CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

MEDICAL REVIEW

DIVISION DIRECTOR'S MEMO

NDA #: 21-905

Sponsor: LG Life Sciences, LTD

Drug name: Valtropin® (somatropin (rDNA origin) for Injection)

Indications: Short stature in patients with pediatric GHD
Short stature in patients with Turner Syndrome
Adult GHD

Background

This is a 505b1 new drug application for recombinant somatropin for the treatment of short stature in pediatric patients with growth hormone deficiency (GHD) or Turner Syndrome and for the treatment of Adult GHD.

The applicant provided original clinical efficacy and safety data for Valtropin or an equivalent formulation. The agency has also approved other recombinant somatropins for these indications as summarized in the following table. Hence, there is extensive clinical experience with use of these products for the indications proposed in this NDA.

Table 1. Marketed Recombinant Growth Hormone Products with Indications for Pediatric GHD, Short Stature in TS, and Adult GHD

Indication	**Pediatric GHD**	**Turner Syndrome**	**Adult GHD**
GH product approved for each indication listed	Genotropin Humatrope Norditropin Nutropin Nutropin AQ Omnitrope Protropin Saizen Tev-Tropin	Genotropin Humatrope Nutropin Nutropin AQ	Genotropin Humatrope Norditropin(cartridges) Nutropin Nutropin AQ Omintrope Saizen

The clinical reviewer, Dr. Perlstein, has summarized the published literature, and while not essential to the approval of this application, does underscore the extensive public information on the safety and effectiveness of recombinant GH therapy for these indications and provides additional support to the rationale in approving Valtropin.

Clinical Studies

Four Phase 3 studies were submitted in support of indications sought with this application. The following tables summarize these 4 studies.

Table 2. Phase 3 Pivotal Studies Submitted to NDA 21-905

Protocol/Indication	Study Design	Age/Gender/# randomized	Primary Endpoint
BP-EU-003/Pediatric GHD	randomized, DB- AC (humatrope), 12-month, non-inferiority, multi-center study	Age 3.2-12 yrs (mean 8.2) Male 68%; Females 32% N=149	change from baseline in height velocity at Month 12
BP-EU-002/Turner Syndrome	uncontrolled, open-label, single-arm, single center study	2.5-9.8 yrs (mean 6.9) Female 100% N=30	change from baseline in height velocity at Month 12
TS-KOR-06102005	uncontrolled, open-label, single-arm, 12-month, multi-center study	1.7-16.4 yrs (mean 11) Female 100% N=60	change from baseline in height velocity at Month 12
HGCL-001/Adult GHD	randomized, DB, PC, multicenter study		reduction in fat mass at Week 12

The applicant conducted these 4 Phase 3 studies using two different formulations, one approved and marketed in Korea under the tradename, Eutropin®, and the other was formulated for US approval and is referred to as Valtropin®. The two formulations differ in composition as summarized in the following table obtained from Dr. Wei's biopharmaceutics review of the NDA.

Table 2: Composition of Eutropin™ INJ and Valtropin™

Regulatory Status		MA in Korea		Submitted for MA in USA and EU	
Drug Product Name		Eutropin™ INJ		Valtropin™	
Composition		4 IU Formulation		15 IU Formulation	
	Function	Per vial	Weight ratio	Per vial	Weight ratio
Active ingredient			[redacted]		[redacted]
Somatropin	drug substance	1.33 mg		5.00 mg	
Excipients					
Mannitol	bulking agent	5.00 mg		45.00 mg	
Glycine	stabiliser	20.00 mg		10.00 mg	
Sodium phosphate buffer, dibasic	buffer	ca. 1.35 mg		2.98 mg	
Sodium phosphate buffer, monobasic	buffer	-		0.22 mg	

MA Marketing authorisation; 1 N sodium hydroxide and 1 N hydrochloric acid are used to adjust pH

b(4)

Throughout this memo, the two tradenames will be used only to identify which formulation was studied in the clinical trial; however, it has already been determined by OCP that no bridging studies are

necessary between the two formulations as a result of similar findings of efficacy and safety in two clinical trials which each evaluated the different formulations. In effect, the efficacy and safety summary of Eutropin will be applied to that of Valtropin.

Efficacy

Short Stature in Pediatric GH Deficiency

Protocol BP-EU-003 was a one-year, randomized, double-blind, active-controlled, multi-center study conducted in children ages 3 to 11 years with short stature and GHD. The patients were randomized 2:1 to Valtropin® (n=99) or Humatrope® (n=50).

The primary efficacy variable was height velocity (HV) at 12 months and the primary objective was to demonstrate non-inferiority between the two treatment groups for mean HV at 12 months. Other efficacy assessments of linear growth included:

- HV SDS for chronological age
- height
- height SDS for chronological age
- height SDS for bone age
- predicted adult height SDS

In addition, assessments of the effect of somatropin on bone age relative to chronologic age, body weight, IGF-1, and IGFBP-3 were also performed.

The primary efficacy variable was analyzed by ANCOVA using treatment and country as the primary factors and chronological age, pre-treatment HV, and log maximum GH level after stimulation as covariates.

See Table 1, page 12 from Dr. Liu's review for subject disposition. Overall, approximately 93% of the randomized population completed the study at Month 12. Approximately 87% of the randomized population was included in the ITT population which was defined as all randomized subjects who received at least 1 dose of study drug and had at least one follow-up primary efficacy assessment.

There were no significant differences between the two treatment groups for most of the relevant demographic and baseline characteristics. The mean age at enrollment was 8.22 yrs (range: 3.2-12 yrs). Approximately 68% were male and the population was predominantly Caucasian (95%). Baseline height SDS for CA was -3.43 ± 1.1 for the randomized population.

The following table obtained from Dr. Liu's statistical review summarizes the primary efficacy variable and analysis in this study.

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.

The mean HV increased from 3.5 cm/year at baseline to 11.36 cm/yr at Month 12 resulting in a mean change from baseline of 7.86 cm (95% CI: 7.18-8.55). The predicted adult height also increased from baseline of 162.3 ± 9.67 cm to 165.8 ± 10 cm.

The effect of Valtropin on linear growth was compared with another approved recombinant somatropin, Humatrope®, that has been evaluated and approved for short stature in GHD patients. The treatment difference in HV between Valtropin- and Humatrope-treated groups was 0.21 cm/year, favoring Valtropin. The pre-defined non-inferiority margin was ± 2 cm/year. As the 95% CI associated with the treatment difference fell within this margin (-0.48 to 0.90), this study demonstrated not only non-inferiority between Valtropin and Humatrope for their effects on HV, but Valtropin's efficacy was considered equivalent to Humatrope's.

A notable finding was an analysis of efficacy by baseline age, log maximum GH level after stimulation, and height SDS which showed that for patients who were younger, had smaller log maximum GH levels after stimulation, or had lower baseline height SDS, there was a trend towards a greater response to GH treatment as measured by HV at Month 12.

All the ITT patients in the Valtropin group had an increase in height velocity at Month 12, and 84/88 (95.5%) had a > 2 cm/yr increase in HV.

All told, the cumulative evidence supports the conclusion that Valtropin®, like other recombinant somatropin products, is effective in treating short stature secondary to GHD.

Short Stature in Turner Syndrome Patients

Two studies evaluating the effect of Eutropin/Valtropin on linear growth in Turner Syndrome were conducted: one in Russia (BP-EU-002 – used Valtropin) and one in Korea (TS-KOR-06102005 – used Eutropin). Both studies were one-year, open-label, single-arm studies. BP-EU-002 (Russian TS Study) was conducted at a single center and enrolled girls aged 2 to 9 years and enrolled 30 girls while TS-KOR-06102002 (Korean TS Study) was a multi-center study which enrolled 50 girls below 14 years of age. The mean age at enrollment in the Russian study was 7 years and the population was comprised entirely

of Caucasians. The mean age at enrollment in the Korean TS Study was 11 years and all the subjects were Asian. Both study cohorts showed severe short stature with mean height SDS for chronological age of -2.34 and -2.99 in the two studies, respectively.

In both these studies, the mean changes from baseline in HV, HV-SDS, and height SDS for chronological age and bone age were significantly greater at Month 12 than baseline. In the Russian TS Study, the mean HV increased from 3.75 cm/year at baseline to 9.73 cm/yr at Month 12. In the Korean TS Study, the increase was slightly less with a baseline mean HV of 3.48 cm/yr increasing to 6.97 cm/year at Month 12. See Table 2, page 7 from Dr. Liu's review for a summary of all the parameters for linear growth. All parameters support the conclusion that in these two independent studies, Valtropin treatment improved HV, HV SDS, height SDS for CA and BA, and also predicted adult height in patients with Turner Syndrome. Although the mean heights of TS patients after 12 months of treatment with Valtropin were still below the average heights for normal age-matched children, the rates of growth improved after 12 months. In other words, initially these children grew at a slower rate than normal age-matched children but treatment with Valtropin resulted in an increased growth rate over the normal children over time. This was also the case with the GHD patient population.

Adult GHD

Data from one study conducted in Korea were submitted in support of this indication. The study was a 24-week/6-month study. The trial was a randomized, double-blind, placebo-controlled study design in which eligible patients were randomized to receive Eutropin for 24 weeks (Group A), Eutropin for 12 weeks then switched to placebo for 12 weeks (Group B), and placebo for 12 weeks then switched to Eutropin for 12 weeks (Group C). The study population was comprised of patients with childhood onset GHD and adult onset GHD as defined on page 5 of Dr. Gebert's statistical review; however, the ITT population was comprised predominantly of adult onset GHD patients. Ninety-five patients were screened and randomized but only 92 received medication; these 92 comprised the ITT population with 31 in Group A, 28 in Group B, and 33 in Group C. Figure 2 in Dr. Gebert's review summarizes the disposition of patients.

The primary efficacy measure was change from baseline in Fat Mass at Week 12. Since both Group A and B received Eutropin for the initial 12 weeks, data from these two groups (minus those without post-baseline measures) were combined and compared to data from Group C which received only placebo in the first 12 weeks. The following table from Dr. Gebert's review summarizes these findings.

Table 3. Change in Fat Mass at Week 12 in Eutropin-treated versus Placebo-treated Adult Patients with GHD.

	Groups A and B Combined (n=58)	Group C (n=31)
Baseline (Mean ± SD)	23.0 ± 7.7	19.9 ± 3.7
Week 12 change from Baseline (Mean ±SD)	-1.25 ± 2.18	+0.16 ± 1.50
Week 12 change from Baseline (LSMean ± SE)	-1.17 ± 0.25	+0.18 ± 0.35
Treatment difference (95% CI)	-1.35 (-0.48,-2.22) P=.003	

Patients receiving Eutropin had a mean change from baseline in Fat Mass of -1.17 ± 0.25 that was statistically significant from the change observed in placebo +0.18 ± 0.35. Similarly, there was a

significant difference between combined Groups A/B and Group C in change from baseline in lean body mass.

Dr. Perlstein pointed out that for the other marketed recombinant GH products with indications for treatment of adult GHD, data supporting approval of this indication relied upon 6-month controlled clinical trials. This applicant has provided only 3-month controlled data; however, an additional 3-month open-label period was assessed and found that: 1) patients randomized to Group A maintained efficacy achieved by Month 3 in an analysis comparing change in FM from Month 6 to Month 3; 2) patients randomized to Group B who were switched from Eutropin to placebo after Month 3 had an increase in FM approximating baseline values; and 3) patients in Group C who were switched from placebo to Eutropin after Month 3 had significant decreases in FM at Month 6 compared to Month 3.

Subgroup analyses did not show any meaningful differences in efficacy as a result of gender or ERT status in females.

In conclusion, treatment with Eutropin in adult GHD patients is effective at reducing fat mass and increasing lean body mass.

Safety
From Dr. Perlstein's review Eutropin/Valtropin was reasonably tolerated in these clinical studies and no new safety findings of concern were identified.

CMC/Microbiology

b(4)
b(5)

The deficiencies pertain primarily to procedures designed to prevent microbiological contamination of the drug product.

Tradename
The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the tradename, Valtropin®, citing potential confusion with Nutropin® and atropine. Dr. Perlstein has provided the counter-arguments including clinical scenarios that would mitigate such risk or if such a medication error should occur, the potential clinical outcome. I concur with his recommendation that this product can be approved under the proprietary name, Valtropin®.

Pediatrics
Under the Pediatric Research Equity Act (PREA) all applicants must addressed whether approved indications warrant further clinical investigation in the pediatric population. This application will be approved for use of Valtropin® in 3 indications:

- Adult GHD – waive pediatric requirement as this condition pertains to the adult population only
- Pediatric GHD – this indication is specific to the condition in pediatric patients, hence the applicant has met all requirements under PREA
- Short Stature in Turner Syndrome – this indication is specific to pediatric patients, hence the applicant has met all requirements under PREA

Financial Disclosure
See Dr. Perlstein's review where he has summarized the applicant's disclosure of financial information from investigators and has found the information sufficient for the agency to rely on the data submitted.

Labeling
The labeling recommendations made by the different disciplines were accepted by the applicant.

Conclusion

I concur with Dr. Perlstein that this application can be approved for the 3 proposed indications based on the clinical efficacy and safety findings; however, pending resolution of the deficiencies cited after the inspection of a manufacturing facility in ——— by the Office of Compliance, an approvable (AE) action is recommended. b(4)

Addendum: In reviewing the electronic records for this NDA, it was brought to my attention that this Director's memo was never placed into DFS. Since that time, the deficiencies noted above have been corrected.

I concur with the reviews of Drs. Perlstein and Liu that this NDA can be approved. This action was taken on April 19, 2007.

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/s/

Mary Parks
10/27/2008 04:28:36 PM
MEDICAL OFFICER
This memo is being placed into DFS retroactively as it was inadvertently excluded from the administrative record at the time of the action letter

1May06

To: DFS for NDA 21-905, Valtropin
From: Robert S. Perlstein, MD – Medical Reviewer, DMEP
Through: Mary Parks MD – Acting Division Director, DMEP
Subject: Response to 7April06 DMETS Consult

Response to DMETS concerns regarding potential confusion of Valtropin and Nutropin, and Valtropin and Atropine:

1. **With regard to Valtropin and Nutropin**, the Division agrees with DMETS that 1) Valtropin and Nutropin are somewhat look-alike when scripted sloppily; and 2) Valtropin will be (if approved) and Nutropin is administered to exactly the same target populations (i.e. short children with pediatric growth hormone deficiency [GHD], short children with Turner Syndrome [TS] , and adults with GHD) in very similar amounts subcutaneously. **However, the Division does not feel that the mistaken administration of Nutropin instead of Valtropin, or Valtropin instead of Nutropin is a matter of import, i.e. in either case, the patient is being treated with what he/she requires – recombinant human growth hormone (rhGH).**

2. **With regard to Valtropin and Atropine**:

   - The Division agrees with DMETS that 1) Valtropin and Atropine are somewhat look-alike when scripted sloppily; and 2) 0.5 mg is the usual dose of Atropine administered parenterally to treat bradyarrhythmias and 0.5 mg could be the dose of Valtropin administered to a child with short stature (i.e., 0.043 mg/kg/day in an ~11-12 kg child). Furthermore, the administration of Valtropin (mistaken for Atropine) to a patient with a bradyarrhythmia could have dire consequences (because of lack of Atropine more than unintended effects of Valtropin); and the administration of Atropine (mistaken for Valtropin) to a patient with GHD could have dire consequences (because of the tachycardic effects of Atropine rather than the lack of Valtropin).

   - Atropine for the most part is administered parenterally to inpatients in critical care units/Emergency Departments (EDs) by nurses and physicians, and is supplied to those units by inpatient pharmacies. On the other hand, Valtropin almost exclusively will be administered parenterally to outpatients at home by self-injection or a parent/caregiver, or in an endocrinologist's office by nurses and physicians, and will be suppled by outpatient pharmacies.

   - **If an inpatient pharmacist were to misread a request for Atropine as one for Valtropin, the Division believes that the pharmacist would find it odd that a critical care unit was requesting a drug (i.e.,**

Valtropin) almost exclusively used in the outpatient setting. Furthermore, if a critical care or ED nurse were to misread an order for Atropine as one for Valtopin, the Division believes that the nurse would question the administration of Valtropin to a critically ill bradycardic patient; in addition, Valtropin is not routinely kept on-hand in critical care units and EDs. On the other hand, an outpatient pharmacist confusing a prescription for Atropine as one for Valtropin might not find it as odd.

- **If an outpatient pharmacist were to misread a prescription for Valtropin as one for Atropine, the Division believes that the pharmacist would find it odd that an endocrinologist was prescribing a drug (i.e., Atropine) primarily used in the inpatient setting. Furthermore, we believe that the likelihood of a nurse in an endocrinologist's office, or a patient/parent/caregiver at home mistakenly self-administering or administering Atropine instead of Valtropin is very small. Valtropin will be supplied as a lyophilized formulation which needs to be reconstituted with diluent, while parenteral Atropine is supplied as a ready-to-use aqueous solution and is not reconstituted by the person administering the drug.** On the other hand, an inpatient pharmacist confusing a request for Valtropin as one for Atropine might not find it as odd.

- **All things considered, the Division does not believe it is likely that Valtropin will be confused with Atropine.**

3. **Therefore, the Division does not agree with DMETS that Valtropin should not be used as the proprietary name for the rhGH formulation manufactured by LG Life Sciences and under review in NDA 21-905.**

Robert S. Perlstein MD, FACP, FACE
Medical Reviewer, DMEP

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/s/

Robert Perlstein
5/1/2006 10:49:43 AM
MEDICAL OFFICER

Mary Parks
5/1/2006 12:53:32 PM
MEDICAL OFFICER

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1 EXECUTIVE SUMMARY

Valtropin (somatropin [rDNA origin] for injection) is an immediate-release, lyophilized formulation of rhGH. The data contained in this submission were submitted to support the approval of this new formulation of rhGH for 3 indications: pediatric growth hormone deficiency (GHD), short stature in Turner syndrome (TS), and adult GHD. Although this application is considered an NDA for a new molecular entity, 7 other formulations of somatropin have been approved by the FDA for multiple indications in children and adults, including the indications sought in this application.

1.1 Recommendation on Regulatory Action

THIS MEDICAL OFFICER RECOMMENDS APPROVAL FOR ALL 3 PROPOSED INDICATIONS.

1.1.1 Efficacy

1.1.1.1 Indication 1 - [redacted] Treatment of Pediatric Patients Who Have Growth Failure Due to Inadequate Secretion of Endogenous Growth Hormone - Pediatric Growth Hormone Deficiency (GHD) b(4)

- No additional efficacy studies are required to obtain approval for this indication.
- **The short-term efficacy data from Study BP-EU-003 presented in this application reflecting the significant linear growth response of short children with GHD after 12 months of treatment with Valtropin (which was non-inferior/equivalent to the linear growth response observed after treatment with Humatrope,** a previously approved short acting formulation of rhGH/somatropin) **is sufficient by itself** to warrant approval of this indication. A comparison of the efficacy findings in Study BP-EU-003 with the results of other published short-term studies **strongly supports** the validity of the sponsor's findings. Published final height (FH) studies not conducted by the sponsor wherein short children with GHD were treated with rhGH formulations other than Valtropin until FH was achieved (which demonstrated substantial improvements in FH) **are not necessary** for approval of this indication and are referenced in this Medical Officer's review **only to provide context**. On the other hand, given that multiple review articles/consensus statements by highly regarded organizations/international societies clearly recommend long-term rhGH treatment for GHD children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current indication.
- The sponsor's proposed language [redacted] b(4)

  was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential changes involved [redacted]

b(4)

The sponsor agreed with all of the Division's suggested edits. In addition, the sponsor's proposed language for the pediatric GHD subsection of the Indications and Usage section, and the pediatric GHD subsection of the Dosage and Administration section was also carefully reviewed and then edited. Once again, the sponsor agreed with all of the Division's suggested edits.

- **The satisfactory and comparable efficacy observed in pediatric GHD patients after treatment with 5 mg = 15 IU Valtropin in Study BP-EU-003 (contained in this NDA submission)** and 1.33 mg = 4 IU Eutropin™ INJ in studies conducted by the sponsor in Korea (label enabling in other countries; 1990s) and China (2000s) (not contained in this NDA submission; sponsor provided comprehensive synopses), as well as the satisfactory and comparable efficacy observed in Turner syndrome (TS) children after treatment with 5 mg = 15 IU Valtropin (Study BP-EU-002) and 1.33 mg = 4 IU Eutropin™ INJ (Korean TS study) (both studies contained in this NDA) 1) mitigate the need for a biopharmaceutical bridging study between the 2 qualitatively identical formulations; and 2) support the approval of the adult GHD indication even though adult GHD patients were treated with 1.33 mg = 4 IU Eutropin™ INJ only during Study HGCL-001 (the solitary study submitted in support of the adult GHD indication in this NDA submission), i.e. it is entirely reasonable to presume that if an adult GHD study was conducted with 5 mg = 15 IU Valtropin, the results obtained would be very similar to the results observed during Study HGCL-001.
- As indicated in Section 1.2.3 below, the Division requests that the sponsor attempt to capture final height data on the children who participated in Study BP-EU-003, if possible.

1.1.1.2 Indication 2 – Treatment of Growth Failure Associated with Turner Syndrome (TS) in Patients Who Have Open Epiphyses b(4)

- No additional efficacy studies are required to obtain approval for this indication.
- The short-term efficacy data from Study BP-EU-002 and TS-KOR-06102005 (hereafter described as the Korean TS study) presented in this application describing the significant linear growth response of short children with TS after 12 months of treatment with Valtropin and Eutropin™ INJ, respectively, **is sufficient by itself** to warrant approval of this indication. A comparison of the efficacy findings in Study BP-EU-002 and the Korean TS study with the results of 4 published short-term studies **strongly supports** the validity of the sponsor's findings. A review of published FH studies not conducted by the sponsor wherein short TS children were treated with rhGH formulations other than Valtropin until FH was achieved (which demonstrated substantial improvements in FH) **is not necessary** for approval of this application and is contained in this Medical

Officer's review **only to provide context**. On the other hand, given that multiple review articles/consensus statements by highly regarded organizations/international societes recommend long-term rhGH treatment for TS children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current application.

- The Sponsor's proposed language

b(4)

The sponsor agreed with all of the Division's suggested edits. In addition, the sponsor's proposed language for the TS subsection of the Indications and Usage section, and the TS subsection of the Dosage and Administration section was also carefully reviewed and then edited. Once again, the sponsor agreed with all of the Division's suggested edits.

- **The satisfactory and comparable efficacy observed in TS children after treatment with 5 mg = 15 IU Valtropin (Study BP-EU-002) and 1.33 mg = 4 IU Eutropin™ INJ (Korean TS study) (both studies contained in this NDA submission)**, as well as the satisfactory and comparable efficacy observed in pediatric GHD patients after treatment with 5 mg = 15 IU Valtropin in Study BP-EU-003 (contained in this NDA submission) and 1.33 mg = 4 IU Eutropin™ INJ in studies conducted by the sponsor in Korea (label enabling in other countries; 1990s) and China (2000s) (not contained in this NDA submission; sponsor provided comprehensive synopses) 1) mitigate the need for a biopharmaceutical bridging study between the 2 qualitatively identical formulations; and 2) **support the approval of the adult GHD indication even though adult GHD patients were treated with 1.33 mg = 4 IU Eutropin™ INJ only during Study HGCL-001** (the solitary study submitted in support of the adult GHD indication in this NDA submission), i.e. it is entirely reasonable to presume that if an adult GHD study was conducted with 5 mg = 15 IU Valtropin, the results obtained would be very similar to the results observed during Study HGCL-001.
- As indicated in Section 1.2.3 below, the Division requests that the sponsor attempt to capture final height data on the children who participated in Study BP-EU-002 and the Korean TS study, if possible.

1.1.1.3 Indication 3 - Replacement of Endogenous Growth Hormone in Adults with Growth Hormone Deficiency - Adult Growth Hormone Deficiency (GHD)

b(4)

- No additional efficacy studies are required to obtain approval for this indication.

- The short-term efficacy data from Study HGCL-001 presented in this application describing the changes in body composition after 3 months of placebo-controlled treatment with Eutropin™ INJ (and 6 months of uncontrolled treatment with Eutropin™ INJ) **is sufficient by itself** to warrant approval of this indication. A comparison of the efficacy findings in Study HGCL-001 with the results of multiple published short-term (3 and 6 month duration) placebo-controlled (and uncontrolled) studies **strongly supports** the validity of the sponsor's findings. The lack of placebo-controlled data for 6 months is not an impediment to approval. **The rationale for the acceptability of data generated with the older "not-to-be-marketed in the USA" 4 IU = 1.33 mg Eutropin™ INJ formulation in support of an indication for the "to-be-marketed in the USA" 15 IU = 5 mg Valtropin formulation can be found in the next bullet.**
- As stated in the previous bullet, Study HGCL-001 (the **single pivotal study in adult GHD patients**) was conducted utilizing the older "not-to-be-marketed-in-the-USA" Eutropin™ INJ formulation. Based on the fact that **both** formulations (the "to-be-marketed-in-the-USA" 5 mg = 15 IU Valtropin formulation and the older "not-to-be-marketed-in-the-USA" 1.33 mg = 4 IU Eutropin™ INJ formulation) **resulted in more than adequate and comparable responses in 1) TS patients** (both studies are part of the NDA submission and described above), **and also in pediatric GHD patients** (the 5 mg = 15 IU Valtropin formulation was used in the pediatric GHD study submitted with the NDA and, on 1Sept06, the sponsor provided this Medical Officer with synopses of 2 pediatric GHD studies using the 1.33 mg = 4 IU Eutropin™ INJ formulation conducted in **Korea [label-enabling] and China), this Medical Officer (as well as the DMEP Division Director and the Biopharmaceutical Reviewers and their superiors) agree that the findings in pediatric GHD and TS children described earlier in this paragraph can readily be extrapolated to the adult GHD population, i.e. if a 5 mg = 15 IU Valtropin study were to be performed in adult GHD patients, the results observed would be very comparable to the results obtained when the 1.33 mg = 4 IU Eutropin™ INJ formulation was used in Study HGCL-001. Therefore, as a group, we agree that the adult GHD indication can be approved (in conjunction with the pediatric GHD and TS indications) - even though the pivotal adult GHD study was conducted utilizing the older Eutropin™ INJ formulation**. Furthermore, as discussed in Section 5.1.1, **we agree that a *biopharmaceutical bridging study* between the "to-be-marketed-in-the-USA" 5 mg = 15 IU Valtropin formulation and the older "not-to-be-marketed-in-the-USA" 1.33 mg = 4 IU Eutropin™ INJ formulation *is unnecessary*.**
- The sponsor's proposed language [redacted] reviewed and then edited (in collaboration with the Division's Statistical Reviewers). b(4)

[redacted] b(4)

. The sponsor agreed with all of the Division's suggested edits. In addition, the Indications and Usage, and Dosage and Administration sections were also edited to harmonize the language with the language contained in the Package Inserts of the 6 rhGH formulations previously approved for the treatment of adults with GHD. In this regard, all 6 sponsors whose rhGH formulations are approved for the treatment of adults with GHD were requested to make these class labeling changes in early June 2006.

1.1.2 Safety

The Contraindications, Warnings and Precautions sections of the proposed Package Insert for Valtropin were edited to harmonize the language with the language contained in the Package Inserts of all other approved somatropin formulations. In this regard, all sponsors with approved somatropin formulations were requested to make these class labeling changes in early June 2006.

1.1.2.1 Indication 1 - Pediatric GHD

- No additional safety data are required to obtain approval for this indication.
- See Section 1.2.3 regarding the Division's request to establish a safety database for children.
- See class labeling statement above.
- The sponsor's proposed language for the Pediatric GHD subsection of the Adverse Reactions section was reviewed and edited. The sponsor agreed with all of the Division's suggested edits.

1.1.2.2 Indication 2 - TS

- No additional safety data are required to obtain approval for this indication.
- See Section 1.2.3 regarding the Division's request to establish a safety database for children and to add an additional section to the Periodic Safety Update (PSUR).
- See above regarding safety-related class labeling changes which were incorporated in the Valtropin Package Insert. This language includes the following: [redacted] b(4)
- The sponsor's proposed language for the TS subsection of the Adverse Reactions section was reviewed and edited. The sponsor agreed with all of the Division's suggested edits.

1.1.2.3 Indication 3 – Adult GHD

- No additional safety data are required to obtain approval for this indication.
- See Section 1.2.3 regarding the Division's request to establish a safety database for adults.
- See class labeling statement above.
- The sponsor's proposed language for the Adult GHD subsection of the Adverse Reactions section was reviewed and edited. The sponsor agreed with all of the Division's suggested edits.

1.1.3 Risk-Benefit Statement

1.1.3.1 Indication 1 – Pediatric GHD

The **efficacy data** submitted in support of Valtropin for the treatment of short stature associated with GHD is **substantial and sufficient**. The **safety data** submitted reveal that Valtropin is **safe and well tolerated** in GHD children. As indicated in Section 1.2.3 below, the Division is requesting that the sponsor **develop a safety database for children treated with Valtropin similar in design to the safety databases maintained by multiple other sponsors approved to market somatropin formulations**. **All things considered, a review of the efficacy and safety data submitted by the sponsor demonstrates a favorable benefit-to-risk ratio, and supports the proposed indication for Valtropin as a [redacted] treatment of growth failure associated with GHD in children who have open epiphyses**. b(4)

1.1.3.2 Indication 2 - TS

The **efficacy data** submitted in support of Valtropin for the treatment of short stature associated with TS is **substantial and sufficient**. The **safety data** submitted reveal that Valtropin is **safe and well tolerated** in TS children. As discussed in Section 1.2.3 below, the Division is requesting that the sponsor **develop a safety database for children treated with Valtropin similar in design to the safety databases maintained by multiple other sponsors approved to market somatropin formulations** and **gather additional long-term data regarding the incidence of certain adverse effects in TS children vs. non-TS children after treatment with Valtropin**. **All things considered, a review of the efficacy and safety data submitted by the sponsor demonstrates a favorable benefit-to-risk ratio, and supports the proposed indication for Valtropin as a [redacted] treatment of growth failure associated with TS in children who have open epiphyses**. b(4)

1.1.3.3 Indication 3 – Adult GHD

As indicated in Section 1.1.1.3 of the Executive Summary, based on the comparable and satisfactory efficacy and safety demonstrated for both Valtropin and Eutropin™ INJ in GHD and TS children, the Division believes that the efficacy and safety demonstrated in the adult GHD study (Study HGCL-001) conducted with the older formulation Eutropin™ INJ (which is qualitatively identical to Valtropin) is sufficient to support an indication for Valtropin for the treatment of adult GHD. As indicated in Section 1.2.3 below, the Division is requesting that the

sponsor develop **a safety database for adults treated with Valtropin similar in design to the safety databases maintained by multiple other sponsors approved to market somatropin formulations. All things considered, a review of the efficacy and safety data submitted by the sponsor demonstrates a favorable benefit-to-risk ratio, and supports the proposed indication for Valtropin as a ——— treatment for adult GHD.** b(4)

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

1.2.3.1 Regarding All 3 Indications

- **The sponsor is strongly encouraged to develop a safety database for both children and adults treated with Valtropin similar in design to the safety databases maintained by multiple other sponsors approved to market somatropin formulations.**

1.2.3.2 Regarding the TS Indication

- In that 1) TS patients are inherently prone to develop type 2 diabetes mellitus, scoliosis, hypertension and otitis media, and may be more prone to develop slipped capital femoral epiphysis (SCFE) and benign intracranial hypertension (BIH); and 2) type 2 diabetes mellitus, aggravation of preexisting scoliosis, SCFE and BIH are currently labeled potential adverse effects associated with rhGH treatment, and hypertension (via rhGH-induced salt retention) and otitis media (related to rhGH-induced adenoidal hypertrophy) are plausible adverse effects of rhGH (though currently unlabeled), **the Division recommends that the sponsor add an additional section to its annual Periodic Safety Update Report (PSUR) wherein the incidence of all AEs (in particular the 6 listed above) are compared in TS children and non-TS children treated with Valtropin.**

1.2.3.3 Regarding the TS Indication and the Pediatric GHD Indication

- **If possible**, an attempt should be made to capture FH data on the TS patients who were treated with Valtropin during Study BP-EU-002 and the Korean TS study, as well as the GHD children treated with Valtropin during Study BP-EU-003.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

1.3.1.1 Indication 1 - Pediatric GHD

As summarized and referenced in detail in Section 2.6.1, GHD occurs in ~1 in 3500 children in the USA. In one large series, ~60-80% of cases were classified as "idiopathic" and 20% were caused by various organic diseases. Males outnumbered females by 2:1 in every etiologic category. GHD may be "isolated", or coexist with multiple pituitary hormone deficiencies (MPHD). **The classic form of GHD is characterized auxologically by severe short stature (height SDS_{CA} <-2) and poor HV (HV SDS_{CA} <-1)** - in the absence of other well established non-GHD etiologies of short stature. Some children with isolated GHD have a characteristic facial appearance. The diagnosis of GHD typically requires a subnormal GH response after GH provocative testing, confirmation of decreased age-/gender-referenced serum IGF-1 levels, and a delayed BA. In most instances, the diagnosis of **severe** GHD is straightforward. However, GH provocative testing may have false negative and false positive results, and the serum IGF-1 level may occasionally be normal. **In the absence of an established absolute standard for making the diagnosis of pediatric GHD, the clinician should always integrate all available data (clinical/auxologic, biochemical and radiological). Of note, it has been clearly established that untreated children with GHD have a delayed puberty/decreased pubertal growth spurt, and FH SDS in the range of -4 to -6.**

Numerous studies conducted during the past 20 years have demonstrated that treatment with rhGH accelerates short-term growth in children with pediatric GHD. **During the last decade,** many published studies have shown that appropriate treatment of children with GHD with rhGH results in FHs which approximate normal adult height and mid-parental target height in the majority of patients. **Dosing guidelines for rhGH for the treatment of children with GHD are discussed at length in Section 1.3.4.1 of the Executive Summary and Section 2.6.1.**

In 1987, Humatrope was approved by the Agency for the treatment of short stature associated with pediatric GHD. Since that time, 6 other rhGH formulations have been approved for the treatment of children with GHD. The sponsor for Valtropin requested a pre-sNDA meeting which was held on 1Dec04. It was agreed at that time that the sponsor would submit the results of Study BP-EU-003 (an active-controlled study) in support of an indication to treat short children with GHD with Valtropin.

1.3.1.2 Indication 2 - TS

As summarized and referenced in detail in Section 2.6.2, TS occurs in approximately 1 in every 1,900 live female births and is caused by a loss or abnormality of the second X chromosome in at least 1 major cell line in the body. The 2 principal features of TS are short stature and ovarian dysgenesis. Absent treatment with rhGH, girls with TS attain a FH approximately 21 cm (~8") shorter than the normal female population. In a classic study reflecting the results of 4 European studies, the historical FH observed in untreated girls with TS

was **143.2 cm**. Ovarian failure occurs in the vast majority of girls, mandating lifelong estrogen therapy beginning in adolescence.

Numerous studies conducted during the past 15 years have demonstrated that treatment with rhGH accelerates short-term growth in girls with TS. More recently, published studies have shown that treatment of TS children with rhGH results in an increase in FH (compared with concurrent untreated controls, historical untreated controls and/or predicted final adult height at baseline), and normalization of FH (i.e., FH >5 feet) in many patients. Therefore, the **standard of care guideline** for the clinical use of rhGH published by the American Association of Clinical Endocrinologists (AACE) in 2003 recommends initiation of rhGH as soon as the height of a TS girl is below the 5th percentile of the normal growth curve. The recommendations published by Saenger et al in 2001 following an international multidisciplinary workshop on the management of patients with TS held in March 2000 are essentially identical. Furthermore, the Lawson Wilkins Pediatric Endocrine Society (LWPES) Drug and Therapeutics Committee cites rhGH as an important pharmacological agent to increase linear growth in children with TS. **Dosing guidelines for rhGH for the treatment of TS patients with short stature are discussed at length in Section 1.3.4.2 of the Executive Summary and Section 2.6.2.**

In 1997, Humatrope and Nutropin were approved by the Agency for the treatment of short stature associated with TS (with an orphan designation). When the period of orphan exclusivity for those 2 products expired in 2004, the sponsor for Valtropin requested a pre-sNDA meeting which was held on 1Dec04. It was agreed at that time that the sponsor would submit the results of Study BP-EU-002 and the Korean TS study (in addition to a review of the literature) in support of an indication to treat short children with TS with Valtropin.

1.3.1.3 Indication 3 - Adult GHD

As summarized and referenced in detail in Section 2.6.3, it is estimated that acquired hypopituitarism associated with GHD annually affects 10 people per million. The syndrome of adult GHD was first characterized ~15 years ago. Adult GHD patients are subcategorized into 1) AO GHD patients (onset during adult life; most often a consequence of clearcut organic pituitary/hypothalamic disease); and 2) CO GHD patients (patients who required rhGH for short stature during childhood and are then **reconfirmed** as having GHD after FH has been achieved). Amongst the multiple manifestations of GHD in the adult patient are alterations in body composition (increased FM, truncal fat, visceral adipose tissue [VAT] and waist/hip ratio [WHR]; reduced LBM), dyslipidemia, insulin resistance, osteopenia, reduced exercise capacity and sense of well-being, and, more than likely, an increased risk of atherosclerotic heart disease and cerebrovascular disease. The diagnosis of adult GHD is typically made by GH provocative testing. The insulin tolerance test and the much less invasive arginine-GHRH (growth hormone releasing hormone) test are preferred. When 3 or 4 other pituitary hormone deficiencies are present and/or serum IGF-1 levels are well below the age- and gender-referenced normal range, GH stimulation testing may not be necessary. However, a substantial number of adult GHD patients (confirmed by provocative testing) have normal serum IGF-1 levels, i.e. a normal serum IGF-1 level does not exclude GHD and the serum IGF-1 level is of diagnostic value only if it is very low in patients with clearcut organic pituitary disease. Furthermore, absent any reasonable

clinical suspicion of organic pituitary disease, a low serum IGF-1 level by itself is not diagnostic of GHD and does not warrant treatment with rhGH; often times, it is the result of the so-called somatopause, i.e. the expected age-related decline in serum IGF-1 levels (and endogenous GH).

Somatropin was first marketed as replacement therapy for adult GHD in 1993, and there are currently **6 different preparations of somatropin approved for the treatment of severe GHD in adults.** Numerous short-term therapeutic trials have demonstrated that treatment with rhGH decreases FM/VAT/truncal fat/WHR, increases LBM, and decreases low density lipoprotein (LDL) cholesterol among other things. After ~2+ years of therapy, BMD may increase. **Reduction in adverse cardiovascular events has not yet been proven in long-term outcome studies.** The most common adverse effects observed after the administration of somatropin to adult GHD patients relate to somatropin-induced fluid accumulation, i.e. edema, arthralgia, myalgia, carpal tunnel syndrome. Furthermore, these patients must be monitored very carefully as well for somatropin-induced disorders of glucose homeostasis. **Dosing guidelines for rhGH for the treatment of adults with GHD are discussed at length in Section 1.3.4.3 of the Executive Summary and Section 2.6.3.**

On the basis of previously submitted NDA supplements, the Agency has granted approval for the marketing of 6 other somatropin products for the treatment of adult GHD - Lilly (Humatrope; 1996); Genentech (Nutropin AQ and Nutropin; 1997); Pfizer (Genotropin; 1997; orphan designation); and, when the period of orphan exclusivity ended on 31Oct04, Serono (Saizen; 1Nov04), Novo Nordisk (Norditropin Cartridges; 1Nov04) and Sandoz (Omnitrope; 2006; 505(b)2). Since the period of orphan exclusivity ended in 2004, the sponsor requested the pre-sNDA meeting described in Section 2.5 ahead - at which time it was agreed that the results of Study HGCL-001 (in addition to a review of the literature) would be submitted in support of the adult GHD indication

1.3.2 Efficacy

1.3.2.1 Indication 1 - Pediatric GHD

1.3.2.1.1 Brief Description of Study Design

Study BP-EU-003 was a Phase III, 12 month, multicenter, multinational (12 countries) randomized, double-blind, parallel group, active-controlled, non-inferiority study conducted in treatment-naïve pediatric GHD patients with short stature comparing the effects of Valtropin and an approved rhGH comparator (Humatrope) on linear growth and bone maturation. Patients were randomized to 12 months of treatment with Valtropin or Humatrope (**0.033 mg/kg/day = 0.23 mg/kg/week**). The primary efficacy endpoint was mean HV (cm/yr) at 12 months, and the primary efficacy objective was to show that the mean HV observed after 12 months treatment with Valtropin was non-inferior to that seen after 12 months treatment with Humatrope. Secondary efficacy parameters included change in HV (cm/yr), HV SDS_{CA} and change in HV SDS_{CA}, height SDS_{CA} and change in height SDS_{CA}, BA/CA (bone maturation index), B-P PredAH and change in B-P PredAH expressed in cm and as a SDS. In order to demonstrate the non-inferiority of Valtropin, the Division's Statistical Reviewer **compared Month 12 HV and change in HV between the 2 treatment groups using ANCOVA** with baseline CA, pre-treatment HV, log maximum stimulated GH level ± baseline height SDS_{CA} as covariates **in the intent-to-treat (ITT)/full analysis set (FAS) population with last observation carried forward (LOCF). Once the adjusted least squares (LS) mean treatment differences and their associated confidence intervals (CIs) were determined, the lower bounds of the 95% CIs surrounding the treatment differences were compared with the mutually agreed to pre-established non-inferiority margin of -2 cm/yr.** Furthermore, the Division's Statistical Reviewer performed paired t-tests to determine if HV, HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, PredAH SDS and PredAH (cm) were significantly improved from baseline at Month 12.

Children who completed the initial Phase III study were considered eligible for inclusion in Study BP-EU-003-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months, and patients previously treated with Humatrope for 12 months were switched to Valtropin for an additional 12 months).

1.3.2.1.2 Efficacy Results

- The ITT/FAS population (the primary focus of the Division's efficacy review) consisted of 129 children (88 treated with Valtropin and 41 treated with Humatrope). Greater than 90% of the 149 children originally randomized completed the study with no disparity between treatment arms. Combining both treatment groups, mean age was 8.2 yr, 60-70% of patients were male, ~95% were Caucasian, **baseline height SDS_{CA} was -3.43, pre-treatment HV was 3.34 cm/yr, and B-P PredAH was 161 cm (~5' 3").** These demographic and baseline characteristics were similar in the 2 treatment groups. GHD was considered to be "idiopathic" in 95.9% and 98% of the children in the Valtropin and Humatrope groups, respectively. **Preexisting central hypothyroidism/"TSH**

deficiency" was reported in ~25-30% of patients in each treatment arm. See Section 1.3.2.1.3 for further comment.

- The adjusted LS mean HV ± SE at Month 12 was **11.21 ± 0.23 cm/yr** in the Valtropin group vs. **11.00 ± 0.32 cm/yr** in the Humatrope group, and the adjusted LS mean change in HV ± SE at Month 12 was **7.75 ± 0.23** cm/yr in the Valtropin group vs. **7.54 ± 0.31** cm/yr in the Humatrope group in the ITT/FAS population. The **mean treatment difference for HV and change in HV was 0.21 in favor of Valtropin** (a statistically and clinically non-significant difference). **Valtropin was non-inferior to Humatrope since the lower bounds of the 95% CIs surrounding the treatment differences (-0.48 in each instance) were greater than the pre-established non-inferiority margin of -2 cm/yr. In fact, in that the lower and upper bounds of the CIs (-0.48, 0.90 in each instance) lied in the interval between -2 and +2, Valtropin was "equivalent" to Humatrope. The within-group mean change from baseline at Month 12 in HV (7.87 cm/yr) for the Valtropin group was highly significant (p<0.0001).**
- The Month 12 HV and change in HV results after treatment of GHD children in Korea (HV 10 cm/yr; ΔHV 6.8 cm/yr) and China (HV ~11.5 cm/yr; ΔHV ~9 cm/yr) with **0.17-0.23 mg/kg/week of Eutropin™ INJ** (a 1.33 mg = 4 IU formulation marketed by the sponsor in other countries and qualitatively identical to the 5 mg = 15 IU Valtropin formulation) **were comparable to the results observed in Study BP-EU-003.**
- **There are multiple publications demonstrating that treatment of GHD children with previously approved rhGH formulations with doses ranging from 0.14 to 0.3 mg/kg/week results in Month 12 HVs ranging from 10.1 to 12.0 cm/yr - which is certainly comparable to the Month 12 HV of 11.36 cm/yr observed after treatment with 0.23 mg/kg/week of Valtropin.**
- **Furthermore, there is a large amount of literature indicating that appropriately administered, long-term treatment of GHD children with rhGH can normalize FH and approximate mid-parental target height. In this regard, change in height SDS_{CA} >0.25 after 1 year of treatment with rhGH has been reported to be a strong positive predictor of the FH response, and CA at the start of treatment, height SDS_{CA} at the start of treatment and log maximum GH after stimulation have been reported to be inverse predictors of the FH response. Based on these findings, it has long been the standard of care to treat GHD children with rhGH until FH is achieved (epiphyseal closure).**
- Cumulative distribution functions revealed that approximately 50% of children treated with Valtropin achieved a Month 12 HV ≥10 cm/yr and a Month 12 change in HV ≥7 cm/yr, and approximately 50% of children treated with Humatrope achieved a Month 12 HV ≥9 cm/yr and a Month 12 change in HV ≥6 cm/yr. All 88 ITT/FAS children in the Valtropin group (as well as the 41 children in the Humatrope group) had responded to treatment at the end of the 12 month trial, i.e. change from baseline in HV >0. In addition, 95.5% (84/88) of children in the Valtropin group manifested a change in HV >2 cm/yr (the value of the non-inferiority margin = the minimal clinically important difference). Furthermore, all 88 ITT/FAS children in the Valtropin group had manifested a positive change in height SDS_{CA} at the end of the 12 month trial (e.g., change from

baseline in height SDS_{CA} >0), and 97.7% (86/88) of children in the Valtropin group manifested a change in height SDS_{CA} >0.25.

- **Baseline height SDS_{CA} and log maximum GH after stimulation were significant inverse predictors of response.**
- Bone maturation expressed as the mean ratio of change from baseline at Month 12 in BA to change from baseline at Month 12 in CA was **1.53 ± 0.89 in the Valtropin group** and 1.5 ± 0.7 in the Humatrope group.
- As expected in GHD children, mean baseline serum IGF-1 levels and IGF-1 SDS were clearly low and increased significantly following12 months of treatment with either Valtropin or Humatrope.
- Eighty two children continued Valtropin treatment for an additional 12 months (Group V/V) and 40 children were switched from Humatrope to Valtropin for an additional 12 months (Group H/V) during the rollover study (Study BP-EU-003-RO). During the second 12 months of somatropin treatment, as expected, mean HVs decreased to 8.55 ± 2.14 and 8.64 ± 1.85 in the V/V and H/V groups, respectively. During the second 12 months of somatropin treatment, as expected, mean height SDS_{CA} levels increased further to -1.79 ± 1.05 and -1.73 ± 0.90, respectively. It is clear that the linear growth response in the V/V and H/V groups remained very similar during the second year of rhGH therapy.

1.3.2.1.3 Efficacy Conclusions

- The 149 prepubertal, rhGH-naïve children who were randomized in Study BP-EU-003 manifested classical pediatric GHD, i.e. combining both groups, **baseline height SDS_{CA} was -3.43, pre-treatment HV was 3.34 cm/yr, and B-P PredAH was 161 cm (~5' 3")**. The Valtrope and Humatrope groups were well matched. The exclusion of patients with craniopharyngiomas and other brain tumors (hence patients S/P radiation therapy) explains why ~95% of these children were classified as "idiopathic" GHD. The fact that ~25-30% of these children with "idiopathic" GHD had preexisting central hypothyroidism is supported by recent literature indicating that the presence of a particular triad of pituitary/hypothalamic abnormalities on MRI scan is not uncommon in patients with "idiopathic" GHD and is often associated with other pituitary insufficiencies.
- **The between-group ANCOVA analyses of Month 12 HV and change in HV data after treatment with 0.23 mg/kg/week of either somatropin in the ITT/FAS population clearly demonstrated that Valtropin is non-inferior to Humatrope**, i.e. the lower bounds of the CIs surrounding the treatment differences were greater than the pre-established non-inferiority margin of -2 cm/yr. **The within-group mean change from baseline at Month 12 in HV (7.87 cm/yr; 11.36 cm/yr at Month 12 minus 3.50 cm/yr at baseline) for the Valtropin group was highly significant** and **further supports the efficacy of Valtropin**.
- The comparability of the Month 12 HV and change in HV results after treatment of GHD children in Korea and China with **0.17-0.23 mg/kg/week of Eutropin™ INJ** (a 1.33 mg = 4 IU formulation marketed by the sponsor in other countries and qualitatively identical

to the 5 mg = 15 IU Valtropin formulation) to the results observed after treatment with Valtropin **0.23 mg/kg week in Study BP-EU-003 also further supports the efficacy of Valtropin (e.g., mean HV at Month 12 was 11.36 cm/yr after treatment with Valtropin vs. 10 and ~11.5 cm/yr in the Korean and Chinese studies, respectively).**

- **The short-term efficacy of Valtropin 0.23 mg/kg/week in Study BP-EU-003 is clearly supported by numerous published studies (some of which have been tabulated/cited in this review) where treatment with similar amounts of previously approved formulations of rhGH has resulted in very similar Month 12 HV results (e.g., 10-12 cm/yr).**
- **There is a large amount of literature indicating that appropriately administered, long-term treatment of GHD children with rhGH can normalize FH and approximate mid-parental target height in the majority of patients. An increase in height SDS_{CA} >0.25 is a strong positive predictor of the FH response. In that the increase from baseline at Month 12 in height SDS_{CA} in Study BP-EU-003 after treatment with Valtropin was 1.21, it is likely that the FH response of these children will be very good if they continue Valtropin therapy until epiphyseal closure. Based on these findings, it has long been the standard of care to treat GHD children with rhGH until FH is achieved. This very fact could be used to further support approval of the pediatric GHD indication for Valtropin.**
- Cumulative distribution functions indicated that the distribution of response with respect to change in HV and change in height SDS_{CA} after 12 months of treatment with Valtropin was quite satisfactory with no non-responders and very few minimal responders. Approximately 50% of children treated with Valtropin achieved a Month 12 HV ≥10 cm/yr and a Month 12 change in HV ≥7 cm/yr **reflecting substantial linear growth responses.** All 88 ITT/FAS children in the Valtropin group had responded to treatment at the end of the 12 month trial and 95.5% of children in the Valtropin group manifested a change in HV >2 cm/yr (the value of the non-inferiority margin). Furthermore, all 88 ITT/FAS children in the Valtropin group had manifested a positive change in height SDS_{CA} at the end of the 12 month trial and **97.7% of children in the Valtropin group manifested a change in height SDS_{CA} >0.25 (generally considered to be a satisfactory 12 month growth response which is predictive of a substantial increase in FH).**
- As previously reported in short-term studies, **baseline height SDS_{CA} and log maximum GH after stimulation were significant inverse predictors of response; surprisingly, CA at baseline was not a significant inverse predictor of response.** Subgroup analyses by age subset and gender were unrevealing.
- The within-group changes from baseline at Month 12 for the Valtropin group in HV SDS_{CA}, height SDS_{CA}, B-P PredAH SDS and B-P PredAH (cm) **were all significant. The 1.21 unit increase in height SDS_{CA} and the 8.05 unit increase in HV SDS_{CA} are robust and indicate substantial catch-up growth. As stated above, the substantial increase in height SDS_{CA} also predicts a very good FH response if these children continue to be treated with Valtropin until epiphyseal closure.**
- Bone maturation expressed as the mean ratio of change from baseline at Month 12 in BA to change from baseline at Month 12 in CA was **1.53 ± 0.89 in the Valtropin group,** and

not inappropriately accelerated, i.e. values >1 more than likely reflect expected catch-up growth during the first year of treatment.

- As expected in GHD children, mean baseline serum IGF-1 levels and IGF-1 SDS were clearly low and increased significantly following12 months of treatment with either Valtropin or Humatrope.
- **The linear growth pattern observed in both groups during the second year of rhGH treatment (e.g., drop off in HV [although still significantly increased from pre-treatment] and continued increase in height SDS_{CA}) has been reported numerous times during extended treatment of GHD children with rhGH.**

1.3.2.2 Indication 2 - TS

1.3.2.2.1 Brief Description of Study Design

Two open-label, single arm, uncontrolled clinical trials were conducted that evaluated the efficacy (linear growth parameters) and safety of Valtropin and Eutropin™ INJ (a 1.33 mg = 4 IU formulation qualitatively identical to the 5 mg = 15 IU formulation, Valtropin) in TS patients with short stature. Study BP-EU-002 was conducted at a single center in Russia; 30 Caucasian girls (mean age = 6.9 yr) were treated with Valtropin 0.053 mg/kg/day SC for 12 months. During the Korean TS study (conducted at four centers in Korea), 60 Asian girls (mean age = 10.8 yrs) were treated with Eutropin™ INJ 0.34 mg/kg/week SC (0.048 mg/kg 7 days each week or 0.056 mg/kg 6 days each week) for 12 months.

1.3.2.2.2/1.3.2.2.3 Efficacy Results/Conclusions

Comparison of the Results Observed in Study BP-EU-002 and the Korean TS Study with Each Other:

- **The most glaring differences between the subjects enrolled and treated in Study BP-EU-002 and the Korean TS study in demographics and baseline characteristics was CA at study entry (~7 vs. 11 yrs, respectively) and race (Caucasian vs. Asian). On the other hand, the dosage administered in the 2 studies was similar (0.37 mg/kg/week in Study BP-EU-002 and 0.34 mg/kg/week in the Korean TS study).**
- **In both the BP-EU-002 and Korean TS study, there was a significant increase from baseline in HV at Month 12 (5.98 [mean HV at Month 12 = 9.73 cm/yr] and 3.49 cm/yr [mean HV at Month 12 = 6.97 cm/yr], respectively) (the primary efficacy variable).** The substantial 6.22 SD unit increase in HV SDS_{CA} changing a negative score at baseline to a markedly positive score at Month 12 in Study BP-EU-002 **indicates that treatment of TS girls with Valtropin induced rates of growth which were greater than that of normal children of the same age.**
- In both the BP-EU-002 and Korean TS study, there was also a robust and significant increase from baseline in height SDS_{CA} (0.88 and 0.35 SD units, respectively). Several investigators have reported that the first year growth of TS patients after treatment with

rhGH is a powerful positive predictor of ultimate height gain in TS children who continue to receive rhGH until FH is attained.

- The significant HV and height SDS_{CA} increases from baseline at Month 12 in both studies are consistent with a highly significant linear growth response after treatment with both Valtropin and Eutropin™ INJ in TS children with short stature, which was apparent as early as Month 3.
- **The more robust HV and height SDS_{CA} responses observed in Study BP-EU-002 compared with the Korean TS study more than likely reflects the fact that CA at entry for Study BP-EU-002 was ~7 yrs (compared with 11 yrs for the Korean TS study), i.e. baseline CA at study entry is a positive predictor of short-term growth response in TS children treated with rhGH. Children in both studies received comparable and adequate amounts of rhGH. The age subgroup analysis in the Korean TS study demonstrating that TS children >12 years old respond significantly less than children 4-8 or 8-12 years old supports this hypothesis. Furthermore, many studies have demonstrated that baseline CA at the time of initiation of rhGH therapy is a powerful inverse predictor of both the short-term and long-term response to rhGH in GHD children. Finally, in this regard, several investigators have reported that baseline CA at the time of initiation of rhGH therapy is a powerful inverse predictor of ultimate height gain in TS children who continue to receive rhGH until FH is attained.**
- **Distribution of response analyses of the Korean TS study results are consistent with previous observations that the linear growth response of TS girls with short stature to treatment with rhGH is less consistent and more variable than the response of children with GHD. On the other hand, when the same analyses are applied to the results of Study BP-EU-002 with its much younger cohort of TS children, a uniformly consistent and substantial response was observed - in keeping with comments made in the previous bullet.**
- In Study BP-EU-002, the mean ratio of change in BA to change in CA was 1.02 and in the Korean TS study, mean HA/BA significantly increased at Month 12 indicating that rhGH treatment had not resulted in inappropriately accelerated bone maturation.
- In Study BP-EU-002-RO, the linear growth pattern observed during the second year of Valtropin treatment (e.g., drop off in HV and continued increase in height SDS_{CA}) has been observed numerous times during extended treatment of TS children (as well as GHD children) with rhGH.

Comparison of the Results Observed in Study BP-EU-002 and the Korean TS Study with the Results of Four Short-Term Published Studies Wherein rhGH was Administered to TS Children with Short Stature:

- **In summary, the HV results at Month 12 from the Korean TS study (an open-label study without an untreated or placebo-treated concurrent control group) compare very favorably with the 12 month results of 2 concurrently controlled studies and 2 open-label studies matched for dosage and baseline CA. The similar results support the validity of the significant increases in HV observed during the Korean TS study.**

We could not find a valid age- and dose-matched comparator for Study BP-EU-002 – where the TS children were much younger and the response exceeded all expectations.

- **The dose of Valtropin administered during Study BP-EU-002 (0.37 mg/kg/week) closely approximates the dosages of rhGH originally approved for the treatment of short stature associated with TS (i.e., up to 0.375 mg/kg/week).**

With respect to published FH studies:

- The results of 16 FH studies (4 concurrently controlled and 12 uncontrolled) in rhGH-treated children with TS supported by other sponsors have been reviewed by this Medical Officer. *It is important to note once again that, in the opinion of this Medical Officer, referral to these FH studies supported by other sponsors is not necessary for the approval of the current submission, i.e. the short-term data submitted by the sponsor are sufficient to grant approval for this indication. The intent of this Medical Officer in summarizing the results of these FH studies supported by other sponsors is only to provide context*. On the other hand, given that multiple review articles by highly regarded organizations recommend rhGH treatment for TS children with short stature as the standard of care, it would not be inappropriate to use this FH literature to directly support the current application.
- The most consequential of the 4 concurrently controlled FH studies not supported by the sponsor of this submission was a large (n=104), randomized Canadian study which demonstrated a robust, highly significant treatment difference in response to 0.3 mg/kg/ week of rhGH, i.e. the mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm ($p<0.001$).
- As a group, the 12 uncontrolled studies further support a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 147 to 152.3 cm when the dosage of rhGH ranged from 0.27 to 0.43 mg/kg per week.
- Furthermore, when the dosage of rhGH ranged from 0.45 to 0.70 mg/kg/week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"!!).
- It appears that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain in TS children who continue to receive rhGH until FH is attained. It has also been reported that CA, BA and height SDS_{CA} correlate negatively with height gain, while rhGH dose, duration of treatment with rhGH and overall prepubertal height gain correlate positively with height gain.
- The fact that there is current literature indicating that treatment of non-TS non-growth hormone deficient short children with rhGH significantly improves FH indirectly supports the use of rhGH for the long-term treatment of short stature associated with TS.

1.3.2.3 Indication 3 - Adult GHD

1.3.2.3.1 Brief Description of Study Design

Study HGCL-001 was a 6 month, multicenter, randomized, double-blind, placebo-controlled, 3-arm (with 2 arms having a crossover design) superiority study conducted in adults with either AO or CO GHD at 6 sites in Korea comparing the body composition effects of Eutropin™ INJ (a 1.33 mg = 4 IU formulation qualitatively identical to the 5 mg = 15 IU formulation, Valtropin) and placebo. During treatment period 1 (baseline through the end of Month 3), patients in the active treatment arms (Groups A and B) were treated with Eutropin™ INJ at an initial dose of 0.33 mg/day administered SC (6 days per week) for 1 month. During the next 2 months, the dose was up-titrated as necessary in small increments to a maximum of 0.66 mg/day (6 days per week) if serum IGF-1 levels were less than optimal or down-titrated in the presence of significant adverse events or inappropriately elevated serum IGF-1 levels. Patients in group C received placebo for the entire 3 month period. During treatment period 2 (Month 4 through the end of Month 6), patients in group A continued to receive Eutropin™ INJ, patients in group B were crossed over to placebo, and patients in group C were crossed over to Eutropin™ INJ.

1.3.2.3.2 Efficacy Results

- Change in FM was the primary efficacy variable. After 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant between-group treatment difference for the change in FM (**-1.35 kg**). At the request of this Medical Officer, the Division's Statistical Reviewer redid the primary between-group ANCOVA after 3 months of treatment excluding 4 patients from Group C (i.e., the placebo group) who had discontinued prior rhGH therapy less than 3 months before being enrolled in Study HGCL-001. It is theoretically possible that these placebo patients could have manifested an increase in FM because they were still returning to their baseline level following previous treatment with rhGH (which had decreased FM) - thereby enhancing the treatment effect. When the ANCOVA was repeated excluding these 4 patients, the adjusted LS mean change from baseline at Month 3 in FM in fact increased to +0.27 kg (from +0.18 kg), and the adjusted LS mean treatment difference therefore increased to -1.44 kg (from -1.35 kg). In other words, the treatment effect increased (rather than decreased) when these patients were not included in the analysis – which is reassuring!
- There were also significant within-group changes in FM after 3 months of treatment with Eutropin™ INJ for groups A+B combined (**-1.3 kg**; Months 0-3; ITT population), group A alone (**-1.7 kg**; Months 0-3; ITT population), Group B alone (**-1 kg**; Months 0-3; PP1 population only) and Group C alone (**-1.2 kg**; Months 3-6; ITT population). There was also a significant within-group change in FM (**-2.3 kg**) after 6 months of treatment with Eutropin™ INJ for group A alone in the ITT population.
- Change in LBM was the most consequential secondary efficacy variable. After 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant between-group treatment difference for the change in LBM (**+0.88 kg**). There were also significant within-group changes in LBM after 3 months of treatment with Eutropin™ INJ for groups A+B combined (**+0.9 kg**; Months 0-3; ITT population), group A alone (+1 kg;

Months 0-3; ITT population), and Group C alone (**+1.4 kg**; Months 3-6; ITT population). For Group B alone, the within-group change in LBM at Month 3 (**+1.0 kg**) bordered on significance in the ITT population as well as the PP1 population. There was also a significant within-group change in LBM (**+2.1 kg**) after 6 months of treatment with Eutropin™ INJ for group A alone in the ITT population.

- The 3 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 were compared with the within-group results in a selection of 5 published studies of 3 months duration. Two of these 3 month studies were randomized, double-blind, placebo-controlled trials and 3 were open-label. The changes observed during Study HGCL-001 were most comparable with the open-label study of Ahmad et al. In both of these studies, non-weight-based doses of rhGH were up-titrated as per serum IGF-1 levels, and the final mean doses were very similar **(0.35 mg/day [0.005 mg/kg/day in a 70 kg individual]) of Valtropin vs. 0.27 mg/day** of the rhGH formulation administered by Ahmad et al). **The decrease in FM was 1.7 kg in both studies, and the increases in LBM were similar.**
- The 6 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 were compared with the within-group results in a selection of 4 published studies of 6 months duration. Three of these 6 month studies were randomized, double-blind, placebo-controlled trials and 1 was an open-label comparison of non-weight-based dose titration based on serum IGF-1 levels vs. fixed weight-based dosing (in both treatment arms, the dose of rhGH was reduced appropriately when serious/severe adverse events occurred). The changes observed during Study HGCL-001 were most comparable with the non-weight-based dose titration arm from the very large, hallmark study published by Hoffman et al. In both of these studies, non-weight-based doses of rhGH were up-titrated as per serum IGF-1 levels, and the final mean doses (for men and women combined) were very similar **(0.35 mg/day of Valtropin vs. 0.54 mg/day** of the rhGH formulation administered by Hoffman et al). **The decrease in FM (men and women combined) in Study HGCL-001 (2.3 kg) was in fact larger than the decrease observed in either men (1.8 kg) or women (2.0) by Hoffman et al ; and the increase in LBM (men and women combined) was identical in both studies (2.1 kg).**
- **It is important to note that 5 of the 6 sponsors currently approved to market rhGH for the treatment of adult GHD submitted placebo-controlled studies with a minimum treatment duration of 6 months. The current sponsor submitted 3 month placebo-controlled data, as well as 6 month duration within-group results. It is therefore somewhat reassuring that the within-group change in FM between the beginning of Month 4 and the end of Month 6 for group A alone in the ITT population (-0.6 kg) was not statistically significant suggesting that most of the decrease in FM after treatment with Eutropin™ INJ occurred by the end of Month 3 (in fact, the change between baseline and the end of Month 3 was 1.7 kg). These findings are supported by a large, placebo-controlled study wherein substantial within-group changes in FM and LBM (-2.5 kg and +2.9 kg, respectively) after 3 months of treatment of adult GHD patients with a previously approved rhGH formulation were maintained for an additional 3 months, i.e. the changes from baseline at Month 3 in FM and LBM were essentially identical to the changes from baseline at Month 6.** In contrast, another very large 6 month open-label study reported

significant changes in FM and LBM after 3 months of treatment of adult GHD patients with rhGH, **and additional significant changes between Month 3 and Month 6** (albeit of a lesser magnitude than the baseline to Month 3 changes). Therefore, we can conclude that the literature is somewhat supportive, but conflicted.

- Analysis of the distribution of response reveals that ~70% of patients in Groups A and B combined responded to 3 months of treatment with Eutropin™ INJ, i.e. change in FM was negative and change in LBM was positive. **In ~60% of patients, the decrease in FM was >1 kg, and in ~45% of patients, the incease in LBM was >1 kg. On the other hand, 30% of treated patients did not demonstrate a FM or LBM response - which is concerning and difficult to explain.**
- As stated above, an unusually large proportion of women were enrolled in each group (~60-70%). This could have explained why the FM and LBM responses after 3-6 months of treatment with Eutropin™ INJ (although significant and comparable to the published literature) were not more robust. However, the gender subgroup analysis did not reveal the expected difference in the response of men vs. women receiving oral ERT, i.e. it is well established that women treated with oral ERT require at least twice as much rhGH as men to achieve a similar IGF-1 and body composition response.
- As expected, mean baseline serum IGF-1 levels were lowish and increased significantly following 3 months of treatment with Eutropin™ INJ in Groups A and B (Baseline to Month 3) and Group C (Month 3 to Month 6). There was significant correlation between the within-group decrease in FM and the within-group increase in serum IGF-1 after 3 months of treatment with Eutropin™ INJ in group A, but not after 6 months of treatment in group A, and not after 3 months of treatment in groups A and B combined. **Inconsistent correlation of body composition and IGF-1 responses after treatment of adult GHD patients with rhGH has been reported in multiple clinical trials and review articles over the last 10 years.**

1.3.2.3.3 Efficacy Conclusions

- Change in FM was the primary efficacy variable. After 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant between-group treatment difference for the change in FM **(-1.35 kg)**. At the request of this Medical Officer, the Division's Statistical Reviewer redid the primary between-group ANCOVA after 3 months of treatment excluding 4 patients from the placebo group who had discontinued prior rhGH therapy less than 3 months before being enrolled in Study HGCL-001. When the ANCOVA was repeated excluding these 4 patients, the adjusted LS mean change from baseline at Month 3 in FM in fact increased, and the adjusted LS mean treatment difference therefore increased to -1.44 kg - which is reassuring!
- There were also significant within-group changes in FM after 3 months of treatment with Eutropin™ INJ for Groups A and B combined, Group A alone, Group B alone and Group C alone ranging from -1 kg to -1.7 kg. There was also a significant within-group change in FM (**-2.3 kg**) after 6 months of treatment with Eutropin™ INJ for group A alone.
- Change in LBM was the most consequential secondary efficacy variable. After 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant between-group

treatment difference for the change in LBM (**+0.88 kg**). There were also significant within-group changes in LBM after 3 months of treatment with Eutropin™ INJ for groups A+B combined, group A alone, and Group C alone ranging from 0.9 kg to 1.4 kg. There was also a significant within-group change in LBM (**+2.1 kg**) after 6 months of treatment with Eutropin™ INJ for group A alone.

- The 3 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 are supported by several 3 month duration studies in the literature, especially those studies where similar amounts of rhGH were administered, i.e. the FM and LBM responses were very similar.
- The 6 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 are also supported by 6 month duration studies in the literature, in particular a large, hallmark study published in July 2004 designed to compare non-weight-based dose titration based on serum IGF-1 levels (the paradigm also used in Study HGCL-001) vs. fixed weight-based dosing. Final mean doses of rhGH were very similar and the changes in FM and LBM almost identical.
- **It is important to note that 5 of the 6 sponsors currently approved to market rhGH for the treatment of adult GHD submitted at least 6 month duration placebo-controlled studies. The current sponsor submitted 3 month duration placebo-controlled data, as well as 6 month duration within-group results. It is therefore somewhat reassuring that the within-group change in FM between the beginning of Month 4 and the end of Month 6 for group A alone in the ITT population was not statistically significant suggesting that most of the decrease in FM after treatment with Eutropin™ INJ occurred by the end of Month 3. These findings are supported by a large placebo-controlled study wherein substantial within-group changes in FM and LBM after 3 months of treatment of adult GHD patients with a previously approved rhGH formulation were maintained for an additional 3 months.** In contrast, another very large 6 month open-label study reported significant changes in FM and LBM after 3 months of treatment of adult GHD patients with rhGH, **and additional significant changes between Month 3 and Month 6** (albeit of a lesser magnitude than the baseline to Month 3 changes). **Therefore, we can conclude that the literature is somewhat supportive, but conflicted.**
- Analysis of the distribution of response reveals that ~70% of patients in Groups A and B combined responded to 3 months of treatment with Eutropin™ INJ, i.e. change in FM was negative and change in LBM was positive. **In ~60% of patients, the decrease in FM was >1 kg, and in ~45% of patients, the incease in LBM was >1 kg. On the other hand, 30% of treated patients did not demonstrate a FM or LBM response - which is concerning and difficult to explain.**
- As stated above, an unusually large proportion of women were enrolled in each group (~60-70%). This could have explained why the FM and LBM responses after 3-6 months of treatment with Eutropin™ INJ (although significant and comparable to the published literature) were not more robust. However, the gender subgroup analysis surprisingly did not reveal that women receiving oral ERT had a lesser response than men.
- As expected, mean baseline serum IGF-1 levels were lowish and increased significantly following 3 months of treatment with Eutropin™ INJ in all treatment groups. As has

been reported in the past, there was inconsistent correlation of body composition and IGF-1 responses.

1.3.3 Safety

1.3.3.1 Indication 1 - Pediatric GHD

1.3.3.1.1 Safety Results

- One of 7 SAEs appeared to be related to Valtropin - a hypersensitivity reaction leading to study discontinuation.
- The most frequent non-serious AEs were the infectious illnesses of childhood.
- No cases of benign intracranial hypertension, slipped capital femoral epiphysis or aggravation of preexisting scoliosis was reported.
- Intensive review revealed a very modest degree of glucose intolerance and there were no new cases of diabetes mellitus.
- Exacerbation of preexisting central hypothyroidism appeared to be reasonably common. During 12 months of Valtropin treatment, 18 out of 26 patients (69%) with preexisting central hypothyroidism (who were being treated **with a thyroxine preparation prior to study entry) required up-titration of their thyroxine replacement dose (primarily based on declining levels of free T4).** On the other hand, none of the 72 patients without preexisting central hypothyroidism manifested *de novo* central hypothyroidism while on-study.
- The 1 patient with preexisting central hypoadrenalism enrolled in this study required a slight increase in her maintenance hydrocortisone replacement dose after treatment with Valtropin, possibly compatible with somatropin-induced exacerbation of preexisting central hypoadrenalism. None of the remaining 97 patients without preexisting central hypoadrenalism manifested *de novo* central hypoadrenalism while on-study.
- The IGF-1 response to Valtropin was appropriate for children with GHD, and only 1 patient had a serum IGF-1 SDS >+2 at Month 12.
- The safety profile observed was almost identical to that of Humatrope.

1.3.3.1.2 Safety Conclusions

Valtropin was very well tolerated in GHD children. The frequency of exacerbated central hypothyroidism was remarkable. This Medical Officer thinks this well known somatropin-induced entity may be underreported in the literature.

1.3.3.2 Indication 2 - TS

1.3.3.2.1 Safety Results

- No SAEs were reported during either TS study.
- The most frequent non-serious AEs were the infectious illnesses of childhood.
- No cases of benign intracranial hypertension, slipped capital femoral epiphysis or aggravation of preexisting scoliosis were reported.
- Intensive review revealed a modest degree of glucose intolerance in Study BP-EU-002, but a much greater amount of glucose intolerance during the Korean TS study (including potentially 3 new cases of somatropin-induced diabetes mellitus (no follow-up data is going to be possible from this study conducted 10 years ago in Korea, so I guess we will never know). **TS patients are predisposed to type 2 diabetes mellitus and somatropin certainly can unmask latent diabetes mellitus.** However, there may another explanation. Going back to the source documents, **it appears that these children did not have to be fasting when they came for their on-study blood work. It will forever be unclear if these elevated blood sugars were actually postprandial sugars and/or whether somatropin induced substantial glucose intolerance in this particular cohort of TS children.**
- Curiously, serum IGF-1 absolute values and, most importantly, IGF-1 SDS were lowish to clearly low at baseline in Study BP-EU-002. Nonetheless, it is clear that the number of patients with serum IGF-1 values >+2 went from 0 to 8 (27.6%) and 9 (31%) at Month 6 and Month 12, respectively. TS children (who are not GHD) require in general 1 ½-2x as much rhGH to grow as GHD children, and therefore, it is not hard to understand why 1/3 of these children manifested serum IGF-1 SDS >+2. This has been reported before, but I cannot find the reference. In any case, **the long-term consequences/significance of serum IGF-1 SDS >+2 during an extended period of rhGH treatment are unknown.**

1.3.3.2.2 Safety Conclusions

Somatropin was well tolerated in both studies.

1.3.3.3 Indication 3 - Adult GHD

1.3.3.3.1 Safety Results

- 3 SAEs were unrelated to Eutropin™ INJ.
- The most frequent non-serious AE was edema, which in a number of instances required somatropin dose reduction.
- Intensive review revealed a mild-moderate degree of somatropin-induced glucose intolerance with potentially 2 new cases of diabetes mellitus (absent any post-study follow-up data). Eight patients with preexisting diabetes allowed into the study did reasonably well during exposure to Eutropin™ INJ – no post-treatment FBG exceeded 164 mg/dL.
- A very large percentage of these patients were panhypopituitary. There was no evidence of decompensation of preexisting central hypothyroidism/central hyoadrenalism or *de novo* central hypothyroidism/central hypoadrenalism.
- Serum IGF-1 levels were high normal post-treatment with Eutropin™ INJ and SDS could not be calculated (absent the appropriate kit-related information). I am a little concerned that the investigators allowed IGF-1 levels to get as high as they did – in that a dose titration paradigm was built into the protocol to avoid just such an occureence.

7.3.2.2 Safety Conclusions

All things considered EutropinTM INJ was reasonably well tolerated in Study HGCL-001.
It goes without saying that 1) monitoring for glucose intolerance is essential in any patient being treated with somatropin and 2) IGF-1 based dose titration should be done very meticulously.

1.3.4 Dosing Regimen and Administration

1.3.4.1 Indication 1 - Pediatric GHD

The dose of Valtropin administered during Study BP-EU-003 which proved to be efficacious and safe in the treatment of children with GHD was **0.033 mg/kg/day (equivalent to 0.23 mg/kg/week)**. In recent consensus guidelines issued by the Growth Hormone Research Society (GRS) and the LWPES, the dose of rhGH recommended for childen with GHD was **0.025 to 0.050 mg/kg/day SC (equivalent to 0.175 to 0.35 mg/kg/week)**. Guidelines issued by the AACE recommend 0.3 mg/kg/week (equivalent to 0.043 mg/kg/day).

Therefore, this Medical Officer strongly supports the following mutually agreed to language in the Dosing and Administration section of the Package Insert:

"*The amount administered during the pivotal study described herein was 0.23 mg/kg of body weight/week (0.033 mg/kg/day). Generally, the recommended dosage is 0.17 - 0.3 mg/kg of body weight/week. The weekly dose should be divided into equal amounts given either daily or 6 days a week by subcutaneous injection.*"

1.3.4.2 Indication 2 - TS

As noted in Section 1.3.2.2 above, **more robust HV and height SDS responses were observed in Study BP-EU-002 (Valtropin 0.37 mg/kg/week) compared with the Korean TS study (Eutropin™ INJ 0.34 mg/kg/week). More than likely, these findings reflect the fact that the mean CA of TS children in Study BP-EU-002 at entry was ~7 yrs compared with 11 yrs in the Korean TS study - not a matter of dosing, which was satisfactory in each study.**

Of note, the dosages previously approved for the treatment of short stature associated with TS was **up to 0.375 mg/kg/week for 2 sponsors and 0.33 mg/kg/week for another sponsor**, and the dose recommended by the AACE recently is **0.35 mg/kg/week**.

Therefore, this Medical Officer strongly supports the following mutually agreed to language in the Dosing and Administration section of the Package Insert:

"The amount administered during the pivotal study utilizing the 5 mg (15 IU) formulation of Valtropin® described herein was 0.37 mg/kg of body weight/week (0.053 mg/kg/day). Generally, the recommended dose is up to 0.375 mg/kg of body weight/week. The weekly dose should be divided into equal amounts given either daily or 6 days a week by subcutaneous injection."

It is important to note that there is Scandanavian literature which suggests that treatment of TS children with rhGH at dosages greater than 0.35 mg/kg per week (i.e., **as much as 0.45-0.7 mg/kg per week**) results in a greater increase in FH, and no apparent increase in adverse events. Therefore, the AACE guideline also recommends that providers should consider individualized dosing of rhGH in girls with TS in accordance with each patient's response.

To amplify further, the AACE recommends therapy with rhGH alone in TS girls younger than 9 to 12 years of age (and treatment of TS girls as young as 2 years of age - although at present only limited experience is available with rhGH treatment for children of this age), and continuation of rhGH treatment until FH or epiphyseal closure has been documented.

1.3.4.3 Indication 3 – Adult GHD

During Study HGCL-001, EutropinTM [INJ] was initially administered at a dose of 0.33 mg/day and then up-titrated based on inadequate serum IGF-1 levels or down-titrated based on the occurrence of rhGH-related adverse effects or excessively high serum IGF-1 levels. The protocol specified a maximum dose of 0.66 mg/day. The mean final dose was 0.35 mg/day.

This dosing paradigm is concordant with extremely current consensus guidelines issued by the Endocrine Society which recommend beginning with small non-weight-based doses (i.e., 0.3 mg/day in patients 30-60 years old, 0.1-0.2 mg/day if >60, 0.4-0.5 if <30) and then gradually up-titrating based on age- and gender-referenced serum IGF-1 (i.e., many, including this Medical Officer/clinician, consider serum IGF-1 SDS between 0 and +1 the ideal target range). Doses may also be up-titrated based on the body composition response, and should be down-titrated in the event of serious and/or severe adverse events or if the serum IGF-1 SDS exceeds +2. Elderly patients are more prone to somatropin-related adverse events, as are obese patients if weight based dosing is utilized. Menopausal/hypogonadal women treated with oral ERT require almost twice as much rhGH as men (i.e., ~0.8 mg/day or more in women on ERT vs. ~0.4 mg/d or less in older men) in order to achieve similar efficacy/IGF-1 levels. Menopausal/hypogonadal women treated with transdermal ERT or not treated with estrogen require doses closer to men. Menstruating women and premenopausal women treated with birth control pills require doses closer to women receiving oral ERT. Younger patients require larger amounts of somatropin (sometimes as much as 2 mg/day = ~0.025 mg/kg/day in an 80 kg person) to achieve satisfactory efficacy, but fortunately tolerate these larger doses better than older adults (as stated above).

In June 2006, all rhGH sponsors approved to market rhGH for the treatment of adult GHD were requested by the Division to make class labeling changes in the Adult GHD subsection of the Dosage and Administration section of the Package Insert. These changes in fact reflect the consensus guidelines discussed in the preceding paragraph.

Therefore, this Medical Officer strongly supports the following mutually agreed to language in the Dosing and Administration section of the Package Insert:

"Based on the pivotal study described herein, the recommended dosage at the start of therapy is 0.33 mg/day (or 0.1 mL of reconstituted solution) (equivalent to 0.005 mg/kg/day in a 66 kg adult) (6 days/week) given as a subcutaneous injection. The dosage may be increased according to individual patient requirements to a maximum of 0.66 mg/day (equivalent to 0.010 mg/kg/day in a 66 kg adult) (6 days/week) after 4 weeks. Clinical response, side effects, and determination of age- and gender-adjusted serum IGF-I levels may be used as guidance in dose titration.

Alternatively, taking into account recent literature, a starting dose of approximately 0.2 mg/day (range, 0.15-0.30 mg/day) may be used. This dose can be increased gradually every 1-2 months by increments of approximately 0.1-0.2 mg/day, according to individual patient requirements based on the clinical response and serum IGF-I concentrations. During therapy, the dose should be decreased if required by the occurrence of adverse events and/or serum IGF-I levels above the age- and gender-specific normal range. Maintenance dosages vary considerably from person to person.

A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women."

1.3.5 Drug-Drug Interactions

Nothing new to report derived from this submission.

1.3.6 Special Populations

Not applicable to this submission.

1.3.7 Special Comment on Clinical Pharmacology/Biopharmaceutics

A comparable somatropin drug product (Eutropin™ INJ [1.33 mg = 4 IU per vial]) which is qualitatively identical (with respect to the drug substance/active pharmaceutical ingredient [API; somatropin/rhGH] and the excipients) to the to-be-marketed-in-the-USA drug product (Valtropin® [5 mg = 15 IU per vial]) has been marketed in Korea since 1992 (and in 11 other countries subsequent to 1992) for the treatment of pediatric patients with GHD. In 1998, Eutropin™ INJ was first approved for the treatment of children with short stature associated with Turner syndrome in Korea, and, in 2003, Eutropin™ INJ was first approved for the treatment of patients with adult GHD in Korea. Subsequently, Eutropin™ INJ was approved for the treatment of TS children and adult GHD patients in 9 other countries and 2 other countries, respectively.

Based on the fact that **both** formulations (the "to-be-marketed-in-the-USA" 5 mg = 15 IU Valtropin formulation and the older "not-to-be-marketed-in-the-USA" 1.33 mg = 4 IU Eutropin™ INJ formulation) **resulted in more than adequate and comparable responses in 1) TS patients** (both studies are part of the NDA submission and described above), **and also in pediatric GHD patients** (the 5 mg = 15 IU Valtropin formulation was used in the pediatric GHD study submitted with the NDA described above and, 1Sept06, the sponsor provided this Medical Officer with synopses of 2 pediatric GHD studies using the 1.33 mg = 4 IU Eutropin™ INJ formulation conducted in **Korea and China), this Medical Officer (as well as the DMEP Division Director and the Biopharmaceutical Reviewers and their superiors) agree that a *biopharmaceutical bridging study* between the "to-be-marketed-in-the-USA" 5 mg = 15 IU**

Valtropin formulation and the older "not-to-be-marketed-in-the-USA" 1.33 mg = 4 IU Eutropin™ INJ formulation *is unnecessary*. In addition, we agree that the findings in pediatric GHD and TS children described earlier in this paragraph can readily be extrapolated to the adult GHD population, i.e. if a 5 mg = 15 IU Valtropin study were to be performed in adult GHD patients, the results would be very comparable to the results obtained when the 1.33 mg = 4 IU Eutropin™ INJ formulation was used in Study HGCL-001. Therefore, as a group, we agree that the adult GHD indication can be approved (in conjunction with the pediatric GHD and TS indications) - even though the pivotal adult GHD study was conducted utilizing the older Eutropin™ INJ formulation.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information and Proposed Indications

Valtropin (somatropin [rDNA origin] for injection) is an new, immediate release, lyophilized formulation of rhGH. The data submitted in this submission support the approval of this new formulation of somatropin for 3 indications. Technically speaking, therefore, this is an NDA for a NME. However, after discussion with the DMEP Division Director, it was agreed that the format of the review would resemble that of a NDA supplement – in that 1) 7 previous formulations of somatropin have been previously approved for multiple indications in adults and short children (including the indications supported by the current submission); 2) the efficacy and safety profile of previously approved somatropin formulations is very well established in many thousands of patients; and 3) the risk/benefit ratio of previously approved somatropin/rhGH formulations is quite satisfactory.

The Valtropin formulation submitted for approval contains 5 mg = 15 IU of rhGH per vial. It was administered during 1) the solitary pivotal clinical study supporting an indication for children with GHD (Study BP-EU-003); 2) 1 of the 2 pivotal clinical studies supporting an indication for children with short stature associated with TS (Study BP-EU-002); and 3) during the PK study (BP-EU-001. It is important to note that Eutropin™ INJ containing 1.33 mg = 4 IU of rhGH per vial was administered during 1) 1 of the 2 pivotal clinical studies supporting an indication for children with short stature associated with TS (the Korean TS study); and 2) the solitary pivotal clinical study supporting an indication for adults with GHD. Eutropin™ INJ is qualitatively identical to Valtropin with respect to the API (rhGH) and all the excipients. The implications of the fact that Eutropin™ INJ was used in 2 of the 4 pivotal clinical studies (rather than Valtropin) are discussed at length in multiple sections in this review, most recently in Sections 1.1.1.3 and 1.3.7 of the Executive Summary.

The sponsor has submitted this initial NDA in support of the following proposed indications:

Valtropin is indicated for the ——— treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. **b(4)**

Valtropin is indicated for the [redacted] treatment of growth failure associated with Turner syndrome in patients who have open epiphyses. b(4)

Valtropin is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency [redacted]

2.2 Currently Available Treatment for Proposed Indications

The rhGH formulations of 7 other sponsors are available in the United States.

- The rhGH formulations of 6 other sponsors are approved for the treatment of adult GHD.
- The rhGH formulations of 7 other sponsors are approved for the treatment of pediatric GHD.
- The rhGH formulations of 3 other sponsors are approved for the treatment of growth failure associated with TS.

2.4 Important Issues With Pharmacologically Related Products

Not applicable to this submission.

2.5 Presubmission Regulatory Activity

Between November 1998 and July 2004, the sponsor and the Division met face-to-face on several occasions and multiple additional communications were exchanged as well to clarify the requirements for a 505(b)2 submission. **However, at the pre-sNDA meeting on 1Dec04, it was mutually agreed that the sponsor's data was sufficient to submit a 505(b)1 application.** More specifically, clinically speaking, it was agreed that 1) the actively controlled, non-inferiority study conducted in children with pediatric GHD (BP-EU-003; 2001-2003) was potentially sufficient to obtain the pediatric GHD indication; 2) the 2 open-label Valtropin studies in TS patients (BP-EU-002 [2001-2003; Russia] and the Korean TS study [1995-1997]), in conjunction with a review of the published literature, were potentially sufficient to obtain the TS indication; and 3) the placebo-controlled study in adults with GHD (HGCL-001; 2001-2002; Korea) was potentially sufficient to obtain the adult GHD indication.

2.6 Background Information Regarding Each Indication

2.6.1 Pediatric GHD - Product Development Rationale; Epidemiology & Clinical

Manifestations; Current Treatment Guidelines Regarding the Use of rhGH

2.6.1.1 Product Development Rationale for Pediatric GHD

Pituitary-derived GH was first administered to children with GHD over 40 years ago (1). In 1987, Humatrope (a rhGH formulation) was approved for the treatment of pediatric GHD in the USA, and since that time, 6 other formulations of rhGH have been approved for the same indication. During the last ~20 years, a very large amount of literature (clinical trials, review articles and consensus guidelines) has been published demonstrating the short-term and long-term benefits of rhGH therapy in GHD children (see Section 2.6.1.3 ahead). The sponsor for Valtropin requested a pre-sNDA meeting which was held on 1Dec04. It was agreed at that time that the sponsor would submit the results of Study BP-EU-003 (an active-controlled study) (in addition to a review of the literature) in support of an indication to treat short children with GHD with Valtropin.

The following overview describing the epidemiology and clinical manifestations of pediatric GHD and current treatment guidelines regarding the use of rhGH in children with GHD is based on review articles and consensus statements summarizing current medical knowledge in this therapeutic area (2-9)

2.6.1.2 Epidemiology and Clinical Manifestations (including diagnosis) of Pediatric GHD **(see review references 2-9 supporting the information in this section)**

GHD occurs in ~1 in 3500 children in the USA (10). In 1 large series of 2331 patients, ~60% of cases were classified as "idiopathic", 20% were caused by various organic diseases (most commonly craniopharyngiomas and others tumors of the central nervous system), 5% were related to septo-optic dysplasia, and causation in the remainder was "unclear" (11). Males outnumbered females by 2:1 in every etiologic category (11). GHD may be "isolated", or coexist with multiple pituitary hormone deficiencies (MPHD). MPHD are most often diagnosed when an organic etiology for GHD is diagnosed, but can be present initially (or develop at a later time) even when "idiopathic" GHD is diagnosed (12-13).

The classic form of GHD is characterised clinically/auxologically by severe short stature (height SDS_{CA} <-2 using normal healthy children as the standard) and poor HV (HV SDS_{CA} <-1 using normal healthy children as the standard) - in the absence of other well established non-GHD etiologies of short stature (e.g., TS, chronic renal insufficiency, untreated hypothyroidism, untreated Cushing syndrome, chondrodysplastic syndromes, etc). Some children with isolated GHD have a characteristic facial appearance (mid-face hypoplasia, delayed dentition, and frontal bossing), microphallus, and increased subcutaneous fat.

The diagnosis of GHD typically requires a subnormal GH response (typical cutpoint for diagnosis is <10 ng/mL) after GH provocative testing (e.g., insulin tolerance test, clonidine, arginine), confirmation of decreased age-/gender-referenced serum IGF-1 levels, and a delayed BA. A MRI scan of the head (focusing on the sella turcica) is mandatory to exclude the most common organic etiologies of GHD, and a complete evaluation of other hypothalamic-pituitary-

end organ axes should be accomplished as well (see first paragraph). In most instances, the diagnosis of **severe** GHD is straightforward. However, GH provocative testing may have false negative and false positive results, and the serum IGF-1 level may occasionally be normal. **In the absence of an established absolute standard for making the diagnosis of pediatric GHD, the clinician should always integrate all available data (clinical/auxologic, biochemical and radiological).**

Of note, it has been clearly established that untreated children with GHD have a delayed puberty/decreased pubertal growth spurt, and FH SDS in the range of -4 to -6 (compared to a normal healthy adult population).

2.6.1.3 Current Treatment Guidelines Regarding the Use of rhGH in Children with GHD
(see review references 2-9 supporting the information in this section)

Numerous studies conducted during the past 20 years have demonstrated that treatment with rhGH accelerates short-term growth in children with pediatric GHD. A small number of representative **studies will be tabulated, briefly discussed and referenced in the Efficacy Summary/Discussion section ahead** (see Section 6.1.6.1 ahead). **During the last decade,** many published studies have shown that appropriate treatment of children with GHD with rhGH results in FHs which approximate normal adult height and mid-parental target height in the majority of patients (but not all) (3, 14-17). **FH results will also be briefly discussed in Section 6.1.6 ahead.**

In recent consensus guidelines issued by the GRS) (2) and the LWPES (4), the dose of rhGH recommended for childen with GHD was 0.025 to 0.050 mg/kg/day SC (equivalent to 0.175 to 0.35 mg/kg/week; or alternatively expressed as 0.67 to 1.34 mg/m^2/day using a conversion factor of 26.8). Guidelines issued by AACE (8) recommend 0.3 mg/kg/week (equivalent to 0.043 mg/kg/day) - which obviously falls within the range recommended by the GRS and the LWPES.

2.6.1.4 Transition from Pediatric to Adult Use of rhGH
(see references 18-19 supporting the information in this section)

It is generally recommended that once epiphyseal closure has occurred and FH has been attained during adolescence, rhGH treatment should be discontinued for 1-3 months, at which time the patient should be retested for the persistence of GHD. Many patients with "idiopathic" GHD will retest normal and not require additional treatment with rhGH (while those with congenital etiologies or severe organic pituitary disease/MPHD will usually retest as persistently GHD; in fact, some authors believe that these patients should not discontinue rhGH therapy and undergo retesting when FH is attained). Transition patients who have retested as GHD should reinitiate treatment with rhGH in order to 1) first achieve optimal adult body composition (i.e., it is generally accepted that peak LBM and bone mineral density [BMD] in GH-replete individuals are not attained until the mid 20s), and 2) then maintain optimal body composition and blood lipid profiles. When rhGH therapy is reinitiated in these patients, they usually require larger doses of rhGH than do older adults with GHD. Starting doses of 0.4 to 0.8 mg/day are recommended with increments of 0.2 to 0.4 mg/day every 4-6 weeks (using serum IGF-1 levels

and the occurrence of rhGH-related adverse effects as indicators for up-titration or down-titration). Maintenance doses for transition patients are usually are in the range of 1.2 to 2.5 mg/day (which is much higher than the ~0.5 mg/day required by the average 50 year old man or the up to ~1.0 mg/day usually required by the average 50 year old woman on hormone replacement therapy. Once these patients are older than ~25 years of age, they will most likely require signficiantly lower doses of rhGH to treat their adult GHD.

2.6.2 TS - Product Development Rationale; Epidemiology & Clinical Manifestations; Current Treatment Guidelines Including the Use of Recombinant Human GH

2.6.2.1 Product Development Rationale for TS

Pituitary-derived GH in TS was first administered to patients with TS over 40 years ago (1). In 1997, Humatrope and Nutropin were approved in the USA for the treatment of short stature associated with TS (with an orphan designation). Subsequently, earlier in 2006, Genotropin was approved for the same indication. Since that time, a large amount of literature has been published demonstrating the short-term and long-term benefits of rhGH therapy in TS patients (see Section 2.6.2.4.1 ahead). When the period of orphan exclusivity ended in 2004, the sponsor requested the pre-sNDA meeting described in Section 2.5 above, and subsequently submitted the 2 TS studies described in Section 2.5 above on 30Nov05 in support of the TS indication.

2.6.2.2 Epidemiology and Clinical Manifestations of TS
(see review references 20-24 supporting the information in this section)

TS occurs in approximately 1 in every 1,900 live female births (25) and is caused by a loss or abnormality of the second X chromosome in at least 1 major cell line in the body. The 2 principal features of TS are short stature and ovarian dysgenesis. Absent treatment with rhGH, girls with TS attain a FH approximately 21 cm shorter than the normal female population (26). Ovarian failure occurs in the vast majority of girls, mandating lifelong estrogen therapy beginning in adolescence. Other TS stigmata include may include neck webbing, cubitus valgus, hyperconvex nails, ptosis, facial nevi, and peripheral lymphedema. In addition, left-sided congenital cardiac anomalies (i.e., coarctation of the aorta, bicuspid aortic valve, higher risk for aortic root dilatation/aortic dissection), renal anomalies (i.e., horseshoe kidney and duplication of the collecting system), middle ear anomalies, type 2 diabetes mellitus, scoliosis, slipped capital femoral epiphysis, thyroid dysfunction and autoimmune disorders are more common in TS than in unaffected girls. Although the distribution of intelligence in TS is similar to the general population, girls with TS may have specific cognitive difficulties (i.e., mathematics, spatial tasks). As a result of these cognitive difficulties, as well as other behavioral issues and their short stature per se, girls with TS often times have significant socialization issues.

2.6.2.3 Growth of Untreated Children with TS

In a study (27-28; Ranke et al) of 150 untreated TS patients at 3 sites in Germany, the mean height at age 5 years was 95.7 cm ± 4.6 (~38 inches=3'2"), at age 14 years was 134.0 cm ± 4.6 (~53 inches=4'5") and **at 16 years was 141.1 cm** ± 5.4 (~56 inches=4'8"), i.e. the pubertal growth spurt (~3 inches) was minimal. Compared with age-matched non-TS girls, an increase in height deficit was apparent until age 14 years when the deficit slowed, i.e. it is well known that the HV of the average non-TS girl decreases after menarche due to the enhancement of epiphyseal closure by estrogen. In another study reflecting the results of 4 European studies (29; Lyon et al), the historical FH observed in untreated girls with TS was similar (i.e., **143.2 cm**). Finally, in a study conducted in Italy, the mean FH of untreated girls with TS was **142.5 ± 7.0** (30). It should be noted that some investigators question the current validity and applicability of these earlier estimations of the FH of untreated girls with TS by Lyon (29) and Ranke (27-28). The mean adult height of 149 of the untreated TS patients followed by Sybert and McCauley in Washington state is **148 cm** (20), and the mean adult height of 69 untreated TS patients in a recent European study published by Massa et al was **147 cm** (31).

In younger children, the reduction in height and weight was of the same relative magnitude; however, with increasing age, weight increased more relative to height. This relative weight increase was primarily due to truncal obesity (27).

In younger children, BA was decreased compared to chronological age (CA), but BA progressed at the same rate observed in non-TS children until ~age 12 years. Thereafter, BA progression fell below 1 year per each chronological year; closure of the epiphyses may not occur until ~age 19 years. Thus, there is retardation in BA compared to CA in TS children at all ages, especially after ~age 12 years (27).

2.6.2.3.1 Predicting Final Adult Height/FH in Untreated Children with TS

Prediction methods for estimating final adult height have been utilized for approximately 60 years, and are generally considered accurate for most purposes (32-33). The most common procedure utilized to predict adult height in children with short statue (including girls with TS) is the B-P PredAH method (wherein the percentage of FH reflected by the patient's current achieved height at an observed Greulich & Pyle BA (34) is read from a table constructed on the basis of the growth data of healthy children, and then used to calculate the B-P PredAH (35). An alternate commonly used adult height prediction method is referred to as the projected adult height (ProjAH). The ProjAH method assumes that the FH SDS will be equivalent to the height SDS at the current actual CA of the subject, i.e. the patient's height SDS at the time of the initial evaluation is extrapolated. The ProjAH method was modified by Lyon et al by applying linear regression to the results of 4 European studies, resulting in the so-called mProjAH method (29).

Zachmann et al reported that in children with TS, the B-P PredAH method was as accurate as in healthy, unaffected children (36). On the other hand, van Teunenbroek et al **concluded that the ProjAH method was superior to methods incorporating BA assessment, such as the B-P PredAH method** (37). Depending on the age and cohort studied, the B-P PredAH method yielded a mean error ranging from 8.0 to 12.1 cm. In contrast, the ProjAH method yielded a mean error of 0.4-2.7 cm, and the mProjAH method 0.1-2.0 cm (37).

The potential greater utility of the mProjAH and unmodified ProjAH methods as compared with the B-P PredAH method in predicting final adult height in TS children is not surprising. BA determinations are commonly felt to be misleading in pathological states such as TS, since BA references are obtained in healthy subjects who presumably manifest normal physiological bone maturation. In TS, the maturation of the wrist and hand bones is frequently discordant which may distort BA measurements. Additionally, in girls with TS, HV decreases with advancing age, and the adolescent growth spurt is minimal, which may also result in less accurate BA-based height prediction methods (e.g., the B-P PredAH method).

Using the mProjAH and ProjAH methods, Lyon (29) retrospectively compared the predicted adult heights (performed at age 3-12 years) with the actual final adult heights (obtained at ages 19-24 years) in untreated girls with TS, and found a correlation coefficient of 0.95 ($p<0.01$). However, the mean error of the unmodified ProjAH was 3.3 cm and that of the mProjAH was 0.6 cm, suggesting a greater utility for the mProjAH method. The mProjAH method appeared to be least useful when the BA was significantly delayed (29).

Confirming the accuracy of the mProjAH, Rosenfeld et al found that the mean error in an untreated control group of 25 American girls with TS was 0.0 cm (38). Lin et al studied a cohort of girls with TS who were naive to rhGH, but treated with low dose estrogen and oxandrolone; in this study, the mProjAH differed from actual final adult height by only 0.37 cm (39). Finally, Dacou-Voutetakis et al evaluated 27 untreated TS girls and found that mProjAH correlated well with FH, with a mean error of only 0.7 cm (40), and Pasquino et al reported that the mProjAH in 18 untreated Italian girls with TS correlated well with actual adult height, with a mean error of only 0.26 SD (41).

In conclusion, it would appear that all of the methods used to predict final adult height in untreated girls with TS have utility, but that the ProjAH and mProjAH methods appear to be more accurate than the BA-based B-P PredAH method, and that the mProjAH method appears to be somewhat more accurate than the unmodified ProjAH method.

In that the B-P PredAH was used to predict final adult height at baseline and following rhGH treatment in Study BP-EU-002, and in that this Medical Officer will be reviewing the results of published FH studies in TS patients (wherein final adult heights after treatment with rhGH were compared with predicted adult heights at baseline) in the Efficacy Summary/Discussion section ahead (see Section 6.2.5.1), the preceding section provides appropriate and necessary background information.

2.6.2.4 Current Treatment Guidelines for Children with Growth Failure Associated with TS

2.6.2.4.1 rhGH

Numerous studies conducted during the past 15 years have demonstrated that treatment with rhGH accelerates short-term growth in girls with TS. More recently, published studies have shown that treatment of TS children with rhGH results in an increase in FH (compared with concurrent untreated controls, historical untreated controls and/or predicted adult height at

baseline), and normalization of FH (i.e., FH >5 feet) in many patients. **The most important of these studies will be tabulated, discussed and referenced in the Efficacy Summary/Discussion section ahead** (see Section 6.2.5.1).

Therefore, the **standard of care guideline** for the clinical use of rhGH published by the AACE in 2003 recommends initiation of rhGH as soon as the height of a TS girl is below the 5th percentile of the normal growth curve (8). The recommendations published by Saenger et al in 2001 following an international multidisciplinary workshop on the management of patients with TS held in March 2000 are essentially identical (42). Furthermore, the LWPES Drug and Therapeutics Committee cites rhGH as an important pharmacological agent to increase linear growth in children with TS (4). Sybert and McCauley (20) reviewed the University of Washington experience with 532 children and adults with TS; they recommend that rhGH should be considered for every girl with TS (but that parents and children should be told of the limitations of current knowledge about treatment [i.e., their uncertainty regarding the current applicability of the 1985 Lyon growth curve in untreated TS patients] and be given realistic expectations with respect to the resulting gain in height, so that they can make informed decisions).

The AACE recommends therapy with rhGH alone in TS girls younger than 9 to 12 years of age, and treatment of TS girls as young as 2 years of age (although at present only limited experience is available with rhGH treatment for children of this age) (8). The AACE guideline **recommends a starting dose of 0.05 mg/kg per day** (0.35 mg/kg per week; ~equal to the dose recommended in the Package Inserts of the rhGH formulations previously approved for the treatment of short stature associated with TS [up to 0.375 mg/kg per week]), and continuation of rhGH treatment until FH or epiphyseal closure has been documented. It is important to note that there is Scandanavian literature which suggests that treatment of TS children with rhGH at dosages greater than 0.35 mg/kg per week (i.e., as much as 0.45-0.7 mg/kg per week) results in a greater increase in FH, and no apparent increase in adverse events (43-45). Therefore, the AACE guideline also recommends that providers should consider individualized dosing of rhGH in girls with TS in accordance with each patient's response.

2.6.2.4.2 Oxandrolone as Adjunctive Therapy to rhGH

A number of publications during the last 15 years indicate that the addition of oxandrolone to rhGH results in improved short-term height increases (46) and FH outcomes (38, 47-48) (compared to treatment with rhGH alone). Oxandrolone seems to be particularly suited for the promotion of growth because, uniquely among the anabolic steroids, it is not aromatized into substances with estrogenic properties (8). The AACE guideline therefore recommends that providers consider the addition of a nonaromatizable anabolic steroid, such as oxandrolone, to rhGH therapy in TS girls older than 9 to 12 years of age, or in girls older than 8 years of age in whom therapy was instituted when the patient already was far below the 5th percentile of the normal growth curve (8). TS girls treated with anabolic steroids (including oxandrolone) should be monitored for signs of virilization and overly rapid skeletal maturation. Anabolic steroids should not be used alone for the promotion of growth.

2.6.2.4.3 Estrogen Therapy in Girls with TS

Current data indicate that estrogen (administered alone or in conjunction with rhGH) has **no role as a growth promoting agent** in TS girls at any age (8, 49) (i.e., no enhancement of growth/ possible detrimental effect). On the other hand, estrogen therapy (including ethinyl estradiol) is **appropriately used to promote feminization**/puberty in TS girls. However, when used to induce puberty, estrogen therapy may cause fusion of the epiphyses, thereby limiting longitudinal bone growth. In this regard, Chernausek et al reported that rhGH-treated TS patients in whom estrogen replacement was delayed until age 15 gained ~8.4 cm over their projected height at baseline (Lyon; mProjAH method), whereas those starting estrogen at age 12 years gained ~5.1 cm (50). Multivariate analysis revealed that the number of years of rhGH therapy before estrogen treatment was a strong factor in predicting height gained, **indicating that the timing of estrogen replacement therapy may be an important determinant of FH in rhGH-treated girls with TS** (50). In contrast, other investigators have reported that the use of a very low initial dose of ethinyl estradiol (i.e., 2.5 μg) at ~age 13 yrs to induce puberty does not adversely impact the final adult height achieved with rhGH treatment (51-52).

2.6.3.1 Adult GHD - Product Development Rationale; Epidemiology & Clinical Manifestations; Current Treatment Guidelines Regarding the Use of rhGH

2.6.3.1 Product Development Rationale for Adult GHD

On the basis of previously submitted NDA supplements, the Agency has granted approval for the marketing of 6 other somatropin products for the treatment of adult GHD - Lilly (Humatrope; 1996); Genentech (Nutropin AQ and Nutropin; 1997); Pfizer (Genotropin; 1997; orphan designation); and, when the period of orphan exclusivity ended on 31Oct04, Serono (Saizen; 1Nov04), Novo Nordisk (Norditropin Cartridges; 1Nov04) and Sandoz (Omnitrope; 2006; 505(b)2). During the last ~15 years, a very large amount of literature (clinical trials, review articles and consensus guidelines) has been published demonstrating the efficacy of rhGH therapy in GHD adults (see Section 2.6.3.3 ahead). Since the period of orphan exclusivity ended in 2004, the sponsor requested the pre-sNDA meeting described in Section 2.5 above - at which time it was agreed that the results of Study HGCL-001 (in addition to a review of the literature) would be submitted in support of the adult GHD indication.

2.6.3.2 Epidemiology and Clinical Manifestations (including diagnosis) of Adult GHD
(see review references 53-58 supporting the information in this section)

It is estimated that acquired hypopituitarism associated with GHD annually affects 10 people per million. The syndrome of adult GHD was first characterized ~15 years ago, and there have been numerous publications regarding the clinical presentation, diagnosis and management of adult GHD since that time. Adult GHD patients are further subcategorized into 1) AO GHD patients (onset during adult life; most often a consequence of clearcut organic pituitary/hypothalamic disease, i.e. pituitary/hypothalamic tumor, S/P surgery for a pituitary/hypothalamic tumor, radiation therapy to the head for any reason when the pituitary/hypothalamic area is exposed, S/P severe head trauma; rarely "idiopathic"); and 2) CO GHD patients (patients who required rhGH for short stature during childhood and are then **reconfirmed** as having GHD after FH has been

achieved; most often "idiopathic" and less often a consequence of organic space-occupying disease). Amongst the multiple manifestations of GHD in the adult patient are alterations in body composition (increased FM, truncal fat, VAT and WHR; reduced LBM), dyslipidemia, insulin resistance, osteopenia, reduced exercise capacity and sense of well-being, and, more than likely, an increased risk of atherosclerotic heart disease and cerebrovascular disease.

The diagnosis of adult GHD is typically made by GH provocative testing. The insulin tolerance test (optimal cutpoint 5.1 ng/mL) and the much less invasive arginine-GHRH test (optimal cutpoint 4.1 ng/mL test are the tests of choice (59; Biller et al, 2002). (Caveat: The arginine-GHRH test may be falsely normal in patients with GHD of hypothalamic origin, i.e. S/P radiation therapy.) When 3 or 4 other pituitary hormone deficiencies are present and/or serum IGF-1 levels are well below the age- and gender-referenced normal range (absent other conditions known to lower serum IGF-1, i.e. severe malnutrition or liver disease, poorly controlled diabetes mellitus), GH stimulation testing may not be necessary (60; Hartman et al, 2002). However, a substantial number of adult GHD patients (confirmed by provocative testing) have normal serum IGF-1 levels, i.e. a normal serum IGF-1 level does not exclude GHD and the serum IGF-1 level is of diagnostic value only if it is very low in patients with clearcut organic pituitary disease. Furthermore, absent any reasonable clinical suspicion for organic pituitary disease, a low serum IGF-1 level by itself is not diagnostic for GHD and does not warrant treatment with rhGH; often times, it is the result of the so-called somatopause, i.e. the expected age-related decline in serum IGF-1 (and endogenous GH).

2.6.3.3 Current Treatment Guidelines Regarding the Use of rhGH in Adults with GHD
(see review references 7-9* & 54*-58, 61-62 supporting the information in this section)

Somatropin was first marketed as replacement therapy for adult GHD in 1993, and there are currently **6 different preparations of somatropin approved for the treatment of severe GHD in adults.** Numerous short-term therapeutic trials (e.g., 3, 6 and 12 months) have demonstrated that treatment with rhGH decreases FM/VAT/truncal fat/WHR, increases LBM, decreases LDL cholesterol, increases markers of bone turnover, increases exercise capacity/left ventricular ejection fraction, and improves sense of well being. During prolonged treatment, the increase in LBM continues. After ~2+ years of therapy, BMD may increase. Reduction in adverse cardiovascular events has not yet been proven in long-term outcome studies. **A representative sample of these studies will be tabulated, discussed and referenced in the Efficacy Summary/Discussion section ahead** (see Section 6.1.5.1).

The most common adverse effects observed after the administration of somatropin to adult GHD patients relate to somatropin-induced fluid accumulation, i.e. edema, arthralgia, myalgia, carpal tunnel syndrome, hypoaesthesia, and paraesthesia. Furthermore, these patients must be monitored very carefully as well for somatropin-induced disorders of glucose homeostasis.

Extremely current consensus guidelines issued by the Endocrine Society (54) recommend beginning with small non-weight based doses (i.e., 0.3 mg/day in patients 30-60 years old, 0.1-0.2 mg/day if >60, 0.4-0.5 if if <30) and then gradually uptitrating based on age- and gender-referenced serum IGF-1 (63) (i.e., many, including this Medical Officer/clinician, consider serum

IGF-1 SDS between 0 and +1 the ideal target range). Doses may also be uptitrated based on the body composition response, and should be down-titrated in the event of serious and/or severe adverse events or if serum IGF-1 SDS exceed +2. Elderly patients are more prone to somatropin-related adverse events, as are obese patients if weight based dosing is utilized. Menopausal/hypogonadal women treated with oral estrogen replacement therapy (ERT) require almost twice as much rhGH as men (i.e., ~0.8 mg/day or more in women on ERT vs. ~0.4 mg/d or less in older men) in order to achieve similar efficacy/IGF-1 levels. Menopausal/hypogonadal women treated with transdermal ERT or not treated with estrogen require doses closer to men. Menstruating women and premenopausal women treated with birth control pills require doses closer to women receiving oral ERT. Younger patients require larger amounts of somatropin (sometimes as much as 2 mg/day = ~0.025 mg/kg/day in an 80 kg person) to achieve satisfactory efficacy, but fortunately tolerate these larger doses better than older adults (as stated above).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

See CMC review.

This Medical Officer coordinated with the Division's CMC reviewer on a number of occasions. He had no concerns with 1) the 5 mg = 15 IU Valtropin (vs. 1.33 mg = 4 IU Eutropin™ INJ) issue discussed at length in Section 5.1 below; 2) the use of the 16 IU UK Humatrope (vs. the 15 IU USA Humatrope) used in Studies BP-EU-003 and BP-EU-001; 3) the use of native vs. recombinant aminopeptidase to remove the methionyl group after the recombinant synthesis of Valtropin; 4) the use of S. cerevisiae (yeast) as the vector for recombinant synthesis of Valtropin (vs. e. coli for most of the other approved rhGH formulations); or 5) the choice of excipients in the formulation, i.e. buffers, stabilizers, preservative (m-cresol)..

The CMC labeling edits/changes for the Description, Stability and Storage, and How Supplied sections, as well as the Administration subsection of the Dosage and Administration section have been incorporated in this Medical Officer's labeling review (including some editorial input by myself) (see Section 10 ahead).

3.2 Animal Toxicology

See review by the Division's Toxicology Reviewers.

Although this NDA was submitted by the 505(1)(a) pathway, in support of, technically speaking, a NME, the Division's Toxicology Teader, determined that the relately abridged toxiciology component of this submission was sufficient - in that **the efficacy and safety profile of the 7 previously approved somatropin formulations is very well established in many thousands of patients, and the risk/benefit ratio of previously approved somatropin formulations is quite satisfactory.**

The Toxicology labeling edits/changes for Carcinogenicity, Mutagenicity and Fertility, and Pregnancy subsections of the Precautions section have been incorporated in this Medical Officer's labeling review (including some editorial input by myself) (see Section 10 ahead).

3.3 Statistics

This Medical Officer collaborated extensively and frequently with 2 of the Division's Statistical Reviewers as well as the Statistical Team Leader in the preparation of the clinical review. The most important findings of the Division's Statistical Reviewers have been incorporated into this Medical Officer's review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The electronically submitted Clinical Overview, Clinical Summary and individual Clinical Study Reports for the pediatric GHD study (BP-EU-003), the 2 TS studies (BP-EU-002 and the Korean TS study) and the adult GHD study (HGCL-001) submitted by the sponsor on 30Nov05, the safety update (containing followup safety [and efficacy] information from BP-EU-003-RO and BP-EU-002-RO) submitted by the sponsor on 28Apr06, as well as the additional information submitted electronically (and by email) by the sponsor at the request of this Medical Officer on 7Aug06, 11Aug06, 14Aug06, 16Aug06, 17Aug06, 22Aug06, 23Aug06, 25Aug06, 30Aug06, 31Aug06 and 1Sept06 (written responses to questions posed during a formal teleconferences held on 7Aug06 and emails sent by this Medical Officer on 21Aug06, 22Aug06, 27Aug06, 30Aug06, 1Sept06, 8Sept06 and 11Sept06), were thoroughly and comprehensively reviewed by this Medical Officer.

4.2 Table Describing Clinical Studies Contained in the NDA Submission

As briefly described in Table 1 below, there were 4 pivotal clinical studies contained in this NDA submission – 1 for the pediatric GHD indication, 2 for the TS indication and 1 for the adult GHD indication. In addition, a pharmacokinetic (PK) study comparing single doses of Valtropin and a comparator, Humatrope, was submitted for review (Study BP-EU-001) by the Division's Biopharmaceutical Reviewers.

Table 1
Tabulation of Clinical Studies Contained in NDA 21-905 Submission

Study Number	Study Design (# Randomized)
BP-EU-003 23 centers in in 11 countries	A Phase III, 12 month, multicenter, randomized, double-blind, active-controlled (Humatrope), non-inferiority study, conducted in **children with GHD** (149)
BP-EU-002 1 center (Moscow)	A Phase III, 12 month, single center, open-label, single arm, uncontrolled study conducted in **children with TS** (30)
TS-KOR-06102005 4 centers in Korea	A Phase III, 12 month, single center, open-label, single arm, uncontrolled study conducted in **children with TS** (60)
HGCL-001 6 centers in Korea	A Phase III, 6 month, multicenter, randomized, double-blind, placebo-controlled, 3-arm (with 2 arms having a crossover design) study was conducted in **adults with GHD** (92)

4.4 Data Quality and Integrity

Monitoring visits by the sponsor were adequate. Case report forms (CRFs) were compared with source documents and checked for completeness and accuracy. Multiple audits of the database were conducted to ensure that the data entered were a true representation of the original CRF entries. In addition, the Division's Statistical Reviewer expressed confidence in the raw SAS data provided by the sponsor.

4.5 Compliance with Good Clinical Practices

The sponsor appeared to adhere to appropriate clinical practices in conducting the 4 clinical studies contained Table 1 above.

4.6 Financial Disclosures

Complete financial disclosure information was submitted by the sponsor and reviewed by this Medical Officer. Seventy five out of the 76 primary investigators/subinvestigators who participated in Study BP-EU-003 (see below), 5 primary investigators/subinvestigators who participated in Study BP-EU-002, 4 primary investigators/subinvestigators who participated in the Korean TS study and 6 primary investigators/subinvestigators who participated in Study HGCL-001 had no financial information to disclose. More specifically, none of these investigators 1) had compensation potentially affected by the outcome of the studies; 2) received

significant payments of other sorts by the sponsor of the studies; 3) had proprietary interest in the tested products; or 4) had significant equity interest in the sponsor of the tested product.

Nine primary investigators/subinvestigators who participated in Study HGCL-001 could not be located. This study was conducted between 1995 and 1997, and the sponsor states that it made a "good faith" effort to locate these people, but could not.

One investigator [redacted] who participated in Study [redacted] at an [redacted] site was hired as a paid consultant by the sponsor's affiliate [redacted] in [redacted] with compensation possibly exceeding $50,000. In order to minimize any potential bias associated with this fact, the sponsor visited with this investigator on 2 occasions prior to study launch in 2001 to 1) verify his credentials, ethics, and integrity; and 2) review with him all relevant federal regulations regarding his participation in the study as a previously retained paid consultant. b(6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

To support the approval of the new Valtropin® (5 mg = 15 IU per vial) formulation for the 3 indications described above, the sponsor submitted a PK study (BP-EU-001), in addition to the 4 clinical studies reviewed by this Medial Officer.

In a double-blind, randomized, single dose study in 24 healthy volunteers, Valtropin® was crossed over to a marketed comparator, Humatrope (UK approved formulation with 16 IU somatropin per vial ["equivalent" to USA-approved Humatrope formulation with 15 IU per vial]), to evaluate relative bioavailability. The study was performed without endogenous growth hormone suppression, and PK analyses were conducted with baseline corrections. A single, SC administration of Valtropin® 0.073 mg/kg of body weight vs. the same dose of Humatrope resulted in a mean maximum serum concentration (C_{max}) of 43.97 ng/mL vs. 38.64 ng/mL, respectively, and an area under the curve ($AUC_{0\text{-}24hr}$) of 369.90 ng·hr/mL vs. 337.50 ng·hr/mL, respectively. C_{max} was reached at 4.00 hr versus 5.00 hr, respectively, and terminal elimination half-life was 3.03 hr vs. 3.12 hr, respectively. **The relative bioavailability of Valtropin® compared to UK-approved Humatrope (expressed as a ratio) was estimated at 109.5% based on AUC - 90% confidence intervals (CI) ranged from 101% to 119% which was within the range of 80% to 125% indicating bioequivalence.**

5.1.1 Waiver of Need for a Bridging Study Between the 5 mg = 15 IU Valtropin formulation (to-be-approved) and the older 1.33 mg = 4 IU Eutropin™ INJ formulation (not-to-be-approved)

A comparable somatropin drug product (Eutropin™ INJ [1.33 mg = 4 IU per vial]) which is qualitatively identical (with respect to the drug substance/active pharmaceutical ingredient [somatropin] and the excipients) to the to-be-marketed-in-the-USA drug product (Valtropin® [5

mg = 15 IU per vial]) has been marketed in Korea since 1992 (and in 11 other countries subsequent to 1992) for the treatment of pediatric patients with GHD. In 1998, Eutropin™ INJ was first approved for the treatment of children with short stature associated with Turner syndrome in Korea, and, in 2003, Eutropin™ INJ was first approved for the treatment of patients with adult GHD in Korea. Subsequently, Eutropin™ INJ was approved for the treatment of TS children and adult GHD patients in 9 other countries and 2 other countries, respectively.

Based on the fact that **both** formulations (the to-be-marketed-in-the-USA 5 mg = 15 IU Valtropin formulation and the older not-to-be-marketed-in-the-USA 1.33 mg = 4 IU Eutropin™ INJ formulation) **resulted in more than adequate and comparable responses in 1) TS patients** (both studies are part of the NDA submission and described above), **and also in pediatric GHD patients** (the 5 mg = 15 IU Valtropin formulation was used in the pediatric GHD study submitted with the NDA described above and, on 1Sept06, the sponsor provided this Medical Officer with synopses of 2 pediatric GHD studies using the 1.33 mg = 4 IU Eutropin™ INJ formulation conducted in **Korea and China**), **this Medical Officer (as well as the DMEP Division Director and the Biopharmaceutical Reviewers and their superiors) agree that a *biopharmaceutical bridging study* between the to-be-marketed-in-the-USA 5 mg = 15 IU Valtropin formulation and the older not-to-be-marketed-in-the-USA 1.33 mg = 4 IU Eutropin™ INJ formulation *is unnecessary*. In addition, we agree that the findings in pediatric GHD and TS children described earlier in this paragraph can readily be extrapolated to the adult GHD population, i.e. if a 5 mg = 15 IU Valtropin study were to be performed in adult GHD patients, the results would be very comparable to the results obtained when the 1.33 mg = 4 IU Eutropin™ INJ formulation was used in Study HGCL-001 (contained in this NDA submission). Therefore, as a group, we agree that the adult GHD indication can be approved (in conjunction with the pediatric GHD and TS indications) - even though the pivotal adult GHD study was conducted utilizing the older Eutropin™ INJ formulation**.

5.2 Pharmacodynamics

Not performed.

5.3 Clinical Pharmacology Labeling Recommendations

These edits/changes recommended by the Division's Biopharmaceutical Reviewers in the Pharmacokinetics and Special Populations subsections of the Clinical Pharmacology section have been incorporated in this Medical Officer's labeling review (see Section 10 ahead).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication Number 1 - Pediatric GHD

6.1.1 Methods

See Section 4.1 above.

6.1.2 General Discussion of Endpoints

The endpoints for this study were standard measures of linear growth. See Section 6.1.3.3 below.

6.1.3 Study Design

6.1.3.1 Study Design for Study BP-EU-003 (2001 - 2003)

6.1.3.1 General Description (including dosing)

Study BP-EU-003 was a Phase III, 12 month, multicenter (26 sites with 2-14 patients per site), multinational (12 countries) randomized, double-blind, parallel group, active-controlled, non-inferiority study conducted in treatment-naïve pediatric GHD patients with short stature comparing the effects of Valtropin (5 mg = 15 IU formulation) and a previously approved somatropin comparator (Humatrope [UK approved formulation with 16 IU somatropin per vial - "equivalent" to USA-approved Humatrope formulation with 15 IU per vial]) on linear growth and bone maturation. Patients were randomized to 12 months of treatment with Valtropin or Humatrope. Daily SC injections of Valtropin or Humatrope (0.033 mg/kg/day) were administered to patients in the 2 treatment groups (i.e., 0.23 mg/kg per week divided into 7 equal injections). To prevent lipoatrophy, the injection site was varied/rotated. The primary efficacy endpoint was mean HV (cm/yr) at 12 months, and the primary efficacy objective was to show that the mean HV observed after 12 months treatment with Valtropin was non-inferior to that seen after 12 months treatment with Humatrope.

Children who 1) completed the initial Phase III study; 2) were willing to continue their participation in the clinical trial; 3) had responded to somatropin therapy; 4) were euthyroid at Month 12; 5) had not developed other chronic systemic diseases (in particular, diabetes mellitus) during the Phase III study; 6) had open epiphyses at Month 12; and 7) had not received other growth promoting medication were considered eligible for inclusion in Study BP-EU-003-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months and patients previously treated with Humatrope for 12 months were switched to Valtropin for an additional 12 months.
A very brief description of the efficacy and safety results of this rollover study are presented later in this Medical Officer's review in Sections 6.1.5 and 7.1.2, respectively.

6.1.3.1.2 Major Inclusion/Exclusion Criteria

Inclusion Criteria:

- Prepubertal children (males age 3-11 yr or females age 3-10 yr)
- Confirmed diagnosis of GHD as determined by two different GH provocation tests (i.e., insulin tolerance test, clonidine test, arginine test) defined as a peak plasma GH level <10.0 ng/ml (measured by the AutoDELFIA method at the Central Laboratory of Leipzig University)
- HT SDS_{CA} <–2 SD (using CDC standard for normal children [64])*
- Pre-treatment HV below the 25th percentile (corresponding to HV SDS_{CA} <-0.7 using the Prader standard for normal children [65]).** **Pre-treatment HV was calculated by regression** using heights obtained 3 months to 2 years prior to study enrollment, and heights obtained at screening/baseline. Height data had to be collected by using a wall-mounted stadiometer
- Confirmed to be rhGH treatment naïve (or previously treated with rhGH with a therapy free interval of at least 2 years prior to enrollment in the study)
- Confirmed to be negative for anti-hGH antibodies during the screening visit
- Open epiphyses; BA ≤10 yr for boys and ≤9 years for girls; ratio of BA/CA <0.9
- Euthyroid - controlled on medication, if needed

*CDC standard reflecting the growth of normal American children (64) was chosen because 1) country-specific standards for the multiple countries included in this study do not exist; 2) the CDC growth chart reference population contains a range of racial and ethnic groups; and 3) CDC growth data are highly regarded internationally, and have been used in multiple published European and American growth studies in the past.
**The normative growth data for HV from the Prader et al paper (65) was used to calculate HV SDS because 1) there are no CDC reference data for HV; and 2) the Prader et al normative data encompasses the ages of the children enrolled in this study, and have been used in multiple published European and American growth studies in the past.

Exclusion Criteria:

Any clinically significant abnormality likely to affect growth or the ability to evaluate growth such as, but not limited to:

- Other well known non-GHD causes of short stature, i.e. Turner syndrome, chronic renal insufficiency, Laron syndrome
- Poorly controlled insufficiencies of other pituitary-end organ axes (e.g., thyroid stimulating hormone [TSH]/thyroxine, adrenocorticotropic hormone [ACTH]/cortisol, vasopressin/antidiuretic hormone [ADH])
- Presence of absolute contraindication to treatment with rhGH (e.g., diabetes mellitus, active malignancy, hypertension, acute critical illness). **Although history of a previous pituitary/hypothalamic tumor (including craniopharyngioma) is not an absolute contraindication to the use of rhGH (if these tumors have been appropriately**

treated and are currently radiographically absent or stable), such children were in fact excluded from this study.

- Major medical illnesses (e.g., human immunodeficiency virus (HIV) positivity or related disease, history of bone marrow transplantation, recent surgery, hyperlipidemia, cardiovascular disease, chronic infection including tuberculosis) or clinically relevant significantly abnormal laboratory tests (e.g., disturbed calcium homeostasis)
- Use of the following medications* (e.g., pharmacologic amounts of glucocorticoids*, estrogen, methylphenidates, anti-infective drugs, immunosuppressants, antitumor therapy); ***stable replacement treatment (for at least 3 months) for associated hypothyroidism, hypoadrenalism and diabetes insipidus was allowed.**
- Drug or alcohol abuse

6.1.3.1.3 Efficacy Endpoints

The primary efficacy parameter reflecting linear growth was HV at Month 12 (as in the case of the pre-treatment HV, HV at Month 12 was calculated by regression).

Secondary efficacy parameters included:

- Change in HV (cm/yr)
- Height gain
- HV SDS_{CA} and change in HV SDS_{CA} (Prader standard for normal children [65])
- Height SDS_{CA} and change in height SDS_{CA} (CDC standard for normal children [64])
- Height SDS_{BA} and change in height SDS_{BA} (CDC standard for normal children [64])
- BA (according to the method of Greulich and Pyle [34]; wrist radiographs were read by the same examiner without knowledge of the age of the patients
- BA/CA (bone maturation index)
- Bayley-Pinneau (B-P) PredAH and change in B-P PredAH (cm) (35)
- B-P PredAH SDS and change in B-P PredAH SDS (35)
- Weight

Standing height was measured with a wall-mounted Harpenden stadiometer or comparable wall-mounted device, and the mean of 3 measurements was recorded at baseline, 3, 6, 9 and 12 months.

6.1.3.1.4 Safety Evaluations

Safety parameters (including anti-GH/anti-S. cerevisiae antibodies, glycemic measures, thyroid function tests, serum IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) levels, and routine hematology/chemistries/urinalysis) were obtained at baseline, 3, 6, 9 and 12 months. Electrocardiograms were obtained at baseline and Month 12. All adverse events and concomitant drug therapy were recorded at each clinic visit.

6.1.3.1.5 Statistical Methods

6.1.3.1.5.1 Sample Size Calculation

With a randomization ratio between the 2 treatment arms of 2:1 (Valtropin:Humatrope), at least 87 patients (58 Valtropin and 29 Humatrope) had to be included in the analysis in order to reject the null hypothesis of inferiority of Valtropin in favor of the alternative hypothesis of non-inferiority of Valtropin with a power of 90 % (with a type I error rate of $\alpha = 0.025$ [one sided]). Expecting that about 20% of randomized patients would not be available for the per protocol (PP) analysis set, a total of 111 patients (74 Valtropin and 37 Humatrope) were to be randomized for the clinical trial. Because of the large number of participating centers across many countries, and the expectation that the screening period would be long and the screening failure rate would be high, it was decided to enroll ~150 (rather than 111) patients.

6.1.3.1.5.2 Populations Analyzed

The Division's Statistical Reviewer focused/performed her primary (and secondary) efficacy analyses on the ITT/FAS population with LOCF (patients who had received at least 1 dose of study drug and who had at least 1 post-treatment efficacy measurement). **Of note, patients 1) whose height had not been measured with an appropriate wall-mounted stadiometer; 2) who discontinued before 6 months on treatment; or 3) whose pre-treatment HV was incomplete/inaccurate were excluded from the ITT/FAS population.** The sponsor focused/performed its primary (and secondary) efficacy analyses on the PP population (which excluded 1) **patients with major protocol violations**; 2) patients who were discontinued at any time during the study for reasons definitely not related to study drug administration; and 3) patients with inadequate documentation). The sponsor also performed primary and secondary analyses on the ITT/FAS population in support of its PP population analyses.

6.1.3.1.5.3 Analyses of the Primary (and Secondary) Efficacy Endpoints

As stated above, the primary efficacy endpoint was mean HV (cm/yr) at 12 months, and the primary efficacy objective was to show that the mean HV observed after 12 months of treatment with Valtropin was non-inferior to that seen after 12 months of treatment with Humatrope.

In order to demonstrate the non-inferiority of Valtropin, both the Division's Statistical Reviewer and the sponsor **compared Month 12 HV across/between the 2 treatment groups using ANCOVA with baseline CA, pre-treatment HV and log of maximum stimulated GH level as covariates** (applying a one-sided t-test [at a level of 2.5%] for 2 independent samples according to the procedure used for sample size justification) **in the ITT/FAS population with LOCF (primary focus of the Division's efficacy review and secondary focus of the sponsor's efficacy review) and the PP population (primary focus of the sponsor's efficacy review).** In addition, the Division's Statistical Reviewer performed an ANCOVA using a fourth covariate (baseline height SDS_{CA}). **Once the adjusted LS mean treatment difference and its associated CI were determined, the lower bound of the 95% CI surrounding the treatment difference was compared with the mutually agreed to pre-established non-inferiority**

margin of 2 cm/yr, i.e. if the lower bound of the CI surrounding the treatment difference was greater than -2, then Valtropin would be deemed non-inferior to Humatrope.

The sponsor also performed ANCOVAs to assess **between-group** differences with respect to Month 12 values of all of the auxological secondary efficacy parameters. At the request of this Medical Officer, the Division's Statistical Reviewer performed ANCOVAs (3 original covariates) to assess **between-group** differences in changes in multiple auxological secondary efficacy endpoints (e.g., **HV**, HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, PAH SDS and PAH [cm]).

Furthermore, the Division's Statistical Reviewer performed paired t-tests (a parametric method) and Wilcoxon's signed rank tests (a non-parametric method) to determine if HV, HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, PAH SDS and PAH (cm) were significantly improved from baseline after 12 months of treatment with Valtropin specifically (i.e., **within-group analyses**).

6.1.3.1.5.4 Safety Analyses

Safety results were presented utilizing descriptive statistics.

6.1.4 Efficacy Findings

6.1.4.1 Enrollment and Disposition

Three hundred and thirty four children were screened, and 185 were screening failures. Therefore, 149 children were randomized in a 2:1 ratio to receive Valtropin (n=99) or Humatrope (n=50). Two patients (1 in each treatment group) were never treated, i.e. there were 147 patients in the safety analysis set (98 treated with Valtropin and 49 treated with Humatrope - see ahead to Integrated Summary of Safety). **The ITT/FAS population (the primary focus of the Division's efficacy review) consisted of 129 children (88 treated with Valtropin and 41 treated with Humatrope), i.e. 18 patients were excluded because of the protocol-specified reasons described in Section 6.1.3.1.5.2 above.** The PP population (the primary focus of the sponsor's efficacy review) consisted of 102 children (70 treated with Valtropin and 32 treated with Humatrope), i.e. 45 patients (~30% of randomized patients) were excluded because of the protocol-specified reasons described in Section 6.1.3.1.5.2, especially major protocol violations (the most common major protocol violations were missed doses [>14 in ~10% of each group] and deviation from the target number of doses or days on-study [>±14 doses or days, respectively]).
As seen in Table 2, greater than 90% of patients in each treatment arm completed the study. Three patients (2 receiving Valtropin and 1 receiving Humatrope) discontinued because of adverse events (see Integrated Summary of Safety).

Table 2 - Study BP-EU-003

Subject Disposition

	Valtropin	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%)
Adverse events	2	1	3
Lack of compliance*	2*	2	4
Withdrawn consent	3	3	6
Violation of exclusion criterion	1	0	1

*One of these children was discontinued because >20% of injections were missed - **the only patient in the study who manifested that degree of non-compliance.**

6.1.4.2 Demographics and Baseline Characteristics

As seen in Table 3, combining both treatment groups, mean age was 8.2 yr (half of the children were between 6.6 and 10 yr), 60-70% of patients were male, ~95% were Caucasian, **baseline height SDS_{CA} was -3.43, pre-treatment HV was 3.34 cm/yr, and B-P PredAH was 161 cm (~5' 3").** These demographic and baseline characteristics were similar in the 2 treatment groups. Almost 60% of the children participated at sites in Russia, Turkey and the Ukraine.

GHD was considered to be "idiopathic" in 94 (95.9%) and 48 (98%) of the children in the Valtropin and Humatrope groups, respectively. Only 5 patients (4 in the Valtropin group and 1 in the Humatrope group) had defined organic etiologies of GHD. This is at least in part explained by the fact that patients with a history of a pituitary/hypothalamic tumor **including craniopharyngioma** were excluded. **Nonetheless, preexisting central hypothyroidism/"TSH deficiency" was reported in 26 (26.5%) and 14 (28.6%) of the children in the Valtropin and Humatrope groups, respectively! In this regard, central hypothyroidism has previously been reported in 10-50% of children with "idiopathic" GHD - especially when associated with the combination of 3 abnormalities on magnetic resonance imaging (MRI) scans, i.e. pituitary hypoplasia, stalk interruption, and posterior pituitary ectopia (insert 1-2 references).** (Note: 31 patients in the Valtropin group and 17 patients in the Humatrope group were being treated with "thyroid therapy" at baseline - which implies that some children with preexisting **primary** hypothyroidism children must have been enrolled.) Preexisting central hypoadrenalism was reported in 2 patients (1 in each group), and diabetes insipidus in 4 children (1 in the Valtropin group and 3 in the Humatrope group).

Only 3 patients in the Valtropin group and no patients in the Humatrope reported remote treatment (>2 years prior to enrollment) with rhGH. The clonidine GH provocation test was performed in all patients who subsequently received somatropin treatment (98+49=147); mean peak GH response was 3.6 ng/mL in the Valtropin group and 4.9 ng/mL in the Humatrope group (similar responses and clearly <10 ng/mL). The insulin tolerance test was performed on 70-80%

of children in both treatment groups; mean peak GH response was 2.0 ng/mL in the Valtropin group and 2.3 ng/mL in the Humatrope group (very similar responses and clearly <10 ng/mL).

Table 3 - Study BP-EU-003

Demographic and Baseline Characteristics of All Randomized Subjects

Characteristic		Valtropin	Humatrope	Total
Age (year):	Mean ± SD	8.10 ± 2.08 (98)	8.45 ± 1.99 (49)	8.22 ± 2.05 (147)
	Range	3.97 - 11.67	3.20 - 11.99	3.20 - 11.99
Gender:	Male (%)	69 (69.7)	31 (62)	101 (67.8)
	Female (%)	30 (30.3)	19 (38)	48 (32.2)
Race:	Asian (%)	2 (2.0)	1 (2.0)	3 (2.0)
	Caucasian (%)	94 (95.0)	47 (94.0)	141 (94.6)
	Negroid (%)	2 (2.0)	0	2 (1.3)
	Other (%)	1 (1.0)	2 (4.0)	3 (2.01)
Height (cm):	Mean ± SD	107.28 ± 11.80 (99)	110.63 ± 10.94 (50)	108.41 ± 11.6 (149)
Height SDS_{CA}:	Mean ± SD	-3.52 ± 1.25 (99)	-3.24 ± 1.03 (50)	-3.43 ± 1.19
	Range	-8.07 ~ -2.07	-6.95 ~ -1.77	-8.07 ~ -1.77
HV (cm/year):	Mean ± SD	3.40 ± 1.52 (98)	3.23 ± 1.19 (49)	3.34 ± 1.42
	Range	0.17 - 8.94	0 - 5.74	0 - 8.94
HV SDS_{CA}:	Mean ± SD	-2.49 ± 1.93 (98)	-2.57 ± 1.46 (49)	-2.52 ± 1.78 (147)
B-P PredAH:	Mean ± SD	162.03 ± 9.50 (34)	160.14 ± 8.06 (21)	161.31 ± 8.95 (55)
	Range	144.58 – 184.12	143.04 – 169.55	143.04 – 184.12
Country:	Russia (%)	23 (23.2)	10 (20.0)	33 (22.2)
	Turkey (%)	21 (21.2)	11 (22.0)	32 (21.5)
	Ukraine (%)	14 (14.1)	7 (14.0)	21 (14.1)
	Serbia (%)	9 (9.1)	4 (8.0)	13 (8.7)
	Poland (%)	8 (8.1)	4 (8.0)	12 (8.1)
	Morocco (%)	6 (6.1)	5 (10.0)	11 (7.4)
	Belorussia (%)	6 (6.1)	3 (6.0)	9 (6.0)
	Slovakia (%)	5 (5.05)	1 (2.0)	6 (4.03)
	South Africa (%)	5 (5.05)	2 (4.0)	7 (4.70)
	USA (%)	0 (0.0)	2 (4.0)	2 (1.34)
	Latvia (%)	2 (2.02)	1 (2.0)	3 (2.01)

6.1.4.3 Dosing

As stated earlier, patients were randomized to 12 months of treatment with Valtropin or Humatrope. Daily SC injections of Valtropin or Humatrope (0.033 mg/kg/day) were administered to patients in the 2 treatment groups (i.e., 0.23 mg/kg per week divided into 7 equal injections).

6.1.4.4 Efficacy Results

The results presented below were obtained from the Division's Statistical Reviewer, who for the most part verified all of the sponsor's analyses, and, in addition, performed supplementary analyses at the request of this Medical Officer.

6.1.4.4.1 **Primary Efficacy Endpoint - HV after 12 Months of Treatment with Valtropin vs. Humatrope**

As seen in Table 4, the adjusted LS mean HV ± SE at Month 12 was **11.21 ± 0.23 cm/yr** in the Valtropin group vs. **11.00 ± 0.32 cm/yr** in the Humatrope group, and the **mean treatment difference was 0.21 in favor of Valtropin** (a statistically and clinically non-significant difference). **Valtropin was non-inferior to Humatrope since the lower bound of the 95% CI surrounding the treatment difference (-0.48) was greater than the pre-established non-inferiority margin of - 2 cm/yr. In fact, in that the lower and upper bounds of the CI (-0.48, 0.90) lied in the interval between -2 and +2, Valtropin was "equivalent" to Humatrope.**

Figure 1 is a box plot representation of the raw mean (and median) HVs at Month 12 after treatment with Valtropin vs. Humatrope. Figure 2, a cumulative distribution function, further demonstrates that the HV responses at Month 12 were very similar between/across the 2 treatment groups. Approximately 50% of children treated with Valtropin achieved a Month 12 HV ≥10 cm/yr, and approximately 50% of children treated with Humatrope achieved a Month 12 HV ≥9 cm/yr - reflecting comparable and substantial linear growth responses.

Almost identical results were obtained with the ANCOVA model using 3 covariates (baseline age, pre-treatment HV and log maximum GH after stimulation) and the ANCOVA model where baseline height SDS_{CA} was added a fourth covariate (data not shown). **In addition, the results were very similar when the sponsor performed this analysis in the PP population - in spite of the fact that ~30% of patients in each group committed major protocol violations** (data not shown). Analysis of HV results by country demonstrated that Valtropin was comparable to Humatrope in Turkey and the Ukraine (~21% and ~14%, respectively, of the children enrolled in the study); for the other countries, a decision in favor of non-inferiority could not be made (data not shown). There was no treatment-by-country interaction at the 10% level.

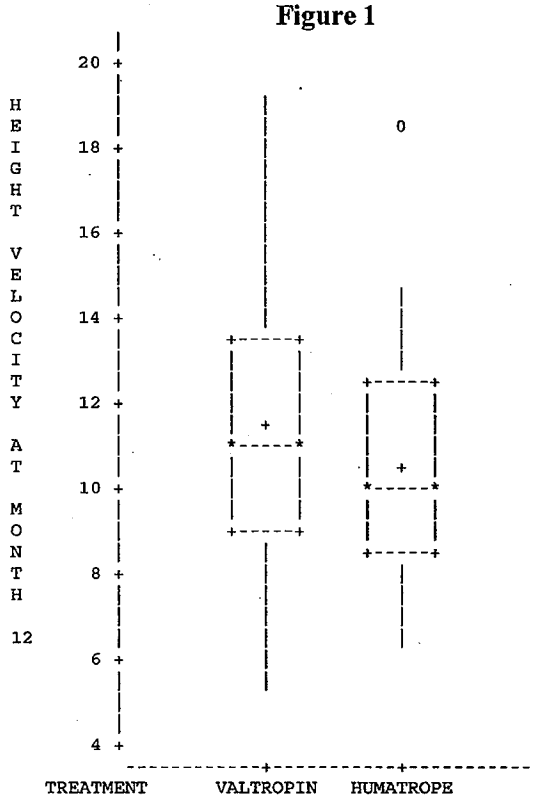
Note: It is reassuring that the HVs at Month 12 **calculated by regression** used in the above analyses were essentially identical to the HVs at Month 12 **based on observed data** (as per the Division's Statistical Reviewer).

Table 4 – BP-EU-003
Difference Between Groups in Height Velocity (Cm/Yr) at Month 12 in a Double-blind Study in Pediatric Patients with GHD

ITT population with LOCF	Valtropin	Humatrope
Raw mean ± SD (n) at Baseline	**3.50 ± 1.45 (88)**	**3.39 ± 1.02 (41)**
Raw mean ± SD (n) at Month 12	**11.36 ± 2.92 (88)**	**10.54 ± 2.61 (41)**
Adjusted LS mean ± SE* (n) at Month 12	**11.21 ± 0.23 (88)**	**11.00 ± 0.32 (41)**
Treatment Difference*	**0.21**	
p-value	**0.54**	
95% CI	**(-0.48, 0.90)**	

*The adjusted LS means were obtained using the sponsor's ANCOVA model, where treatment and country were the fixed factors, and CA at baseline, pre-treatment HV, and log maximum GH level after stimulation were the covariates.

Figure 1

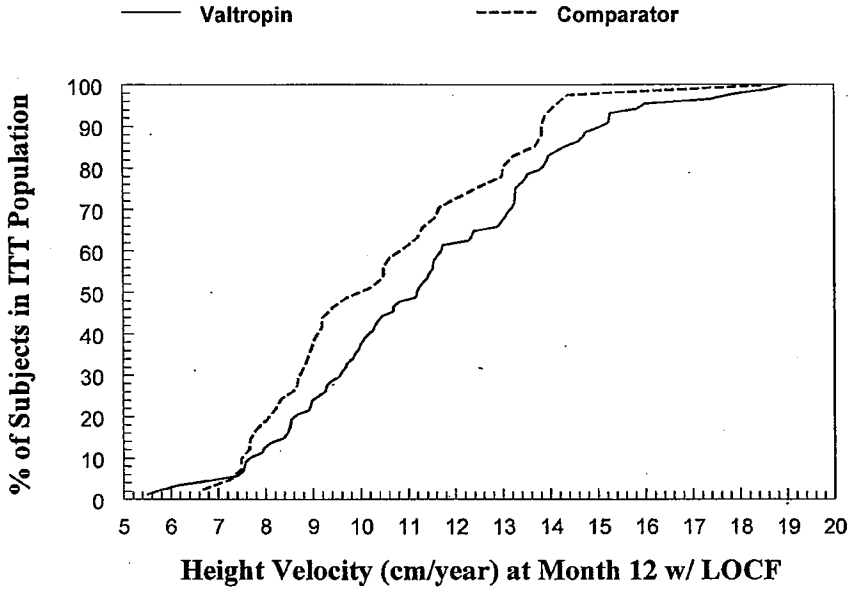


Note: The horizontal line inside the box shows the median and + sign shows the mean. Any value exceeding the 75th percentile value by more than 1.5 times the interquartile range (=75th-25th percentiles) is marked with a 0.

Figure 2

Study BP-EU-003: Cumulative Distribution Function

Height velocity at 12 months expressed as cumulative % of subjects



6.1.4.4.1.1 **Change in HV** after 12 Months of Treatment with Valtropin vs. Humatrope (a secondary efficacy endpoint very closely related to the primary efficacy endpoint, HV at Month 12)

At the request of this Medical Officer, the Division's Statistical Reviewer analyzed the change in HV at Month 12 (a secondary efficacy endpoint very closely related to the primary efficacy endpoint, HV at Month 12).

As seen in Table 5, the adjusted LS mean change in HV ± SE at Month 12 was **7.75 ± 0.23** cm/yr in the Valtropin group vs. **7.54 ± 0.31** cm/yr in the Humatrope group, and the **mean treatment difference was 0.21 in favor of Valtropin** (a statistically and clinically non-significant difference). **Once again, Valtropin was non-inferior to Humatrope since the lower bound of the 95% CI surrounding the treatment difference (-0.48) was greater than the pre-established non-inferiority margin of -2 cm/yr. In fact, in that the lower and upper bounds of the CI (-0.48, 0.90) lied in the interval between -2 and +2, Valtropin once again was "equivalent" to Humatrope.**

As seen in Table 6, the within-group (raw) mean change from baseline at Month 12 in HV (7.87 cm/yr) for the Valtropin group was highly significant (p<0.0001). The results in the Humatrope group were very similar (data not shown).

Table 5 - BP-EU-003
Between-Group Change from Baseline at Month 12 in HV

ITT with LOCF	Adjusted LS Mean Change ± SE (n)				
Efficacy Variable	Valtropin	Humatrope	Treatment Difference	p-value	95% CI (LCI, UCI)
HV	**7.75 ± 0.23 (88)**	**7.54 ± 0.31 (41)**	**0.21**	**0.54**	**(-0.48, 0.90)**

*The adjusted LS means were obtained using the sponsor's ANCOVA model, where treatment and country were the fixed factors, and CA at baseline, pre-treatment HV, and log maximum GH level after stimulation were the covariates.

Table 6 - BP-EU-003 - Valtropin Group Only
Within-Group Change from Baseline at Month 12 in HV

ITT with LOCF	**Valtropin**: Raw Mean ± SD (n)		Raw Mean Change	
Efficacy Variable	Month 0	Month 12	from Baseline	(95% CI)
HV (cm/yr)	**3.50 ± 1.45 (88)**	**11.36 ± 2.92 (88)**	**7.87***	**(7.18, 8.55)**

*p-value for the mean change from baseline at Month 12 was < 0.0001 (paired t-test).

Figure 3, a cumulative distribution function, demonstrates that the change in HV at Month 12 was very similar between/across the 2 treatment groups. Approximately 50% of children treated with Valtropin achieved a Month 12 change in HV ≥7 cm/yr, and approximately 50% of children treated with Humatrope achieved a Month 12 change in HV ≥6 cm/yr - reflecting comparable and substantial linear growth responses. Although the 2 curves had similar profiles, Figure 3 also demonstrates that for almost any cumulative percentage of patients, Valtropin resulted in greater efficacy (i.e., a larger change in HV at Month 12).

As calculated from Figure 3 and depicted in Table 7, all 88 ITT/FAS children in the Valtropin group (as well as the 41 children in the Humatrope group) had responded to treatment at the end of the 12 month trial, i.e. change from baseline in HV at Month 12 >0. In addition, 95.5% (84/88) of children in the Valtropin group manifested a change in HV >2 cm/yr (the value of the non-inferiority margin = the minimal clinically important difference). Furthermore, as seen in Table 7, all 88 ITT/FAS children in the Valtropin group had manifested a positive change in height SDS_{CA} at the end of the 12 month trial (e.g., change from baseline in height SDS_{CA} >0), and 97.7% (86/88) of children in the Valtropin group manifested a change in height SDS_{CA} >0.25 (generally considered to be a very satisfactory 12 month growth response predictive of a substantial increase in FH) (see Section 6.1.4.4.2.1 ahead regarding more information on the change in height SDS_{CA} after treatment with Valtropin vs. Humatrope).

Figure 3

Study BP-EU-003: Cumulative Distribution Function

Change in height velocity expressed as cumulative % of subjects

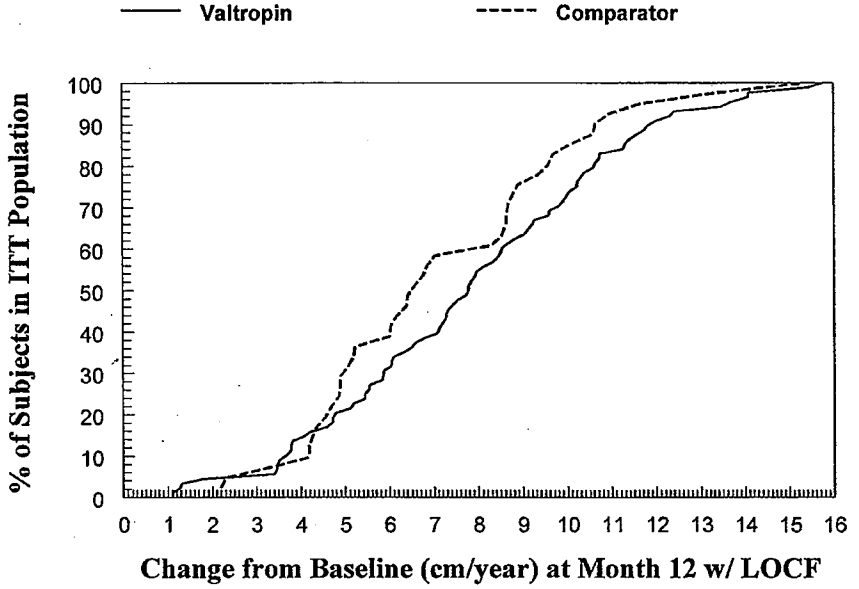


Table 7 – BP-EU-003
Responder Rate for Change from Baseline at Month 12 in HV and Height SDS_{CA} in the Valtropin Group Alone

ITT Population	Height Velocity (cm/year)		Height SDS_{CA}	
Study	>0	>2	>0	>0.25
BP-EU-003	88/88 (100%)	**84/88 (95.5%)**	88/88 (100%)	**86/88 (97.7%)**

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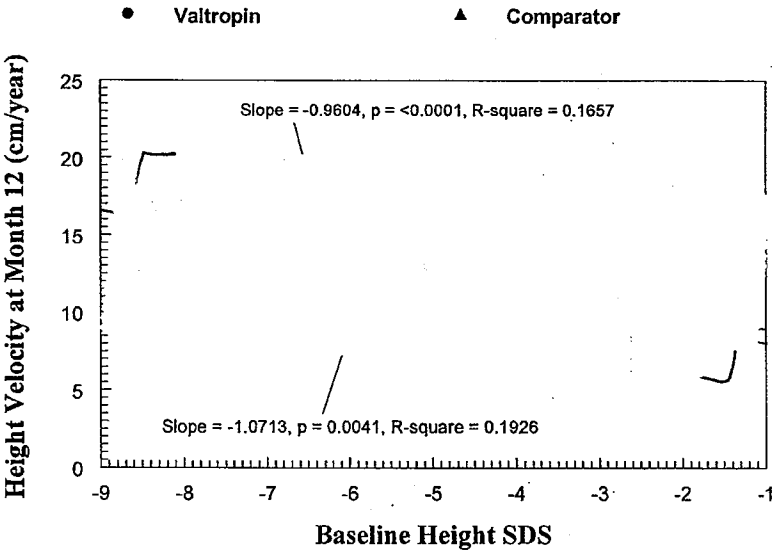
6.1.4.4.1.2 **Covariate Analyses** for the Primary Efficacy Endpoint - **HV** after 12 Months of Treatment with Valtropin vs. Humatrope

As stated earlier, the sponsor's original ANCOVA model contained 3 covariates - age at baseline, pre-treatment HV and log maximum GH after stimulation. The Division's Statistical Reviewer verified the sponsor's findings using the original ANCOVA model, and obtained similar results when baseline height SDS_{CA} was added as a fourth covariate. The Division's Statistical Reviewer then performed regression analyses for the significant covariates (baseline height SDS_{CA} and log maximum GH after stimulation), as well as age at baseline (which has been found in many previous studies to be an inverse predictor of the extent of response of pediatric GHD children to treatment with rhGH). **As can be seen in Figures 4 and 5, baseline height SDS_{CA} and log maximum GH after stimulation were significant inverse predictors of response, i.e. the lower the height SDS_{CA} or log maximum GH after stimulation, the greater the HV at Month 12 in both the Valtropin and Humatrope groups.** On the other hand, as seen in Figure 6, age at baseline was not a significant inverse predictor of response (although a trend was seen in the Valtropin group [p=0.08]).

Figure 4

Study BP-EU-003: Height Velocity vs. Height SDS

ITT Population with LOCF

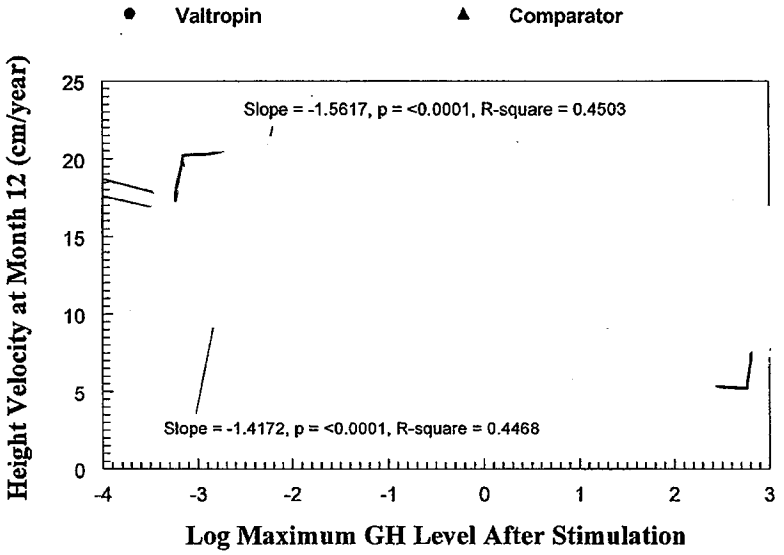


b(4)

Figures 5 and 6

Study BP-EU-003: Height Velocity vs. Growth Hormon

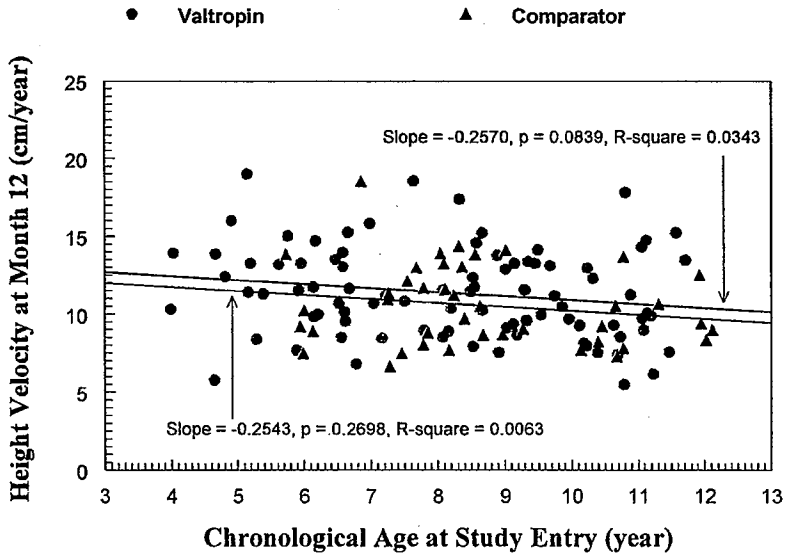
ITT Population with LOCF



b(4)

Study BP-EU-003: Height Velocity vs. Age

ITT Population with LOCF



6.1.4.4.1.3 Subgroup Analyses

Within-group changes from baseline at Month 12 in HV, HV SDS_{CA}, and height SDS_{CA} after treatment with Valtropin or Humatrope were consistent across age subgroups, i.e. no significant treatment-by-age subgroup interactions were seen ($p>0.10$; analysis of variance [ANOVA]; data not shown). Furthermore, for any age subgroup, there were no statistically significant differences between the Valtropin and Humatrope groups (ANCOVA; data not shown).

Within any of the age subgroups (or either sex), the mean changes from baseline at Month 12 in HV, HV SDS_{CA}, and height SDS_{CA} after treatment with Valtropin or Humatrope were significant (all p-values <0.01; data not shown).

6.1.4.4.2 Secondary Efficacy Endpoints

6.1.4.4.2.1 Other Auxological Secondary Efficacy Endpoints

As seen in Table 8, the between-group treatment differences for the changes from baseline at Month 12 in HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, B-P PredAH SDS and B-P PredAH (cm) after treatment with Valtropin vs. Humatrope were not significant (as was the case for HV and the change in HV as discussed earlier).

Table 8 - BP-EU-003
Between-Group Changes from Baseline at Month 12 in HV SDS_{CA}, Height SDS_{CA}, Height SDS_{BA}, B-P PredAH SDS, and PAH (cm)

ITT with LOCF Efficacy Variable	Adjusted LS Mean Change ± SE (n)		Treatment Difference	p-value	95% (LCI, UCI)
	Valtropin	Humatrope			
HV SDS_{CA}	7.95 ± 0.30 (88)	8.24 ± 0.41 (41)	**-0.29**	**0.52**	(-1.19, 0.61)
Height SDS_{CA}	1.17 ± 0.05 (88)	1.14 ± 0.06 (41)	**0.02**	**0.73**	(-0.11, 0.16)
Height SDS_{BA}	0.09 ± 0.15 (86)	0.11 ± 0.21 (41)	**-0.02**	**0.92**	(-0.48, 0.43)
B-P PredAH SDS	0.50 ± 0.15 (32)	0.59 ± 0.22 (15)	**-0.10**	**0.68**	(-0.58, 0.38)
B-P PredAH (cm)	3.84 ± 1.14 (32)	4.32 ± 1.65 (15)	**-0.48**	**0.79**	(-4.21, 3.24)

*The adjusted LS means were obtained using the sponsor's ANCOVA model, where treatment and country were the fixed factors, and CA at baseline, pre-treatment HV, and log maximum GH level after stimulation were the covariates.

The within-group changes from baseline at Month 12 for the Valtropin group only in HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, B-P PredAH SDS and B-P PredAH (cm) are displayed in Table 9. **All within-group changes were significant** (except for the change in height SDS_{BA}). **The 1.21 unit increase in height SDS_{CA} and the 8.05 unit increase in HV SDS_{CA} are robust and indicate substantial catch-up growth.** The results observed in the Humatrope group were very similar (data not shown).

See Table 7 in Section 6.1.4.4.1.1 regarding the distribution of response for change in height SDS_{CA} in the ITT/FAS population.

Table 9 - BP-EU-003 - Valtropin Group Only
Within-Group Changes from Baseline at Month 12 in HV SDS_{CA}, Height SDS_{CA}, Height SDS_{BA}, B-P PredAH SDS, and PAH (cm)

ITT with LOCF Efficacy Variable	Valtropin: Mean ± SD (n)		Mean Change from Baseline	(95% CI)
	Month 0	Month 12		
HV SDS_{CA}	-2.34 ± 1.78 (88)	5.71 ± 3.44 (88)	**8.05***	(7.16, 8.94)
Height SDS_{CA}	-3.54 ± 1.24 (88)	-2.33 ± 1.01 (88)	**1.21***	(1.08, 1.34)
Height SDS_{BA}	-0.16 ± 1.47 (86)	-0.00 ± 1.82 (86)	0.16	(-0.12, 0.44)
B-P PredAH SDS	-1.71 ± 1.10 (32)	-1.22 ± 1.08 (32)	0.49*	(0.22, 0.76)
B-P PredAH (cm)	162.27 ± 9.7x (32)	165.77 ± 10.0 (32)	3.51*	(1.57, 5.44)
Bone Maturation (ratio of change in BA divided by change in CA)	NA	1.53 ± 0.89 (86)	NA	NA

Except for height SDS_{BA} ($p = 0.26$), *all p-values for the mean changes from baseline at Month 12 were < 0.01 (paired t-test).

Bone maturation expressed as the mean ratio of change from baseline at Month 12 in BA to change from baseline at Month 12 in CA was 1.53 ± 0.89 in the Valtropin group (Table 9) and 1.5 ± 0.7 in the Humatrope group (data not shown), and not inappropriately accelerated, i.e. values >1 more than likely reflect expected catch-up growth during the first year of treatment.

Note: This Medical Officer elected not to present the results for height gain and change in weight in this review.

6.1.4.4.2.2 Other Secondary Efficacy Endpoints

6.1.4.4.2.2.1 Serum IGF-1 and IGF-1 SDS

As expected in GHD children, mean baseline serum IGF-1 levels and IGF-1 SDS were clearly low and increased significantly into an acceptable range following12 months of treatment with either Valtropin or Humatrope (see Tables 10 and 11). The responses to Valtropin and the Humatrope were very similar. Please see the Integrated Summary of Safety regarding further analysis of the serum IGF-1 and IGF-1 SDS responses.

Table 10 - BP-EU-003
Mean Serum IGF-1 Levels and IGF-1 SDS
Before and After Treatment with Valtropin vs. Humatrope

	Valtropin		Humatrope	
Mean ± SD	IGF-1 (ng/mL)	IGF-1 SDS	IGF-1 (ng/mL)	IGF-1 SDS
Baseline	44.7 ± 37.7 (n=87)	-3.21 ± 1.45 (n=87)	63.2 ± 42.6 (n=46)	-2.79 ± 1.43 (n=46)
Month 6	123.1 ± 86.7 (n=95)	-1.43 ± 1.41 (n=95)	143.8 ± 77.9 (n=46)	-1.30 ± 1.48 (n=46)
Month 12	147.8 ± 98.3 (n=92)	-1.26 ± 1.49 (n=92)	182.4 ± 92.7 (n=45)	-0.90 ± 1.54 (n=45)

Table 11 - BP-EU-003
Changes from Baseline in Serum IGF-1 Levels and IGF-1 SDS
After Treatment with Valtropin vs. Humatrope

	Valtropin		Humatrope	
Changes from baseline	IGF-1 (ng/mL)	IGF-1 SDS	IGF-1 (ng/mL)	IGF-1 SDS
Month 6	+87.7 ± 72.6 (n=84)	+1.93 ± 1.16 (n=84)	+84.1 ± 62.1 (n=43)	+1.61 ± 1.20 (n=43)
Month 12	+111.3 ± 86.8 (n=83)	+2.08 ± 1.47 (n=83)	+120.0 ± 79.5 (n=42)	+1.89 ± 1.36 (n=42)

6.1.5 **Efficacy Results from Study BP-EU-003-RO**

As stated in Section 6.1.3.1.1, children who completed the initial Phase III study (Study BP-EU-003), who had responded to somatropin therapy, and who met other criteria specified earlier were considered eligible for inclusion in Study BP-EU-003-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months, and patients previously treated with Humatrope for 12 months were switched to Valtropin for an additional 12 months). Efficacy results are summarized briefly below.

Eighty two children continued Valtropin treatment for an additional 12 months (Group V/V) and 40 children were switched from Humatrope to Valtropin for an additional 12 months (Group H/V). These 122 children constitute the ITT/FAS population for Study BP-EU-003-RO. During the first 12 months of somatropin treatment, mean HVs had significantly increased to 11.46 ± 2.99 and 10.58 ± 2.63 cm/yr in the V/V and H/V groups, respectively. During the second 12 months of somatropin treatment, as expected, mean HVs decreased to 8.55 ± 2.14 and 8.64 ± 1.85 in the V/V and H/V groups, respectively. Concordantly, mean HV SDS_{CA} values decreased in each group as well. During the first 12 months of somatropin treatment, mean height SDS_{CA} levels had significantly increased to -2.36 ± 1.03 and -2.32 ± 0.86 in the V/V and H/V groups, respectively. During the second 12 months of somatropin treatment, as expected, mean height SDS_{CA} levels increased further to -1.79 ± 1.05 and -1.73 ± 0.90. It is clear that the linear growth response in the V/V and H/V groups remained very similar during the second year of therapy. The linear growth pattern observed in both groups during the second year of rhGH treatment (e.g., drop off in HV and continued increase in height SDS_{CA}) has been observed numerous times during extended treatment of GHD children with rhGH.

6.1.6 Efficacy Summary/Discussion, Conclusions and Recommendations

6.1.6.1 Efficacy Summary/Discussion

Study BP-EU-003 was a Phase III, 12 month, multicenter, multinational (12 countries) randomized, double-blind, parallel group, active-controlled, non-inferiority study conducted in treatment-naïve pediatric GHD patients with short stature comparing the effects of Valtropin and a previously approved rhGH comparator (Humatrope) on linear growth and bone maturation. Patients were randomized to 12 months of treatment with Valtropin or Humatrope (**0.033 mg/kg/day = 0.23 mg/kg/week**). The primary efficacy endpoint was mean HV (cm/yr) at 12 months, and the primary efficacy objective was to show that the mean HV observed after 12 months treatment with Valtropin was non-inferior to that seen after 12 months treatment with Humatrope. Secondary efficacy parameters included change in HV (cm/yr), HV SDS_{CA} and change in HV SDS_{CA}, height SDS_{CA} and change in height SDS_{CA}, BA/CA (bone maturation index), B-P PredAH and change in B-P PredAH expressed in cm and as a SDS. In order to demonstrate the non-inferiority of Valtropin, **the Division's Statistical Reviewer compared Month 12 HV and change in HV across/between the 2 treatment groups using ANCOVA** with baseline CA, pre-treatment HV, log maximum stimulated GH level ± baseline height SDS_{CA} as covariates **in the ITT/FAS population with LOCF. Once the adjusted LS mean treatment differences and their associated CIs were determined, the lower bounds of the 95% CIs surrounding the treatment differences were compared with the mutually agreed to pre-established non-inferiority margin of 2 cm/yr.** Furthermore, the Division's Statistical Reviewer performed paired t-tests to determine if HV, HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, PAH SDS and PAH (cm) were significantly improved from baseline at Month 12.

Children who completed the initial Phase III study were considered eligible for inclusion in Study BP-EU-003-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months, and patients

previously treated with Humatrope for 12 months were switched to Valtropin for an additional 12 months.

The ITT/FAS population (the primary focus of the Division's efficacy review) consisted of 129 children (88 treated with Valtropin and 41 treated with Humatrope), i.e. 18 patients were excluded because of protocol-specified reasons including inaccurate pre-treatment HV and failure to be measured with an appropriate wall-mounted stadiometer. Greater than 90% of the 149 children originally randomized completed the study with no disparity between treatment arms. Combining both treatment groups, mean age was 8.2 yr (half of the children were between 6.6 and 10 yr), 60-70% of patients were male, ~95% were Caucasian, **baseline height SDS_{CA} was -3.43, pre-treatment HV was 3.34 cm/yr, and B-P PredAH was 161 cm (~5' 3").** These demographic and baseline characteristics were similar in the 2 treatment groups. GHD was considered to be "idiopathic" in 94 (95.9%) and 48 (98%) of the children in the Valtropin and Humatrope groups, respectively. This is at least in part explained by the fact that patients with a history of a pituitary/hypothalamic tumor **including craniopharyngioma** were excluded. **Nonetheless, preexisting central hypothyroidism/"TSH deficiency" was reported in 26 (26.5%) and 14 (28.6%) of the children in the Valtropin and Humatrope groups, respectively. In this regard, central hypothyroidism has previously been reported in 10-50% of children with "idiopathic" GHD - especially when associated with a combination of 3 abnormalities on MRI scans, i.e. pituitary hypoplasia, stalk interruption, and posterior pituitary ectopia (insert 1-2 references). Only 3 patients in the Valtropin group and no patients in the Humatrope reported remote treatment (>2 years prior to enrollment) with rhGH.**

The adjusted LS mean HV ± SE at Month 12 was **11.21 ± 0.23 cm/yr** in the Valtropin group vs. **11.00 ± 0.32 cm/yr** in the Humatrope group, and the adjusted LS mean change in HV ± SE at Month 12 was **7.75 ± 0.23** cm/yr in the Valtropin group vs. **7.54 ± 0.31** cm/yr in the Humatrope group in the ITT/FAS population. The **mean treatment difference for HV and change in HV was 0.21 in favor of Valtropin** (a statistically and clinically non-significant difference). **Valtropin was non-inferior to Humatrope since the lower bounds of the 95% CIs surrounding the treatment differences (-0.48 in each instance) were greater than the pre-established non-inferiority margin of -2 cm/yr. In fact, in that the lower and upper bounds of the CIs (-0.48, 0.90 in each instance) lied in the interval between -2 and +2, Valtropin was "equivalent" to Humatrope.** The results were very similar when the sponsor performed these analyses in the PP population - in spite of the fact that ~30% of patients in each group committed major protocol violations. **The within-group mean change from baseline at Month 12 in HV (7.87 cm/yr) for the Valtropin group was highly significant ($p<0.0001$).** The results in the Humatrope group were very similar.

Of note, the Month 12 HV and change in HV results after treatment with 5 mg = 15 IU Valtropin in Study BP-EU-003 are comparable to the growth response observed after the administration of 1.33 mg = 4 IU Eutropin™ INJ (a formulation marketed by the sponsor for many years in many countries around the world which is qualitatively identical to the 5 mg = 15 IU Valtropin formulation with regard to the API [rhGH] and all excipients). In this regard, the sponsor supplied this Medical Reviewer with synopses of 2 studies where

Eutropin™ INJ was administered to GHD children with short stature: 1) a label-enabling study performed in Korea (1991-1994) (66) where treatment with Eutropin™ INJ 0.17-0.23 mg/kg/week resulted in a Month 12 HV of 10 cm/yr (change from baseline at Month 12 in HV was 6.8 cm/yr); and 2) a more recent study performed in China (2004-2005) (67) where treatment with Eutropin™ INJ 0.17 mg/kg/week resulted in a Month 6 annualized HV of ~11.5 cm/yr (annualized change from baseline at Month 6 in HV was ~9 cm/yr).

As seen in Table 12 ahead (comparing the results of Study BP-EU-003 with 3 representative published studies [68-70]), treatment of GHD children with previously approved rhGH formulations with doses ranging from 0.14 to 0.3 mg/kg/week resulted in Month 12 HVs ranging from 10.1 to 12.0 cm/yr – which is certainly comparable to the Month 12 HV of 11.36 cm/yr observed after treatment with 0.23 mg/kg/week of Valtropin.

Furthermore, as stated previously in Section 2.6.1.3, there is a large amount of literature indicating that appropriately administered, long-term treatment of GHD children with rhGH can normalize FH (e.g., FH SDS approaching 0 using normal, healthy adult standard) and approximate mid-parental target height (e.g., FH - mid-parental height SDS approaching 0) in the majority of patients, especially when treatment is started at an early age (3, 14-17). In this regard, change in height SDS_{CA} >0.25 after 1 year of treatment with rhGH has been reported to be a strong positive predictor of the FH response (4), and CA at the start of treatment, height SDS_{CA} at the start of treatment and log maximum GH after stimulation have been reported to be inverse predictors of the FH response (14-17). Based on these findings, it has long been the standard of care to treat GHD children with rhGH until FH is achieved (epiphyseal closure) (2-4, 8). These children should be retested shortly after the discontinuation of rhGH therapy to determine whether GHD is still present (as discussed previously in Section 2.6.1.4).

Cumulative distribution functions revealed that approximately 50% of children treated with Valtropin achieved a Month 12 HV ≥10 cm/yr and a Month 12 change in HV ≥7 cm/yr, and approximately 50% of children treated with Humatrope achieved a Month 12 HV ≥9 cm/yr and a Month 12 change in HV ≥6 cm/yr. All 88 ITT/FAS children in the Valtropin group (as well as the 41 children in the Humatrope group) had responded to treatment at the end of the 12 month trial, i.e. change from baseline in HV >0). In addition, 95.5% (84/88) of children in the Valtropin group manifested a change in HV >2 cm/yr (the value of the non-inferiority margin = the minimal clinically important difference). Furthermore, all 88 ITT/FAS children in the Valtropin group had manifested a positive change in height SDS_{CA} at the end of the 12 month trial (e.g., change from baseline in height SDS_{CA} >0), and 97.7% (86/88) of children in the Valtropin group manifested a change in height SDS_{CA} >0.25.

Baseline height SDS_{CA} and log maximum GH after stimulation, but not CA at baseline, were significant covariates and (by regression analysis) **significant inverse predictors of response,** i.e. the lower the height SDS_{CA} or log maximum GH after stimulation, the greater the HV at Month 12 in both the Valtropin and Humatrope groups. Subgroup analyses by age subset and gender were unrevealing.

As was the case for HV and the change in HV, the between-group treatment differences for the changes from baseline at Month 12 in HV SDS_{CA}, height SDS_{CA}, height SDS_{BA}, B-P PredAH SDS and B-P PredAH (cm) after treatment with Valtropin vs. Humatrope were not significant. The within-group changes from baseline at Month 12 for the Valtropin group only in HV SDS_{CA}, height SDS_{CA}, B-P PredAH SDS and B-P PredAH (cm) **were all significant. The 1.21 unit increase in height SDS_{CA} and the 8.05 unit increase in HV SDS_{CA} are robust and indicate substantial catch-up growth.** The results observed in the Humatrope group were very similar.

Bone maturation expressed as the mean ratio of change from baseline at Month 12 in BA to change from baseline at Month 12 in CA was **1.53 ± 0.89 in the Valtropin group** and 1.5 ± 0.7 in the Humatrope group.

As expected in GHD children, mean baseline serum IGF-1 levels and IGF-1 SDS were clearly low and increased significantly into an acceptable range following12 months of treatment with either Valtropin or Humatrope.

Eighty two children continued Valtropin treatment for an additional 12 months (Group V/V) and 40 children were switched from Humatrope to Valtropin for an additional 12 months (Group H/V) during the rollover study (Study BP-EU-003-RO). During the first 12 months of somatropin treatment, mean HVs had significantly increased to 11.46 ± 2.99 and 10.58 ± 2.63 cm/yr in the V/V and H/V groups, respectively. During the second 12 months of somatropin treatment, as expected, mean HVs decreased to 8.55 ± 2.14 and 8.64 ± 1.85 in the V/V and H/V groups, respectively. During the first 12 months of somatropin treatment, mean height SDS_{CA} levels had significantly increased to -2.36 ± 1.03 and -2.32 ± 0.86 in the V/V and H/V groups, respectively. During the second 12 months of somatropin treatment, as expected, mean height SDS_{CA} levels increased further to -1.79 ± 1.05 and -1.73 ± 0.90. It is clear that the linear growth response in the V/V and H/V groups remained very similar during the second year of rhGH therapy.

Table 12 - Study BP-EU-003

Height Velocity at Month 12 in Study BP-EU-003 Compared with Selective Studies Utilizing Other Somatropin Formulations in Children with GHD

Study	Product	Dose regimen	N	Height Velocity (cm/year) Mean ± SD	
				Baseline	Month 12
Study BP-EU-003	Valtropin	0.23 mg/kg/w (7d/w)	70	3.6±1.5	11.3±3.0
MacGillivray et al. 1996 (ref 68)	Nutropin	0.30 mg/kg/w (7d/w)	23	4.1±1.6	11.4±2.5
Pavia et al. 1992 (ref 69)	Saizen	0.17 mg/kg/w (7d/w)	17	4.0±1.5	10.1±2.4
Bierich. 1987 (ref 70)	Genotropin	0.14 mg/kg/w (6d/w)*	77	3.7±1.7	12.0±4.2

w = week; d = day
*body surface area/weight conversion was calculated based on 1 m^2 = 28 kg.

6.1.6.2 Efficacy Conclusions

- The 149 prepubertal, rhGH-naïve children who were randomized in Study BP-EU-003 manifested classical pediatric GHD, i.e. combining both groups, **baseline height SDS_{CA} was -3.43, pre-treatment HV was 3.34 cm/yr, and B-P PredAH was 161 cm (~5' 3").** The Valtrope and Humatrope groups were well matched. The exclusion of patients with craniopharyngiomas and other brain tumors (hence patients S/P radiation therapy) explains why ~95% of these children were classified as "idiopathic" GHD. The fact that ~25% of these children with "idiopathic" GHD had preexisting central hypothyroidism is supported by recent literature indicating that the presence of a particular triad of pituitary/hypothalamic abnormalities on MRI scan is not uncommon in patients with "idiopathic" GHD and is often associated with other pituitary insufficiencies.
- **The between-group ANCOVA analyses of Month 12 HV and change in HV data after treatment with 0.23 mg/kg/week of either somatropin in the ITT/FAS population clearly demonstrated that Valtropin is non-inferior to Humatrope**, i.e. the lower bounds of the CIs surrounding the treatment differences were greater than the pre-established non-inferiority margin of -2 cm/yr. **The within-group mean change from baseline at Month 12 in HV (7.87 cm/yr; 11.36 cm/yr at Month 12 minus 3.50 cm/yr at baseline) for the Valtropin group was highly significant** and **further supports the efficacy of Valtropin.**
- The comparability of the Month 12 HV and change in HV results after treatment of GHD children in Korea and China with **0.17-0.23 mg/kg/week of Eutropin™ INJ** (a 1.33 mg = 4 IU formulation marketed by the sponsor in other countries and qualitatively identical to the 5 mg = 15 IU Valtropin formulation) to the results observed after treatment with Valtropin **0.23 mg/kg week in Study BP-EU-003 also further supports the efficacy of Valtropin (e.g., mean HV at Month 12 was 11.36 cm/yr after treatment with Valtropin vs. 10 and ~11.5 cm/yr in the Korean and Chinese studies, respectively).**
- **The short-term efficacy of Valtropin 0.23 mg/kg/week in Study BP-EU-003 is clearly supported by numerous published studies (some of which have been tabulated/cited in this review) where treatment with similar amounts of previously approved formulations of rhGH has resulted in very similar Month 12 HV results (e.g., 10-12 cm/yr).**
- **There is a large amount of literature indicating that appropriately administered, long-term treatment of GHD children with rhGH can normalize FH and approximate mid-parental target height in the majority of patients. As stated earlier in Section 6.1.6.1, an increase in height SDS_{CA} >0.25 is a strong positive predictor of the FH response. In that the increase from baseline at Month 12 in height SDS_{CA} in Study BP-EU-003 after treatment with Valtropin was 1.21, it is likely that the FH response of these children will be very good if they continue Valtropin therapy until epiphyseal closure. Based on these findings, it has long been the standard of care to treat GHD children with rhGH until FH is achieved. This very fact could be used to further support approval of the pediatric GHD indication for Valtropin.**

- Cumulative distribution functions indicated that the distribution of response with respect to change in HV and change in height SDS_{CA} after 12 months of treatment with Valtropin was quite satisfactory with no non-responders and very few minimal responders. Approximately 50% of children treated with Valtropin achieved a Month 12 HV ≥10 cm/yr and a Month 12 change in HV ≥7 cm/yr **reflecting substantial linear growth responses.** All 88 ITT/FAS children in the Valtropin group had responded to treatment at the end of the 12 month trial and 95.5% of children in the Valtropin group manifested a change in HV >2 cm/yr (the value of the non-inferiority margin). Furthermore, all 88 ITT/FAS children in the Valtropin group had manifested a positive change in height SDS_{CA} at the end of the 12 month trial and **97.7% of children in the Valtropin group manifested a change in height SDS_{CA} >0.25 (generally considered to be a satisfactory 12 month growth response which may be predictive of a substantial increase in FH) (4).**
- As previously reported in short-term studies, **baseline height SDS_{CA} and log maximum GH after stimulation were significant inverse predictors of response; surprisingly, CA at baseline was not a significant inverse predictor of response.** Subgroup analyses by age subset and gender were unrevealing.
- The within-group changes from baseline at Month 12 for the Valtropin group in HV SDS_{CA}, height SDS_{CA}, B-P PredAH SDS and B-P PredAH (cm) **were all significant. The 1.21 unit increase in height SDS_{CA} and the 8.05 unit increase in HV SDS_{CA} are robust and indicate substantial catch-up growth. As stated above, the substantial increase in height SDS_{CA} also predicts a very good FH response if these children continue to be treated with Valtropin until epiphyseal closure.** As was the case for HV and the change in HV, the between-group treatment differences for the changes from baseline at Month 12 for these secondary efficacy variables after treatment with Valtropin vs. Humatrope were not significant.
- Bone maturation expressed as the mean ratio of change from baseline at Month 12 in BA to change from baseline at Month 12 in CA was **1.53 ± 0.89 in the Valtropin group,** and **not inappropriately accelerated, i.e. values >1 more than likely reflect expected catch-up growth during the first year of treatment.**
- As expected in GHD children, mean baseline serum IGF-1 levels and IGF-1 SDS were clearly low and increased significantly into an acceptable range following12 months of treatment with either Valtropin or Humatrope.
- **The linear growth pattern observed in both groups during the second year of rhGH treatment (e.g., drop off in HV [although still significantly increased from pre-treatment] and continued increase in height SDS_{CA}) has been reported numerous times during extended treatment of GHD children with rhGH (Mac reference).**

6.1.6.3 Efficacy Recommendations

- No additional efficacy studies are required to obtain approval for this indication.
- **The short-term efficacy data from Study BP-EU-003 presented in this application reflecting the significant linear growth response of short children with GHD after 12 months of treatment with Valtropin (which was non-inferior/equivalent to the linear**

growth response observed after treatment with Humatrope, a previously approved short acting formulation of rhGH/somatropin) **is sufficient by itself** to warrant approval of this indication. A comparison of the efficacy findings in Study BP-EU-003 with the results of other published short-term studies **strongly supports** the validity of the sponsor's findings. Published FH studies not supported by the sponsor wherein short children with GHD were treated with rhGH formulations other than Valtropin until FH was achieved which demonstrated substantial improvements in FH **are not necessary** for approval of this indication and is referenced in this Medical Officer's review **only to provide context**. On the other hand, given that multiple review articles by highly regarded organizations clearly recommend long-term rhGH treatment for GHD children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current indication.

- The sponsor's proposed language for the [redacted] section of the Valtropin Package Insert describing the effects of Valtropin on linear growth in Study BP-EU-003 was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential changes involved [redacted]

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[redacted] The sponsor agreed with all of the Division's suggested edits. In addition, the sponsor's proposed language for the pediatric GHD subsection of the Indications and Usage section, and the pediatric GHD subsection of the Dosage and Administration section was also carefully reviewed and then edited. Once again, the sponsor agreed with all of the Division's suggested edits.

- **The satisfactory and comparable efficacy observed in pediatric GHD patients after treatment with 5 mg = 15 IU Valtropin in Study BP-EU-003 (just reviewed and obviously contained in this NDA submission)** and 1.33 mg = 4 IU Eutropin™ INJ in studies conducted by the sponsor in Korea (label enabling in other countries; 1990s) and China (2000s) (not contained in this NDA; sponsor provided comprehensive synopses), as well as the satisfactory and comparable efficacy observed in TS children after treatment with 5 mg = 15 IU Valtropin (Study BP-EU-002) and 1.33 mg = 4 IU Eutropin™ INJ (Korean TS study) (both studies contained in this NDA 1) mitigate the need for a biopharmaceutical bridging study between the 2 qualitatively identical formulations; and 2) support the approval of the adult GHD indication even though adult GHD patients were treated with 1.33 mg = 4 IU Eutropin™ INJ only during Study HGCL-001 (the solitary study submitted in support of the adult GHD indication in this NDA submission), i.e. it is entirely reasonable to presume that if an adult GHD study was conducted with 5 mg = 15 IU Valtropin, the results obtained would be very similar to the results observed during Study HGCL-001.

6.2 Indication Number 2 - Turner Syndrome

6.2.1 Methods

See Section 4.1 above.

6.2.2 General Discussion of Endpoints

The endpoints for these 2 studies were standard measures of linear growth. See Sections 6.2.3.1.3 and 6.2.3.2.3 below.

6.2.3 Study Design

6.2.3.1 Study Design for Study BP-EU-002 (2001 – 2003)

6.2.3.1.1 General Description (including dosing)

Study BP-EU-002 was an open-label study conducted in **young** prepubertal girls with TS at 1 center in Moscow, Russia to demonstrate the effect of 12 months of treatment with Valtropin on linear growth and bone maturation. Valtropin 0.053 mg/kg/day (0.37 mg/kg/week divided into 7 equal injections) was administered for 12 months. To prevent lipoatrophy, the injection site was varied.

Children who completed Study BP-EU-002 and who had responded to somatropin therapy were considered eligible for inclusion in Study BP-EU-002-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months). A very brief description of the efficacy and safety results of this rollover study are presented later in this Medical Officer's review in Sections 6.2.5 and 7.2.2, respectively.

6.2.3.1.2 Major Inclusion/Exclusion Criteria

Inclusion Criteria:

- Girls, age 2 to 9 years, with short stature associated with TS (diagnosis by karyotypic examination must be documented in patient records)
- Confirmed to be rhGH (and pituitary-derived hGH) treatment naïve
- Absolute height below the 5th percentile compared to a normal population at screening (in reference to nomograms for normal Russian girls [71], and **apparently** also using the CDC standard for normal children [64])
- BA <8 years and open epiphyses
- Euthyroid, controlled on medication, if needed

*CDC standard reflecting the growth of normal American children (64) was chosen because the CDC growth data are highly regarded internationally, and have been used in multiple published European and American growth studies in the past.

Exclusion Criteria:

- At screening, presence of anti-GH antibodies with a binding ≥5 times the binding of background value
  - Any clinically significant abnormality likely to affect growth or the ability to evaluate growth such as, but not limited to: GHD, chronic renal insufficiency, untreated hypothyroidism/Cushing syndrome, malnutrition etc
  - Presence of absolute contraindication to treatment with rhGH (e.g., **diabetes mellitus**, active malignancy, hypertension, acute critical illness).
  - Major medical illnesses (e.g., HIV positivity or related disease, history of bone marrow transplantation, recent surgery, hyperlipidemia, cardiovascular disease, chronic infection including tuberculosis) or clinically relevant significantly abnormal laboratory tests (e.g., disturbed calcium homeostasis)
  - Use of the following medications (e.g., rhGH, glucocorticoids, estrogen, methylphenidates, anti-infective drugs, immunosuppressants, antitumor therapy)
  - Drug or alcohol abuse

6.2.3.1.3 Efficacy Endpoints

The primary efficacy parameter reflecting linear growth was change from baseline in HV at Month 12^.

^Pre-treatment HV was calculated by regression using heights obtained 3 months to 2 years prior to study enrollment, and heights obtained at screening/baseline. **Month 12 HV** was also calculated by regression.

Secondary efficacy parameters included:

- Change in HV SDS_{CA} at Month 12 (Prader standard for normal children [65])**
- Change in height SDS_{CA} (CDC standard for normal children [64])*
- Change in height SDS_{BA} (CDC standard for normal children [64])*
- Height gain
- BA (according to the method of Greulich and Pyle [34]; wrist radiographs were read by the same examiner without knowledge of the age of the patients)
- BA/CA (bone maturation index)
- Change in B-P PredAH (cm) (35)
- Change in weight
- Change in serum IGF-1 levels

Standing height was measured with a wall-mounted Harpenden stadiometer or comparable wall-mounted device, and the mean of 3 measurements was recorded at baseline, 3, 6 and 12 months.

*CDC standard reflecting the growth of normal American children (64) was chosen because the CDC growth data are highly regarded internationally, and have been used in multiple published European and American growth studies in the past.
**The normative growth data for HV from the Prader et al paper (65) was used to calculate HV SDS because 1) there are no CDC reference data for HV; and 2) the Prader et al normative data encompasses the ages of the children enrolled in this study, and have been used in multiple published European and American growth studies in the past.

6.2.3.1.4 Safety Evaluations

Safety parameters (including anti-GH/anti-S. cerevisiae antibodies, glycemic measures, thyroid function tests, serum IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) levels, and routine hematology/chemistries/urinalysis) were obtained at baseline, 3, 6 and 12 months. Electrocardiograms were obtained at baseline and Month 12. All adverse events and concomitant drug therapy were recorded at each clinic visit.

6.2.3.1.5 Statistical Methods

6.2.3.1.5.1 Sample Size Calculation

Formal sample size calculations were not performed. 30 patients were enrolled.

6.2.3.1.5.2 Populations Analyzed

The Division's Statistical Reviewer (as well as the sponsor) focused/performed her primary (and secondary) efficacy analyses on the ITT/FAS population with LOCF (patients who had received at least 1 dose of study drug and who had at least 1 post-treatment efficacy measurement).

6.1.3.1.5.3 Analyses of the Primary (and Secondary) Efficacy Endpoints

The Division's Statistical Reviewer (as well as the sponsor) performed paired t-tests (a parametric method) and Wilcoxon's signed rank tests (a non-parametric method) to determine if HV, HV SDS_{CA}, height SDS_{CA}, height SDS_{BA} and PAH were significantly improved from baseline after 12 months of treatment with Valtropin.

6.1.3.1.5.4 Safety Analyses

Safety results were presented utilizing descriptive statistics.

6.2.3.2 Study Design for Korean TS Study (1995 – 1997)

6.2.3.2.1 General Description (including dosing)

The Korean TS study was an open-label, multicenter study conducted in prepubertal girls with TS at 4 sites (2-14 patients per site) in Korea to demonstrate the effect of 12 months of treatment with Eutropin™ INJ on linear growth and bone maturation. As discussed earlier in Section 5.1.1, Eutropin™ INJ (a rhGH formulation marketed by the sponsor in many countries for many years) is qualitatively identical to Valtropin (same API and excipients) - except that each vial contains 1.33 mg [4 IU] of rhGH as opposed to the 5 mg [15 IU] of rhGH in each vial of Valtropin. Eutropin™ INJ 0.34 mg/kg/week (0.048 mg/kg 7 days each week or 0.056 mg/kg 6 days each week) was administered for 12 months. To prevent lipoatrophy, the injection site was varied.

6.2.3.2.2 Major Inclusion/Exclusion Criteria

Inclusion Criteria:

- Prepubertal girls <14 years of age
- TS proven by karyotype
- Height SDS_{CA} <-1 (Korean Pediatric Society standard for healthy, normal non-TS girls)

Exclusion Criteria:

- Any clinically significant abnormality likely to affect growth or the ability to evaluate growth such as, but not limited to: GHD, chronic renal insufficiency, untreated hypothyroidism/Cushing syndrome etc
- Presence of absolute contraindication to treatment with rhGH (e.g., **diabetes mellitus**, active malignancy)
- Patients treated with rhGH, sex hormone preparations or anabolic agents within the last 3 months
- Presence of epiphyseal fusion

6.2.3.2.3 Efficacy Endpoints

The primary efficacy parameter reflecting linear growth was change from baseline in HV at Month 12^.

^HV at Month 12 was calculated by subtracting observed baseline height from observed height at Month 12; pre-treatment HV was calculated by subtracting height measured at least 6 months prior to enrollment and as close to 12 months prior to enrollment as possible from height at baseline [and then annualizing the difference]).

Secondary efficacy parameters included:

- Change in height SDS_{CA} (Korean Pediatric Society standard for healthy, normal non-TS girls)*
- BA (method not stated in the study report - according to the method of Greulich and Pyle [34]?)
- HA/BA
- Change in weight
- Change in serum IGF-1 levels

Standing height was measured with a Harpenden stadiometer or comparable wall-mounted device, and the mean of 3 measurements was recorded at baseline, 6 and 12 months.

6.2.3.2.4 Safety Evaluations

Routine hematology/chemistries/urinalysis were obtained at baseline, 3, 6, 9 and 12 months. **Blood sugar was included each time. Apparently, the patient was NOT absolutely required to be fasting!** Anti-GH/anti-S. cerevisiae antibodies, thyroid function tests, serum IGF-1 levels, and Chest Xrays were obtained at baseline, 6 and 12 months. All adverse events and concomitant drug therapy were recorded at each clinic visit.

6.2.3.2.5 Statistical Methods

6.2.3.2.5.1 Sample Size Calculation

Formal sample size calculations were not performed. 60 patients were enrolled.

6.2.3.2.5.2 Populations Analyzed

The Division's Statistical Reviewer focused/performed her primary (and secondary) efficacy analyses on the ITT/FAS population with LOCF (patients who had received at least 1 dose of study drug and who had at least 1 post-treatment efficacy measurement). The sponsor focused on the PP population (excluding dropouts).

6.2.3.2.5.3 Analyses of the Primary (and Secondary) Efficacy Endpoints

The Division's Statistical Reviewer (as well as the sponsor) performed paired t-tests (a parametric method) and Wilcoxon's signed rank tests (a non-parametric method) to determine if HV, height SDS_{CA}, and HA/BA were significantly improved from baseline after 12 months of treatment with Eutropin^{TM} INJ. Apparently, patients were not excluded from the height SDS analysis if they were "too old" for the Korean normal standard to be applied accurately. Non-TS healthy girls undergo spontaneous puberty and a pubertal growth spurt, whereas the vast majority of TS girls do not, i.e. therefore, height SDS values for the "older" TS girls in this study

(between 11 and 14 years old - the age at which many healthy non-TS girls undergo a pubertal growth spurt) will be even lower both at baseline and post-treatment.

6.2.3.2.5.4 Safety Analyses

Safety results were presented utilizing descriptive statistics.

6.2.4 Efficacy Findings

6.2.4.1 Enrollment and Disposition

6.2.4.1.1 Study BP-EU-002

A total of 30 subjects were enrolled in this study and 29 of them completed the 12 month trial. One subject withdrew her consent at the Month 6 visit. **All 30 subjects were included in the ITT/FAS (LOCF) population analyzed by the Division's Statistical Reviewer.**

6.2.4.1.2 Korean TS Study

A total of 60 subjects were enrolled in this study and 50 of them completed the 12 month trial (the PP population analyzed by the sponsor). 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 the sponsor (1 patient). **Fifty eight of these 60 subjects were included in the ITT (LOCF) population,** i.e apparently no post-treatment auxological data whatsoever were provided for 2 patients and LOCF was not possible.

6.2.4.2 Demographics and Baseline Characteristics

6.2.4.2.1 Study BP-EU-002

All 30 enrolled subjects (equal to the number of patients in the ITT/FAS [LOCF] population) were female and Caucasian. **The mean CA at entry was ~7 years** and mean baseline BA was ~5 years, i.e. markedly delayed. Mean height was 107.5 cm (~3' 4") and mean height SDS_{CA} was -2.34. Mean baseline HV was 3.75 cm/yr. **These are the findings one would expect in a slowly growing, growth-retarded TS cohort.** See Table 13 below.

Table 13 - Study BP-EU-002
Demographic and Baseline Characteristics of All Subjects

	Age (year)	Height (cm)	Height SDS for CA	Bone Age (year)	Height Velocity (cm/year)	Height Velocity SDS CA	Predicted Adult Height
n	30	30	30	30	30	30	14
Mean	6.93	107.51	-2.34	5.05	3.75	-2.39	151.97
SD	2.19	10.87	0.91	2.18	1.76	1.90	5.23

6.2.4.2.2 Korean TS Study

All 60 enrolled subjects were female and Korean/Asian. **The mean CA at entry was ~11 ± 3.15 years; CA ranged from 4.2 to 14.9 (excluding a 16 year old girl who was discontinued).** Mean baseline BA was ~9.4 years, i.e. markedly delayed. Mean height was ~122 cm (~4') and mean height SDS_{CA} was -2.99. Mean baseline HV was 3.48 cm/yr. **These are also the findings one would expect in a slowly growing, growth-retarded TS cohort.** See Table 13 below.

Table 14 - Korean TS Study
Demographic and Baseline Characteristics of All Subjects

	Age (year)	Height (cm)	Height SDS for CA	Height Velocity (cm/year)	Bone Age (year)
n	60	60	60	58	59
Mean	11.01	122.35	-2.99	3.48	9.37
SD	3.15	15.22	0.95	1.40	2.90

6.2.4.2.3 Comparison of Demographics and Baseline Characteristics of Subjects Enrolled in Study BP-EU-002 and the Korean TS Study

The most glaring difference between the subjects enrolled and treated in Study BP-EU-002 and the Korean TS study in demographics and baseline characteristics was age at study entry (~7 vs. 11 yrs)!! The older subjects enrolled in the Korean TS study were growing a bit slower than the subjects in Study BP-EU-002 (3.48 vs. 3.75 cm/yr, respectively), and their baseline height SDS_{CA} was somewhat lower as well (-2.99 vs. -2.34, respectively). Mean baseline BA was markedly delayed in both studies (~1.5-2 yrs less than CA). **In addition, Study BP-EU-002 was conducted in Russia between 2001 and 2003, while the Korean TS study was conducted in Korea between 1995 and 1997.**

6.2.4.3 Dosing

The doses administered in the 2 studies were similar (and compatible with consensus guidelines for the treatment of short stature associated with TS):
Study BP-EU-002: Valtropin 0.053 mg/kg/day (0.37 mg/kg/week) SC for 12 months.
Korean TS study: Eutropin™ INJ 0.34 mg/kg/week SC (0.048 mg/kg 7 days each week or 0.056 mg/kg 6 days each week.

6.2.4.4 Efficacy Results

Although the doses of Valtropin (Study BP-EU-002) and Eutropin™ INJ (Korean TS study) administered were similar across the 2 studies (0.37 vs. 0.34 mg/kg/week, respectively), it was decided by this Medical Officer and the Division's Statistical Reviewer **not** to perform a combined, consolidated analysis for the following reasons: **1) differences in CA at study entry (~7 yrs in Study BP-EU-002 and 11 yrs in the Korean TS study;** 2) Study BP-EU-002 was conducted in Caucasian/Russian children between 2001 and 2003, while the Korean TS study was conducted in Asian/Korean children between 1995 and 1997; and **3) different methods were used to calculate pre-treatment and post-treatment HV (regression in Study BP-EU-002 vs. simple subtraction of 1 height from another height in the Korean TS study). Therefore, the results of Study BP-EU-002 and the Korean TS study will be discussed together and compared side-by-side.**

6.2.4.4.1 Auxological Primary (and Secondary) Efficacy Endpoints

As seen in Table 15, **mean change in HV from baseline at Month 12 (the primary efficacy variable for both studies) was 5.98 cm/yr (mean HV at Month 12 = 9.73 cm/yr) and 3.49 cm/yr (mean HV at Month 12 = 6.97 cm/yr) in the ITT (LOCF) populations in Study BP-EU-002 and the Korean TS study, respectively.** Very similar results were obtained when the PP populations were analyzed by the sponsor (data not shown).

The results obtained with respect to other auxological secondary efficacy parameters are also presented for both studies in Table 15. A **significant increase in mean height SDS_{CA}** was observed in both studies (**0.88 and 0.35 in Study BP-EU-002 and the Korean TS study, respectively**), and a substantial **increase in mean HV SDS_{CA}*** was seen in Study BP-EU-002 (**6.22**). B-P PredAH increased significantly as well (~4 cm) in Study BP-EU-002.

*Figure 7 (a scatter plot of all individual pre-treatment and post-treatment HVs [from the sponsor]) graphically demonstrates that all but 6 of pre-treatment HVs were below the HV -1 SD reference line for normal children between the ages of 2 and 10, **and all but 1 of the post-treatment HVs were above the HV +1 SD reference line for normal children between the ages of 2 and 10.**

All of the abovedescribed linear growth responses in both studies were clearly apparent as early as Month 3 (data not shown). As previously reported, annualized HV at Months 3 and 6 overestimates the true annual HV at Month 12.

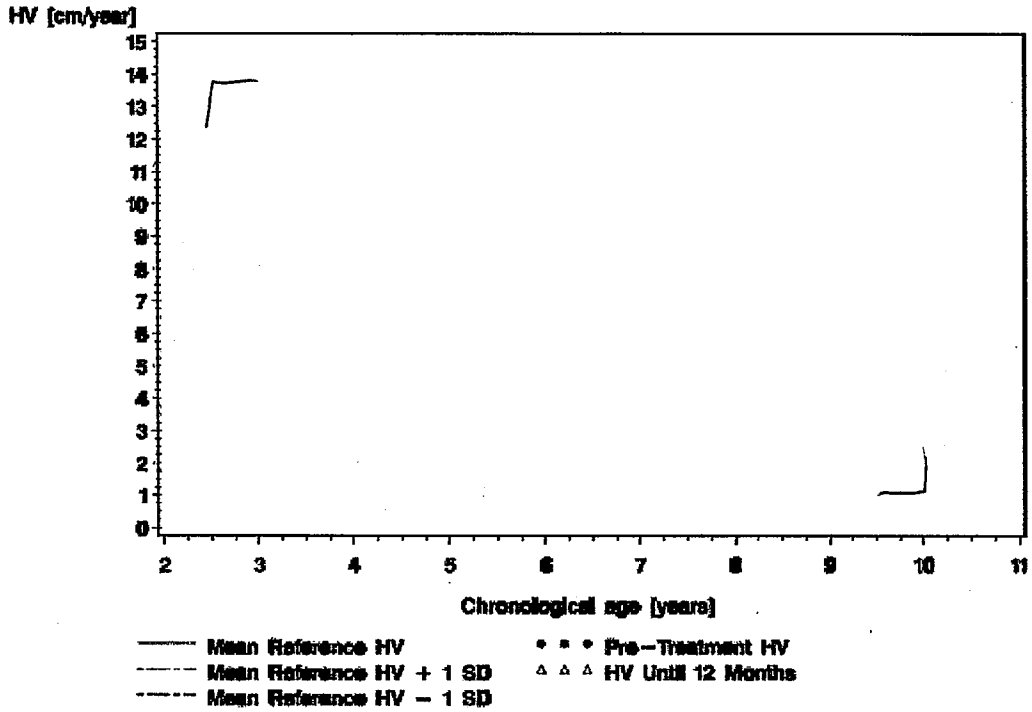
Bone maturation (calculated as the mean ratio of change in BA to change in CA) **was not accelerated (1.02 ± 0.35)** in Study BP-EU-002. In the Korean TS study, mean HA/BA ratio increased from 0.85 at baseline to 0.88 at Month 12, indicating that HA advanced more rapidly than BA (Table 15).

Table 15 - Study BP-EU-002 vs. Korean TS Study
Within-Group Change from Baseline at Month 12
in HV (Primary Efficacy Variable)
and Multiple Other Auxological Secondary Efficacy Variables
After Treatment with Valtropin or Eutropin™ INJ in Girls with Short Stature Associated with Turner Syndrome in 2 Open-label Studies

Efficacy Variable	Study	Mean ± SD (n)		Mean Change from Baseline	(95% CI)
		Month 0	Month 12		
HV (cm/yr)*	***BP-EU-002***	***3.75 ± 1.76 (30)***	***9.73 ± 1.55 (30)***	***5.98****	***(5.20, 6.76)***
	Korean TS Study	***3.48 ± 1.40 (58)***	***6.97 ± 1.84 (58)***	***3.49****	***(2.94, 4.03)***
HV SDS_{CA}	BP-EU-002	-2.39 ± 1.90 (30)	3.82 ± 1.95 (30)	6.22**	(5.22, 7.21)
	Korean TS Study	NA	NA	NA	NA
Height SDS_{CA}	BP-EU-002	-2.42 ± 0.91 (30)	-1.54 ± 0.94 (30)	0.88**	(0.78, 0.98)
	Korean TS Study	-3.02 ± 0.96 (58)	-2.67 ± 0.99 (58)	0.35**	(0.23, 0.46)
Height SDS_{BA}	BP-EU-002	0.09 ± 1.52 (29)	0.50 ± 1.23 (29)	0.42**	(0.20, 0.63)
	Korean TS Study	NA	NA	NA	NA
Bone Maturation^	BP-EU-002	NA	1.02 ± 0.35 (29)	NA	(0.02, 0.07)
	Korean TS Study	NA	NA	NA	NA
B-P PAH (cm)	BP-EU-002	152.0 ± 5.23 (14)	156.0 ± 4.21 (14)	4.04**	(2.89, 5.19)
	Korean TS Study	NA	NA	NA	NA
HA/BA	BP-EU-002	NA	NA	NA	NA
	Korean TS Study	0.85 ± 0.15 (58)	0.88 ± 0.12 (58)	0.03**	(0.00, 0.05)

*Change in HV was the primary efficacy endpoint in both studies and the results are therefore ***boldened and italicized.***
**p<0.05 for all mean changes from baseline at Month 12 (paired t-test)
^Mean ratio of change in BA divided by change in CA
NA=Not available.

Figure 7 - BP-EU-003
Pre-Treatment and Post-Treatment HV
Superimposed on a Normal Growth Curve



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6.2.4.4.1.1 Distribution of Response for HV and Height SDS_{CA}

A change of >1 cm/yr and >0.1 SD unit were categorically chosen as additional "responder cutpoints" for change in HV and change in height SDS_{CA}, respectively, by this Medical Officer because they are approximately 50% of the lower bounds of the CIs surrounding the change in HV and change in height SDS_{CA}, respectively, when a "typical" change in HV occurs after 12 months of treatment of TS children with rhGH (including the sponsor's Korean TS study [the TS children in Study BP-EU-002 did not have a "typical" response after treatment with Valtropin; rather, an extraordinary response as will be discussed further on) - and potentially reflect the "minimal clinical important differences". As seen earlier in Table 7 in Section 6.1.4.4.1.1, this Medical Officer chose larger additional "responder cutpoints" for GHD children in Study BP-EU-003 (>2 cm/yr and >0.25 SD units) for reasons explained in Section 6.1.4.4.1.1 (i..e., it is well known that GHD children typically respond much more briskly and consistently than non-GHD TS children after treatment with rhGH). As seen in Table 16, 100% and 100% of children treated with Valtropin in Study BP-EU-002 compared with 95% and 81.7% of children treated with Eutropin™ INJ in the Korean TS study manifested changes in HV >0 and >1 cm/yr, respectively. Analogously, 100% and 100% of children treated with Valtropin in Study BP-EU-002 compared with 80% and 73.3% of children treated with Eutropin™ INJ in the

Korean TS study manifested changes in height SDS_{CA} >0 and >0.1 SD, respectively. **The reasonable but "imperfect" responses observed in the Korean TS study are consistent with what has been observed in previously published studies when short TS children are treated with rhGH for 12 months. The remarkable response observed in Study BP-EU-002 more than likely relates to the fact that the mean CA at entry was ~7 yrs (vs. 11 yrs in the Korean TS study and most previously published studies).**

Table 16 - BP-EU-002 and the Korean TS Study
Responder Rate for Change from Baseline at Month 12
in HV and Height SDS_{CA} After Treatment with rhGH

Study	Change in Height Velocity (cm/year)		Change in Height SDS_{CA}	
	>0	>1	>0	>0.1
BP-EU-002	30/30 (100%)	30/30 (100%)	30/30 (100%)	30/30 (100%)
Korean TS Study	57/60 (95%)	49/60 (81.7%)	48/60 (80%)	44/60 (73.3%)

6.2.4.4.1.2 Subgroup Analyses for Age

Of significant interest, as seen in Table 17, there were significant treatment differences in change from baseline in HV at Month 12 across the subgroups of age in the Korean TS study. Children in the 4-8 years old and 8-12 years old age subgroups each had a significantly greater mean change from baseline at Month 12 in HV than children in the >12 years old age subgroup (~4 & 4.3 cm/yr vs. ~2.5 cm/yr) (p = 0.0092 in each instance). However, no significant differences between age subgroups were found in mean change from baseline at Month 12 in height SDS_{CA} in the Korean TS study.

In Study BP-EU-002, there were no significant differences in either change from baseline at Month 12 in HV or change from baseline at Month 12 in height SDS_{CA} between the 4-8 years old and 8-12 years old age subgroups (see Table 17).

Table 17 - BP-EU-002 and the Korean TS Study
Change in HV and Change in Height SDS_{CA} by Age Subgroup

Study	Subgroup	Mean Change from Baseline at Month 12 ± SD (n)	
		Change in Height Velocity	Change in Height SDS_{CA}
BP-EU-002	Age ≤ 4	4.88 ± 2.75 (4)	0.68 ± 0.42 (4)
	4 < Age ≤ 8	**6.60 ± 2.03 (14)**	0.98 ± 0.29 (14)
	8 < Age ≤ 12	**5.62 ± 2.09 (12)**	0.83 ± 0.17 (12)
Korean TS Study	**4 < Age ≤ 8**	**4.01 ± 1.79 (11)***	0.58 ± 0.36 (11)
	8 < Age ≤ 12	**4.30 ± 2.10 (22) ***	0.30 ± 0.54 (22)
	Age > 12	**2.54 ± 1.94 (25)**	0.28 ± 0.34 (25)

6.2.4.4.2 Serum IGF-1 and IGF-1 SDS

As seen in Table 18 and 19, in Study BP-EU-002, mean serum IGF-1 and IGF-1 SDS levels were lowish at baseline (**which is curious**), and, as expected, increased significantly after 6 and 12 months of Valtropin treatment; levels did not change between Month 6 and Month 12 (see Tables 17 and 18). Also, as seen in Table 20, in the Korean TS study, mean serum IGF-1 was apparently low normal at baseline, and, as expected, increased significantly after 6 and 12 months of Eutropin™ INJ treatment (see footnote for Table 20 explaining why IGF-1 SDS could not be calculated for the Korean TS study). **Also see Section 7.2.1.7.2.1 in the Integrated Summary of Safety regarding further analysis of the serum IGF-1 and IGF-1 SDS responses (in particular for Study BP-EU-002), and associated commentary,.**

Table 18 - BP-EU-002
Mean Serum IGF-1 and IGF-1 SDS Levels
Before and After Treatment with Valtropin

	Valtropin	
	IGF-1 (ng/mL)	IGF-1 SDS
Baseline	108.3 ± 42.0 (n=29)	-1.16 ± 1.16 (n=29)
Month 6	289.5 ± 140.5 (n=29)	+1.02 ± 1.45 (n=29)
Month 12	309.2 ± 129.7 (n=29)	+1.02 ± 1.53 (n=29)

Table 19 - BP-EU-002
Changes from Baseline in Serum IGF-1 and IGF-1 SDS Levels After Treatment with Valtropin

	Valtropin	
Changes from baseline	IGF-1 (ng/mL)	IGF-1 SDS
Month 6	+ 181.1 ± 119.2 (n=29)	+ 2.18 ± 1.10 (n=29)
Month 12	+ 200.8 ± 111.4 (n=29)	+ 2.18 ± 1.18 (n=29)

Table 20 - Korean TS Study
Mean Serum IGF-1 and IGF-1 SDS Levels Before and After Treatment with Valtropin

	Valtropin	
	IGF-1 (ng/mL)	IGF-1 SDS
Baseline	167.4 ± 85.8 (n=)	Not obtainable*
Month 6	368.4 ± 158.1** (n=)	Not obtainable*
Month 12	423.2 ± 181.0** (n=)	Not obtainable*

*During the Korean TS study, serum IGF-1 levels were measured using multiple center-specific assays. The reference ranges, means and SDs for different age groups by gender are not available. Therefore, the sponsor could not calculate serum IGF-1 SDS values, and one can only "guesstimate" how low or high these mean values are by referring to the reference ranges provided for the centralized assay used in Study BP-EU-002 - clearly, a less than satisfactory methodology.
**p<0.0001

6.2.5 Efficacy Results from Study BP-EU-002-RO

As stated in Section 6.2.3.1.1, children who completed Study BP-EU-002 and who had responded to somatropin therapy were considered eligible for inclusion in Study BP-EU-002-RO (a rollover study during which patients who had already received Valtropin for 12 months were treated with Valtropin for an additional 12 months).

All 29 of the children who completed Study BP-EU-002 continued Valtropin treatment for an additional 12 months during Study BP-EU-002-RO. These 29 children constitute the ITT/FAS population for Study BP-EU-003-RO. **During the first 12 months of Valtropin treatment, mean HV had significantly increased to 9.74 ± 1.58. During the second 12 months of Valtropin treatment, as expected, mean HV decreased to 8.61 ± 1.16.** Concordantly, mean HV SDS_{CA} values decreased as well. **During the first 12 months of Valtropin treatment, mean height SDS_{CA} levels had significantly increased to -1.53 ± 0.95. During the second 12 months of Valtropin treatment, as expected, mean height SDS_{CA} increased further to -1.17 ± 0.96. The linear growth pattern observed during the second year of rhGH treatment**

(e.g., drop off in HV and continued increase in height SDS_{CA}) has been observed numerous times during extended treatment of TS children (as well as GHD children) with rhGH.

6.2.6 Efficacy Summary/Discussion, Conclusions and Recommendations

6.2.6.1 Efficacy Summary/Discussion

Two open-label, single arm, uncontrolled clinical trials were conducted that evaluated the efficacy (linear growth parameters) and safety of Valtropin and Eutropin™ INJ (a 1.33 mg = 4 IU formulation qualitatively identical to the 5 mg = 15 IU formulation, Valtropin) in TS patients with short stature. Study BP-EU-002 was conducted at a single center in Russia; 30 Caucasian girls (mean age = 6.9 yr) were treated with Valtropin 0.053 mg/kg/day SC for 12 months. During the Korean TS study (conducted at four centers in Korea), 60 Asian girls (mean age = 10.8 yrs) were treated with Eutropin™ INJ 0.34 mg/kg/week SC (0.048 mg/kg 7 days each week or 0.056 mg/kg 6 days each week) for 12 months.

6.2.6.1.1 Comparison of the Results Observed in Study BP-EU-002 and the Korean TS Study with Each Other

- **The most glaring differences between the subjects enrolled and treated in Study BP-EU-002 and the Korean TS study in demographics and baseline characteristics was CA at study entry (~7 vs. 11 yrs, respectively) and race (Caucasian vs. Asian).** The older subjects enrolled in the Korean TS study were growing a bit slower than the subjects in Study BP-EU-002 (3.48 vs. 3.75 cm/yr, respectively), and their baseline height SDS_{CA} was somewhat lower as well (-2.99 vs. -2.34, respectively). It is well known that older girls with TS have accrued a greater standardized height deficit and grow at a slower rate compared with younger girls with TS (cite reviews). Mean baseline BA was markedly delayed in both studies (~1.5-2 yrs less than CA). **On the other hand, the dosage administered in the 2 studies was similar (0.37 mg/kg/week in Study BP-EU-002 and 0.34 mg/kg/week in the Korean TS study).** As stated earlier, this Medical Officer and the Division's Statistical Reviewer decided **not** to perform a consolidated analysis primarily because 1) of the **differences in CA at study entry; 2)** different methods were use to calculate pre- and post-treatment HV; and 3) the Korean TS study was an older study conducted in Asian girls and Study BP-EU-002 was a more recent study conducted in Caucasian girls.
- **In both the BP-EU-002 and Korean TS study, there was a significant increase from baseline in HV at Month 12 (5.98 [mean HV at Month 12 = 9.73 cm/yr] and 3.49 cm/yr [mean HV at Month 12 = 6.97 cm/yr], respectively) (the primary efficacy variable).** The substantial 6.22 SD unit increase in HV SDS_{CA} changing a negative score at baseline to a markedly positive score at Month 12 in Study BP-EU-002 **indicates that treatment of TS girls with Valtropin induced rates of growth which were greater than that of normal children.**
- In both the BP-EU-002 and Korean TS study, there was also a robust and significant increase from baseline in height SDS_{CA} (0.88 and 0.35 SD units, respectively). Ranke et al (72) and other investigators have reported that the first year growth of TS patients after

treatment with rhGH is a powerful positive predictor of ultimate height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained.

- The significant HV and height SDS increases from baseline at Month 12 in both studies are consistent with a highly significant linear growth response after treatment with both Valtropin and Eutropin™ INJ in TS children with short stature, which was apparent as early as Month 3.
  Note: It is well known that the annualized HVat Month 3 or 6 overestimates the true annual HV at Month 12 in children with many forms of short stature treated with rhGH, i.e. the response to rhGH between Month 6 and Month 12 is less than the response between Month 0 and Month 6.
- **The more robust HV and height SDS responses observed in Study BP-EU-002 compared with the Turner TS study more than likely reflects the fact that CA at entry for Study BP-EU-002 was ~7 yrs (compared with 11 yrs for the Korean TS study, i.e. baseline CA at study entry is a positive predictor of short term growth response in TS children treated with rhGH. Children in both cohorts received comparable and adequate amounts of rhGH. The age subgroup analysis in the Korean TS study demonstrating that TS children >12 years old respond significantly less than children 4-8 or 8-12 years old supports this hypothesis. Furthermore, many studies have demonstrated that baseline CA at the time of initiation of rhGH therapy is a powerful inverse predictor of both the short-term and long-term response to rhGH in GHD children (parenthetically, in the sponsor's Study BP-EU-002 in GHD children, regression analysis was not significant for baseline CA as an inverse predictor, but did show a trend). Finally, in this regard, Ranke et al (72) and other investigators have reported that baseline CA at the time of initiation of rhGH therapy is a powerful inverse predictor of ultimate height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained. In summary, the extraordinary response observed during Study BP-EU-003 was remarkable for a TS cohort and more than likely is a reflection of the fact that CA is a powerful inverse predictor of the short-term (as well as the long-term [i.e., FH]) linear growth response of TS children after treatment with rhGH.**
- **Distribution of response analysis reveals that 5% and 20% of the TS girls enrolled and treated in the Korean TS study did not manifest any change in HV and height SDSCA, respectively (i.e. they were "non-responders), and 18.3% and 26.7% of this same cohort did not manifest a change in HV >1 cm/yr and a change in height SDSCA >0.1 (i.e., they were "poor" responders). In contrast, 100% of the TS girls enrolled and treated in Study BP-EU-002 met all of these criteria. These findings 1) are further evidence of the difference in response between the 2 studies (see previous bullet); and 2) are consistent with previous observations that the linear growth response of TS girls with short stature to treatment with rhGH is less consistent and more variable than the response of children with GHD (41, 72).**

- After 12 months of treatment with Valtropin in Study BP-EU-002, the mean B-P PredAH (147.4 cm) of the TS girls was significantly increased from baseline (144.6 cm). This supportive efficacy parameter was not measured in the Korean TS study.

- In Study BP-EU-002, the mean ratio of change in BA to change in CA was 1.02 and in the Korean TS study, mean HA/BA significantly increased at Month 12 indicating that rhGH treatment had not resulted in inappropriately accelerated bone maturation.
- In Study BP-EU-002-RO, during the second 12 months of Valtropin treatment mean HV decreased to 8.61 ± 1.16 cm/yr to 9.74 ± 1.58, while mean height SDS_{CA} **increased further to** -1.17 ± 0.96 from -1.53 ± 0.95. The linear growth pattern observed during the second year of rhGH treatment (e.g., drop off in HV and continued increase in height SDS_{CA}) has been observed numerous times during extended treatment of TS children (as well as GHD children) with rhGH.

6.2.6.1.2 Comparison of the Results Observed in Study BP-EU-002 and the Korean TS Study with the Results of Four Short-Term Published Studies Wherein rhGH was Administered to TS Children with Short Stature

A review of the literature reveals 4 concurrently controlled short-term studies wherein rhGH was administered for at least 1 year to TS children with short stature. Two of these studies (both with an untreated concurrent control group) will not be compared to the results from Study BP-EU-002 and the Korean TS study because in 1 instance an appropriate dose of rhGH for TS children (0.375 mg/kg/week) was administered 3 times a week rather than daily and also because oxandrolone was administered as well as rhGH to most of the patients (46), and in another instance the TS children were underdosed (0.26 mg/kg/week) (40).

The remaining 2 controlled studies (1 with a placebo control where we will only use results from the 0.36 mg/kg/week arm(s) [49], and 1 with a concurrent untreated control group [73]), and 2 other open-label studies (74-75) will be used for short-term comparison with the sponsor's TS studies (see Table 21). The amount of rhGH administered during the 4 selected studies ranged from 0.30 to 0.36 mg/kg/week (similar to the 0.34 and 0.37 mg/kg/week administered during the Korean TS study and Study BP-EU-002, respectively), and the mean baseline CAs across these 4 studies ranged from 9.9 to 10.8 yr (with 1 exception), and therefore approximated the mean baseline CA in the Korean TS study. Baseline HVs were remarkably consistent across all 6 studies (~3.4-4.3 cm/year [with 1 exception]). During the first year of the 2 concurrently controlled studies in Table 21, HV remained essentially unchanged from baseline (3.8-4.0 cm/year) in the control groups. **The changes in HV at Month 12 across the 4 comparator studies were tightly clustered at 3.2-3.4 cm/yr (with 1 exception) - which approximates the change in HV at Month 12 in the Korean TS study (3.7 cm/yr).**

It is difficult to find literature where younger TS children were treated to compare with Study BP-EU-003 (where mean CA at entry was 6.9 yr). Group A from the Lagrou et al study (75; data not shown in Table 21) is a flawed comparator because even though mean baseline CA was 4.8 yr and HV after 12 months of rhGH treatment was on its face quite robust at 9.0 cm/yr, a curiously and perhaps spuriously elevated pre-treatment HV of 5.7 cm/yr diminished the change from baseline in HV to 3.3 cm/yr.
In summary, the HV results at Month 12 from the Korean TS study (an open-label study without an untreated or placebo-treated concurrent control group) compare very favorably with the 12 month results of 2 concurrently controlled studies and 2 open-label studies

matched for dosage and baseline CA. The similar results support the validity of the significant increases in HV observed during the Korean TS study. We could not find a valid age- and dose-matched comparator for Study BP-EU-002 – where the TS children were much younger and the response exceeded all expectations (as has been discussed already in great detail).

It has previously been established that treatment with 0.30–0.36 mg/kg/week of rhGH for 12 months results in a greater linear growth response (~1 cm/year more) than treatment with 0.26–0.27 mg/kg/week (or less) for 12 months (40, 49, 73). The dose of Valtropin administered during Study BP-EU-002 (0.37 mg/kg/week) closely approximates the dosages of rhGH originally approved for the treatment of short stature associated with TS (i.e., up to 0.375 mg/kg/week). In addition, as noted earlier, it has been reported that treatment of TS children with rhGH at dosages greater than 0.30–0.36 mg/kg per week (i.e., as much as 0.45-0.70 mg/kg/week) results in a greater increase in FH, and no apparent increase in adverse events (43-45).