chosen as a Pre-treatment(previous) height.
3. If in the case of a patient with a GH Therapy History, only those with more than 3 months of Drug Free period prior to screening visit were included in the study. Also in this a case, the height value closest to 12M from screening visit, which is within the drug free period, was chosen as a pre-treatment height.

Based on above, pre-treatment height velocity was calculated by the following equation:

$$\text{Pre-treatment HV} = \frac{\text{Screening height - Pre-treatment height}}{\text{(Day difference between screening date - pre-treatment height date/365.25)}}$$

8. APPENDIX III

As requested by the reviewing medical officer, the following table shows the ANCOVA results for the BP-EU-003 study for **change from baseline or screening at Month 12** using the sponsor's model.

ITT with LOCF Efficacy Variable	Least-Squares Mean Change ± SE (N)		Treatment Difference	p-value	95% (LCL, UCL)
	Eutropin	Humatrope			
HV	7.7487 ± 0.2309 (88)	7.5371 ± 0.3149 (41)	0.2116	0.5430	(-0.4754, 0.8985)
HVSDS CA	7.9471 ± 0.3009 (88)	8.2385 ± 0.4106 (41)	-0.2913	0.5213	(-1.1884, 0.6057)
HSDS CA	1.1674 ± 0.0457 (88)	1.1438 ± 0.0623 (41)	0.0236	0.7319	(-0.1124, 0.1595)
HSDS BA	0.0896 ± 0.1536 (86)	0.1140 ± 0.2081 (41)	-0.0244	0.9156	(-0.4795, 0.4307)
Predicted Adult Height	3.8403 ± 1.1404 (32)	4.3233 ± 1.6504 (15)	-0.4830	0.7939	(-4.2109, 3.2448)
Predicted Adult Height SDS	0.4959 ± 0.1476 (32)	0.5931 ± 0.2151 (15)	-0.0972	0.6840	(-0.5785, 0.3841)

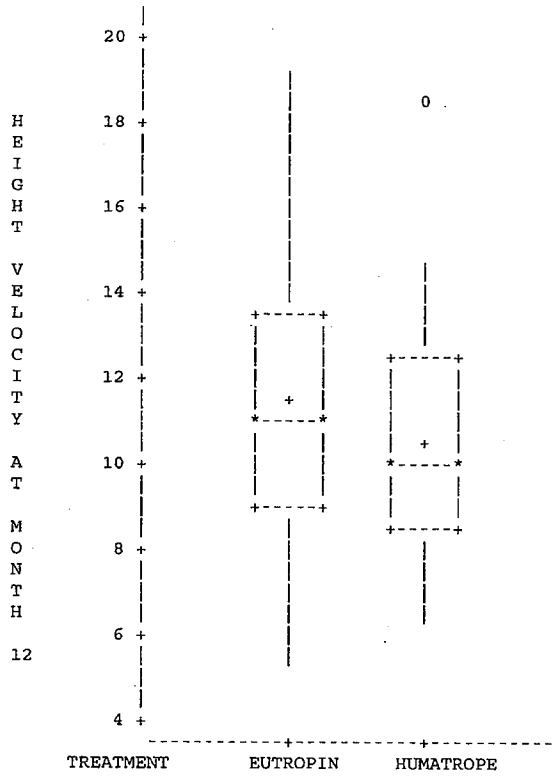
Bone maturation was calculated as ratio of change from screening in bone age at Month 12 to change from screening in chronological age at Month 12. Therefore, no analysis on change in ratio from screening was performed here.

9. APPENDIX IV

To facilitate the medical officer's review, the following table summarizes the results of the primary efficacy variable (height velocity at 12 months) for the BP-EU-003 study. The box plots below show the data distribution of height velocity at 12 months for each group.

ITT population with LOCF	Eutropin	Humatrope
Raw mean ± SD (N) at Month 0	3.4958 ± 1.4501 (88)	3.3867 ± 1.0183 (41)
Raw mean ± SD (N) at Month 12	11.3614 ± 2.922 (88)	10.5381 ± 2.606 (41)
Least-squares mean ± SE (N) at Month 12	11.2098 ± 0.231 (88)	10.9982 ± 0.315 (41)
Treatment difference	0.2116	
p-value	0.5430	
95% confidence interval of the difference	(-0.4754, 0.8985)	

The least-squares means were obtained using the sponsor's model, where treatment and country were the fixed factors and baseline height velocity, chronological age, and log maximum GH level after stimulation were the covariates.



Note: The horizontal line inside the box shows the median and + sign shows the mean. Any value more than 1.5 interquartile range (= 75th - 25th percentiles) is marked with a 0.

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