Table 21
Treatment of Turner Syndrome with rhGH:
Comparison of HV Results in Two Controlled and Two Uncontrolled Short-Term Published Studies with the Sponsor's Two Open-label Studies

Study HV in cm/yr*	CA	Baseline HV Control Somatropin	Month 12 HV Control Somatropin	Change in HV Control Somatropin
BP-EU-002/2001-2003 Open-label (n=30) 0.37 mg/kg/week	6.9	3.8	9.7	5.9
Korean TS/1995-1997 Open-label (n=60) 0.34 mg/kg/week	10.8	3.4	7.1	3.7
Stephure/1993[73] Untreated Control (n=55) 0.30 mg/kg/week (n=56)	10.5 10.8	4.2 4.3	3.8 7.6	-0.4 3.3
Quigley+/2002[49] Placebo Control (n=41) 0.36 mg/kg/week (n=91)	9.9++	4.1 4.3++	4.0++ 7.2++	-0.1++ 3.4++
Takano/1993[74] Open-label (n=93) 0.33 mg/kg/week	10.3	3.6	6.9	3.3
Lagrou/1998[75] **Open-label** **Group B (n=13)** **Group C (n=9)** **0.35 mg/kg/wk in both groups**	9.9 14.2	3.5 2.7	8.4 5.9	4.9 3.2

*All values in Table 20 represent the mean.
+Only data from high dose group shown – with/without low dose estrogen; the change in HV may not be readily calculated from the preceding column as this reflects the range of changes, and not the changes in the range.
++1 year data calculated from the reference (which provided 18 month data).

6.2.6.1.3 A Limited Review of Published FH Studies Wherein rhGH was Administered to TS Children with Short Stature (as well as non-TS non-GHD children with short stature)

Background statement:

During the last 10-15 years, most of the published studies reporting FH results in TS children treated with rhGH did not have a concurrent control group. Absent a concurrent control group, these authors have evaluated their FH results in several ways: **1) by comparing their FH results with historical data, i.e. the FH attained by untreated TS children** (141.1–143.2 cm/year; see references 27-30 and Section 2.6.2.3 above); 2) **by comparing their FH results with the**

mProjAH at baseline (29; see Section 2.6.2.3.1 above); and 3) by comparing their FH results with mid-parental target height.

In this section, this Medical Officer will briefly describe 4 concurrently controlled and 16 uncontrolled published FH studies in TS children treated with rhGH not supported by the sponsor of this submission. Please refer to Table 22 below.

These FH studies include the 4 label-enabling studies which led to the original approval of Humatrope and Nutropin AQ/Nutropin for the treatment of short stature associated with TS. **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 discussed in Sections 6.2.6.1.1 and 6.2.6.1.2 above 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 (4, 8, 42) 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.

6.2.6.1.3.1 Concurrently Controlled FH Studies **Not** Supported by the Sponsor

In this section, this Medical Officer will briefly describe 4 concurrently controlled published FH studies in TS children treated with rhGH not supported by the sponsor of this submission. Please refer to rows 4 through 7 in Table 22 below. The largest and most consequential study was published **in 2005** by the Canadian Growth Hormone Advisory Committee (51). Sixty one prepubertal TS patients (mean age 10.3) were **randomized to treatment** with **0.3 mg/kg/week** of rhGH, and 43 prepubertal TS patients (mean age 10.9) were randomized to no rhGH treatment, i.e the untreated control group. **The mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm ($p<0.001$)** (FH in the treated group was 147.5 cm). Hochberg et al (76) and Pasquino et al (41) published the results of **smaller, non-randomized**, concurrently controlled FH studies; mean FH in the rhGH-treated groups (**0.3 mg/kg/week in each study**) exceeded mean FH in the untreated control groups by 4.4 (5.3 when corrected for mProjAH at baseline) and 5.4 cm, respectively (FHs in the treatment groups were 147.3 and 147.6, respectively). Dacou-Voutetakis et al (40) also reported the results of a small, non-randomized, concurrently controlled study; FH in the treated group (146.1 cm) was only **2.1 cm greater** than FH in the untreated group, more than likely because of suboptimal dosing (0.23 mg/kg/week).

6.2.6.1.3.2 Uncontrolled FH Studies Not Supported by the Sponsor

In this section, this Medical Officer will very briefly and selectively describe 12 uncontrolled published FH studies in TS children treated with rhGH not supported by the sponsor of this submission. Please refer to rows 1-3 through 8-16 in Table 22 below.

Quigley et al (49) (dose of rhGH = 0.27-0.36 mg/kg/week) reported that the mean near final height (NFH) of 99 treated girls (whose BA was ≥14 years) was **148.7 cm**, a mean **increase of 1.3 SDS from baseline** (TS standard); **NFH was >152.4 cm (60") in 29% compared with the expected 5-10% of untreated historical controls.** Chernausek et al (50) (dose of rhGH = 0.375 mg/kg/ week) reported FHs of **150.4 cm** (height gain over mProjAH at baseline = **8.4 cm**) when estrogen therapy was delayed until age 15, and **147 cm** (height gain over mProjAH at baseline = **5.1 cm**) when estrogen therapy was started at age 12.

Massa et al (52) (dose of rhGH = 0.27-0.43 mg/kg per week) reported that the mean NFH of 45 TS patients completing the treatment protocol was **152.3 cm, 5.3 cm greater than the final adult height of 63 historically untreated TS patients.** Johnston et al (77) reported the results of 49 TS girls in the UK treated with **0.3 mg/kg per week** of rhGH until FH was attained. The mean NFH was **146.8 cm** and height gain over mProjAH at baseline was **4.6 cm.** NFH was greater than 152.4 cm (60") in 31% of these TS children compared with the expected 5-10% of untreated historical controls. The FHs observed by Rosenfeld et al (38), Nilsson et al (47) and Attanasio et al (48) were similar to those described above (please refer to Table 22 for details).

Ranke et al (72) recently **retrospectively reviewed** the FH response of **188** TS patients treated with Genotropin; this information was contained in the **German subset of the KIGS database.** KIGS is a very large postmarketing surveillance database established by Pharmacia many years ago to monitor the safety and efficacy of Genotropin administered to children with short stature. The median dose of Genotropin was **0.29 mg/kg per week.** Median FH was **152.2 cm,** gain over mProjAH at baseline was **6 cm,** and change from baseline in height SDS (Ranke) was 1. He also performed a detailed analysis of factors predictive of substantial height gain (please see Section 6.2.6.1.3.3 below). Betts et al (78) **retrospectively reviewed** the FH response of 52 TS girls treated with Genotropin; this information was contained in the United Kingdom subset of the KIGS database. The median dose of Genotropin was **0.24 mg/kg per week.** Median FH was **148 cm** and the gain over mProjAH at baseline was **5.2 cm.** Less than optimal dosing may account for the lesser growth response in this study compared with the Ranke study described above.

Finally, Sas et al (43), von Pareren et al (44) and Carel et al (45) reported mean FHs of **154.3 to 163.6 cm** after treatment with larger dosages of rhGH (**0.45 to 0.70 mg/kg per week**).

As a group, these uncontrolled studies further support a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 145.5 to 152.3 cm when the dosage of rhGH ranged from 0.23 to 0.43 mg/kg/week, and treatment arms including oxandrolone were excluded). Furthermore, when the dosage of rhGH ranged from 0.45 to 0.70 mg/kg per week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"!!). To put all of these FH results in context, it is important to restate that 1) the historical FH observed in untreated girls with TS reported by Lyon et al in 1985 (29 and see Section 2.6.2.3.1) was 143.2 cm; and 2) some investigators believe that the so-called Lyon curve may not be currently applicable, i.e. Sybert et al recently reported a FH of 148 cm in untreated TS girls in Washington state (20).

6.2.6.1.3.3 Predictors of FH After Treatment of TS Children with rhGH

As stated in Section 6.2.6.1.1, **Ranke et al (72) and other investigators have reported that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained.** It has also been reported that height gain over mProjAH 1) correlates inversely with CA (49-51, 72), BA (72) and height SDS (Turner standard) (72) at baseline, and 2) correlates positively with rhGH dose (72), duration of treatment with rhGH (51, 72), and overall prepubertal height gain (72). As discussed earlier in Section 2.6.3.3 above, years of rhGH treatment prior to the initiation of estrogen to induce puberty remains a somewhat controversial issue.

6.2.6.1.3.4 FH Results After Treatment of non-TS, non-Growth Hormone Deficient Children with rhGH

Various formulations of rhGH have been previously approved to treat short stature in non-GHD target populations **other than TS girls**. Several recent publications have reported that treatment with rhGH results in significantly improved FH in short children with CRI (pre-transplantation) (79), SGA (80, 81) and ISS (82-84). **The fact that there is current literature indicating that treatment of non-TS non-GHD short children with rhGH (i.e., CRI, SGA, ISS) significantly improves FH indirectly supports the use of rhGH for the** [redacted] b(4)

Table 22
Treatment of Turner Syndrome with Recombinant Human Growth Hormone
Review of Consequential Final Height Studies in the Literature

Author Year	Control group	GH/Manuf	n	GH dose (mg/kg/week)	Aver age at GH start (yrs)	Concomitant medications	Final Height or Near Final Height (NFH) (cm)	Notes
Row (1) Ranke 2002[72]	**None**	**Genotropin/ Pfizer**	**188**	**0.29**	**11.7**	**E2 started at age 14**	**152.2 Height gain c/w projected height at baseline was 6 cm**	**Data are from a retrospective analysis of the German subset of the KIGS surveillance study**
Row (2) Betts 1999[78]	None	Genotropin/ Pfizer	52	0.24	10.7	E2 added at various times	**148@ Height gain c/w projected height at baseline was 5.2 cm**	Data are from a retrospective analysis of the UK subset of the KIGS surveillance study; @given as +0.42 SDS, and converted by the sponsor from the Lyon curves
Row (3) Johnston 2001[77]	Concurrent untreated for 1 yr only	Genotropin/ Pfizer	12	0 for 1 yr, then 0.3	9.1	E2 started at entry	145.5 (NFH)	
			17	0.3	9.0	E2 started after age 12	146.2 (NFH)	The mean NFH of all 49 girls was 146.8 cm; height gain c/w projected height at baseline was 4.6 cm; NFH >152.4 cm (60") in 31% c/w the expected 5-10% of untreated historical controls
			20	0.3	9.1	E2 started at entry	148.2 (NFH)	
Row (4) Dacou-Voutetakis 1998[40]	Concurrent untreated; Non-Randomized	Genotropin/ Pfizer ---	35 27	**0.23** 0	12.0 NA	E2 started age 15.6 E2 started age 14.2	146.1 144.0	GH group – untreated control group = 2.1 cm

Row (5) Stephure 2005[51]	**Concurrent untreated; Randomized**	Humatrope/ Eli Lilly ---	61 43	0.3 0	10.3 10.9	E2 added age 13	**147.5** **141.0**	**The mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001)**
Row (6) Hochberg 1999[76]	**Concurrent untreated; Non-Randomized**	Humatrope/ Eli Lilly and Biotropin/ BTG ---	25 24	0.3 0	10.7 NA	E2 added age 13.2 E2 added age 13.4	**147.3** **142.9**	**GH group minus untreated control group = 4.4 cm;** In the untreated group, the projected height ~final height in almost all subjects
Row (7) Pasquino 1996[41]	**Concurrent untreated; Non-Randomized**	Sponsor not specified ---	18 18	0.15 for 1 year, then 0.3 0	13.0 NA	E2 started age 15.7	**147.6** **142.2**	**GH group minus untreated control group = 5.4 cm**
Row (8) Quigley 2002[49]	Placebo-controlled for 18 mos only Historical untreated for NFH	Humatrope/ Eli Lilly	15 24 38 22 41	0.27 0.27 0.36 0.36 placebo	10.6 10.4 11.2 11.1 NA	placebo E2 (low dose) after age 8 placebo E2 (low dose) after age 8 placebo	149.9 (NFH) 145.1 (NFH) 150.4 (NFH) 149.1 (NFH) NA*	**The mean NFH of 99 treated girls whose bone age was ≥14 was 148.7 cm - a mean increase of 1.3 SDS from baseline (TS standard); NFH >152.4 cm (60") in 29% c/w the expected 5-10% of untreated historical controls** *merged into Group 3 after 18 mos
Row (9) Chernausek 2000[50]	Historical untreated for FH	Nutropin/ Genentech	30	0.375	9.6	E2 added at 12 yrs of age	**147.0**	**Height gain** c/w projected height at baseline was **8.4 cm** when estrogen treatment was delayed until age 15 yrs, and **height gain** c/w projected height at baseline was **5.1 cm** when estrogen treatment was started at age 12 yrs
			30		9.4	E2 added at 15 yrs of age	**150.4**	
		---	69	0	NA	E2 added at mean age 15-16.2 yrs	144.1	
Massa 1995[52]	Historical untreated for FH	Humatrope/ Eli Lilly	19 35	0.27 0.27 for 2 yrs, then 0.43	<12 >12	E2 added after age 12 yrs E2 added from beginning	**151.3** **152.0**	The NFH of the 45 patients completing the treatment protocol was **152.3 cm, 5.3 cm greater than the final adult height of 63 historically untreated TS patients**
		---	63	0	NA	0	**147**	

Row (11) Rosenfeld 1998[38]	Concurrent untreated for 1 yr only	Protropin/ Genentech	17	0.375 from the beginning	9.1	E2**	**150.4**	**E2 added to all groups after age 14
			43*	0 for 1-2 yrs, then 0.375 0.375 from the beginning	9.7	Oxandrolone, E2** Oxandrolone, E2**	**152.1**	
	Historical untreated for FH	---	25	0	9.2	---	144.2	
Row (12) Nilsson 1996[47]	None	Somatonorm/ Kabi, then Genotropin/ Pfizer	6	0 for 1year, then 0.23	12.3	Oxandrolone from beginning	151.0	
			7	0 for 1year, then 0.23		Oxandrolone from beginning, and E2 after 1 year	151.1	
			17	0.23	12.1	Oxandrolone from beginning	**154.2**	
			15	0.23	12.3	Oxandrolone and E2 from beginning	**151.1**	
Row (13) Attanasio 1995[48]	None	Humatrope/ Eli Lilly	6	Between 0.15 and 0.3	11#	E2 started after BA 12.5 yrs	150.9	FH data collected as part of the NCGS surveillance study; #Age at start not expressly stated, but calculated by the sponsor; some subjects may have received no GH for the first year of the study

Row (14) Sas 1999[43]	None	Norditropin/ Novo Nordisk	9 10	**0.46** given qHS **0.46**, given as 1/3 qAM, 2/3 qHS	13.3 13.8	E2 from the beginning	**154.3** **156.5**	
Row (15) van Pareren 2003[44]	None	Norditropin/ Novo Nordisk	19 20 21	0.3 0.3 for 1 year and **0.45 thereafter** 0.3 for 1 year and **0.45 for the second year, and 0.60 thereafter**	6.5 6.9 6.5	17β E2 started in all girls at average age 12.7 yrs	157.6 **162.9** **163.6**	
Row (16) Carel 1998[45]	None	Maxomat/ Sanofi	17	0.3	11.0	E2 added at 14 yrs	148.3	Treatment stopped when BA ≥13.5 yrs; Data from 0.3 group was a retrospective analysis
			14	**0.23 increasing to 0.7 over 4 yrs**	10.2	E2 added at 15.3 yrs	**155.3**	

6.2.5.2 Efficacy 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——— b(4)

6.2.5.3 Recommendations

- No additional efficacy studies are required to obtain approval for this indication.
- The short-term efficacy data from Study BP-EU-002 and 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 controlled studies **strongly supports** the validity of the sponsor's findings. A review of published final height (FH) studies not supported 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 by highly regarded organizations 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 for the——— section of the Valtropin Package Insert describing ——— was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential edits involved 1) 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.

6.3 Indication Number 3 - Adult GHD

6.3.1 Methods

See Section 4.1.

6.3.2 General Discussion of Endpoints

The endpoints for this study were standard measures of body composition. See Section 6.3.3.3 below.

6.3.3 Study Design

6.3.3.1 Study Design for Study HGCL-001 (2001 – 2002)

6.3.3.1.1 General Description (including dosing)

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 and placebo. 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. 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.

6.3.3.1.2 Major Inclusion/Exclusion Criteria

Inclusion Criteria:

- Subjects ≥ 18 years of age
- CO GHD criteria included attainment of maximal growth; reconfirmation of GHD at screening with an insulin tolerance test (cutpoint ≤5 ng/mL); no exposure to rhGH within the past 2 years
- AO GHD criteria included defined organic pituitary/hypothalamic disease; GHD present for at least 12 months prior to enrollment; 1 of the following: 1) insulin tolerance test (cutpoint ≤5 ng/mL) at screening or within 3 years of enrollment; or 2) >3 other pituitary hormone deficiencies; or 3) serum IGF-1 level below the normal range confirmed at least 1 year prior to enrollment; diagnosed with at least 1 other pituitary hormone deficiency, excluding prolactin; no exposure to rhGH within the past 1 month
- If applicable, stable replacement therapy for other pituitary hormone deficiencies for at least 1 month prior to enrollment

Exclusion Criteria:

- Subjects with proliferative and progressive diabetic retinopathy
- History of malignancy or concurrent anti-tumor therapy.
- Benign intracranial hypertension.
- Subjects with active acromegaly.
- Significant renal or hepatic disease
- Pregnant or breast-feeding woman
- Subjects on chronic medication (excluding standard pituitary hormone replacement therapy, contraceptives, mild hypertension medications, or asthma treatments)

6.3.3.1.3 Efficacy Endpoints

The primary efficacy parameter was change in FM (by dual energy X-ray absorptiometry [DEXA] scan).

Secondary efficacy parameters included:

- Change in LBM by DEXA

- Serum IGF-1
- Lipid panel
- Osteocalcin
- Waist/hip ratio (WHR)
- Quality of Life assessment using the QOL AGHDA

DEXA scans were performed at baseline, Month 3 and Month 6 (study termination). Blood work and QOL questionnaires were accomplished at the same timepoints.

6.3.3.1.4 Safety Evaluations

Physical examinations/safety parameters (including serum IGF-1 levels, and routine hematology/chemistries/urinalysis) were performed/obtained at baseline, 3 and 6 months. All adverse events and concomitant drug therapy were recorded at each clinic visit.

6.3.3.1.5 Statistical Methods

6.3.3.1.5.1 Sample Size Calculation

After estimating the treatment effect based on prior relevant clinical studies, the sample size was calculated to achieve 90% power with a 5% significance level. The required sample size was estimated to be 25 subjects per treatment group.

6.3.3.1.5.2 Populations Analyzed

The Division's Statistical Reviewer focused/performed his primary (and secondary) efficacy analyses on the ITT population with LOCF (patients who had received at least 1 dose of study drug and who had at least 1 post-treatment efficacy measurement, i.e. baseline measurements of FM and LBM were **not** carried forward). The sponsor also performed primary (and secondary) efficacy analyses on the PP1 population (which was defined as subjects who satisfied all of the inclusion/exclusion criteria, participated in the study for at least 3 months, and had relevant data obtained at Month 3), and the PP2 population (which was defined as subjects who satisfied all of the inclusion/exclusion criteria, participated in the study for its entire 6 month duration, and had relevant data obtained at Month 6).

6.3.3.1.5.3 Analyses of the Primary (and Secondary) Efficacy Endpoints

As stated above, the primary efficacy endpoint was change in FM, and the most consequential secondary efficacy endpoint was change in LBM.

Period 1 (baseline to Month 3) and Period 2 (Month 3 to Month 6) were analyzed separately; in addition, changes in FM and LBM were analyzed from baseline to Month 6 for patients in Group A (who received Eutropin™ INJ continuously for 6 months).

ANCOVA (with baseline FM or LBM, age and center as covariates) was utilized for between-group analyses, and the paired t-test was used for within-group analyses. **The Division's Statistical Reviewer focused his analysis on the treatment difference between Groups A and B combined vs. Group C (placebo) at Month 3.**

6.1.3.1.5.4 Safety Analyses

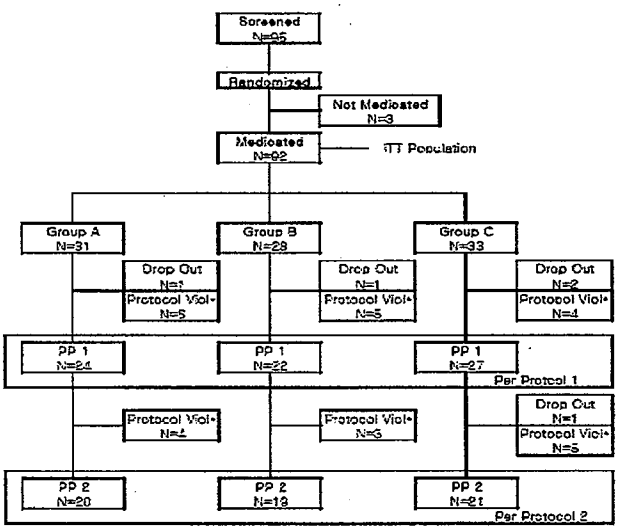
Safety results were presented utilizing descriptive statistics.

6.3.4 Efficacy Findings

6.3.4.1 Enrollment and Disposition

As seen in Figure 8, 92 patients were randomized and treated (31 in Group A, 28 in Group B, and 33 in Group C) - the so-called ITT population. In fact, the true ITT population consisted of 89 patients (31 in Group A, 27 in Group B, and 31 in Group C) because 1 patient in Group B and 2 patients in Group C did not have FM or LBM determinations at Month 3 (and it was thought unproductive to carry forward baseline values). 87 out of 92 patients completed the study (94.6%). Two patients discontinued because of adverse events unrelated to treatment with Eutropin™ INJ (see Integrated Summary of Safety). Figure 8 demonstrates that protocol violations were by far the most common reason for the exclusion of patients from the PP1 and PP2 populations.

Figure 8



* Including only the ineligible subjects that had completed the study

Figure 2. Subject Disposition

6.3.4.2 Demographics and Baseline Characteristics

Baseline characteristics and demographics are presented in Table 23. Mean age ranged from 46 to 52 years across the 3 groups. **There was a remarkably large proportion of women in each of the groups (ranging from ~57 to 72%), many of whom who were receiving ERT - an issue which will be discussed further on in this review. The number of patients in each group with a remote history of rhGH usage ranged from ~30 to 50%) - this issue will also be addressed again later on in this review.** Not surprisingly, about 50% of the patients in each group had 3 other pituitary hormone deficiencies. Pituitary tumors (and related treatment) and Sheehan's syndrome were by far the most common etiologies of GHD and associated hypopituitarism in the study population. Only 6 out of the 92 randomized and treated had CO GHD.

Table 23 - Study HGCL-001
Demographics and Baseline Characteristics

Demographic characteristics	Group A (n=31)	Group B (n=28)	Group C (n=33)	p-value
Age (yr; mean±SD)	47.4 ± 9.9	46.3 ± 15.4	52.6 ± 13.7	0.13
Male (n [%])	11 (35.5)	12 (42.9)	9 (27.3)	NA
Female	**20 (64.5%)**	**16 (57.1%)**	**24 (72.7%**	**NA**
Height (cm;mean±SD)	159.6 ± 8.3	161.3 ± 10.6	158.2 ± 8.8	0.45
Weight (kg; mean±SD)	64.5 ± 12.7	67.7 ± 18.6	61.1 ± 11.2	0.20
Waist (cm; mean±SD)	86.2±9.8	88.9±13.3	85.9±8.4	0.50
Hip (cm; mean±SD)	95.6±7.3	98.4±11.5	95.0±6.6	0.26
Panhypopituitarism (x3)*	**17 (54.8%)**	**14 (50%)**	**17 (51.5%)**	
Panhypopituitarism (x4)**	1 (3.2%)	2 (7.1%)	4 (12.1%)	
Isolated FSH/LH Deficiency	4 (12.9%)	5 (17.9%)	2 (6.1%)	
ACTH&TSH Deficiency	5 (16.1%	2 (7.1%)	1 (3.0%)	
Prior Treatment with rhGH	**13 (41.9%)**	**9 (32,1 %)**	**16 (48.5%)**	

*FSH/LH&ACTH&TSH
**FSH/LH&ACTH&TSH&Vasopressin

6.3.4.3 Dosing

The initial dose of Eutropin^{TM} INJ was 0.33 mg/day 6 days per week. Subsequently, the following criteria were used by investigators at the 6 sites in Korea which participated in Study HGCL-001 with regard to up-titrating or down-titrating the amount of Eutropin^{TM} INJ administered (up to a maximum of 0.66 mg/day:

a. Dose could have been decreased because of the occurrence of rhGH-related adverse events (e.g., edema, arthralgia), or when the age- and gender-referenced serum IGF-1 level from the previous visit was "significantly" elevated (i.e., >97.5th percentile for age/gender)

b. Dose could have been increased when the age- and gender-referenced serum IGF-1 level from the previous visit was below the "targeted range" (<2.5th percentile for age/gender), or because of persistent clinical symptoms potentially indicative of suboptimal rhGH therapy, i.e. persistence of fatigue.
c. Typically, the dose of Eutropin^{TM} INJ was adjusted by increments or decrements of 0.17 mg (but these changes may have been as small as 0.067-0.1 mg depending upon the clinical judgment of individual investigators).

The mean final dose of Eutropin^{TM} INJ administered was 0.35 mg/day.

6.3.4.4 Efficacy Results

6.3.4.4.1 Primary Efficacy Variable - **Change in FM**

Change in FM was the primary efficacy variable. The results obtained for changes (decreases) in FM are presented in Tables 24-28. As seen in Table 24, after 3 months of treatment with Eutropin^{TM} INJ vs. placebo, there was a significant (p=0.003) between-group treatment difference for the change in FM (**-1.35 kg**)*. Table 25 depicts the significant (p<0.0001) within-group change in FM (**-1.3 kg**) after 3 months of treatment with Eutropin^{TM} INJ for groups A+B combined in the ITT population. For group A alone in the ITT population, the significant within-group change in FM after 3 months of treatment was **-1.7 kg** (see Table 26). For Group B alone, the within-group change in FM at Month 3 was not significant in the ITT population; however, this change was significant in the PP1 population (see Table 27). During treatment period 2, when patients in group C were crossed over to Eutropin^{TM} INJ from placebo, a significant within-group change in FM was observed as well (**-1.2 kg**; see Table 28). Table 25 also reflects the significant (p<0.0001) within-group change in FM (**-2.3 kg**) after 6 months of treatment with Eutropin^{TM} INJ for group A alone in the ITT population. Furthermore, as seen in Table 28, 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 **-0.6 kg; this change was not statistically significant suggesting that most of the decrease in FM after treatment with Eutropin^{TM} INJ occurred by the end of Month 3.**

*Note: 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. 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).

Table 24 - Study HGCL-001
Between-Group Changes in Fat Mass after 3 Months of Treatment with Eutropin™ INJ (Groups A+B Combined) vs. Placebo (Group C)

FM expressed in kg	Groups A and B Combined (n=58)	Group C (n=31)
ANCOVA* in ITT Population**	Eutropin™ INJ	Placebo
Baseline (Mean ± SD)	23.0 ± 7.7	19.9 ± 3.7
Change from Baseline to Month 3 (Mean ± SD)	-1.25 ± 2.18	+0.16 ± 1.50
Change from Baseline to Month 3 (Adjusted Mean ± SE)	-1.17 ± 0.25	+0.18 ± 0.35
Treatment Difference (95% CI)	**-1.35** (-0.48, -2.22) p = 0.003	

*The adjusted LS means were obtained using the sponsor's ANCOVA model, where baseline FM, age and country were the covariates.
****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward.**

Table 25 - Study HGCL-001
Within-Group Changes in Fat Mass After 3 Months of Treatment (Groups A+B Combined Compared With Group C)

FM expressed in kg	Group A+B Combined EutropinTM INJ		Group C Placebo
ITT Population**	n	n	
Baseline (Mean ± SD)	58	23.0 ± 7.7	31	19.9 ± 3.7
Month 3 (Mean ± SD)	58	21.7 ± 7.7	31	20.2 ± 3.5
Paired t-test p-value		**<0.0001***		0.5471

*Statistically significant within-group change from baseline at Month 3 ($p<0.05$).
****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward.**

Table 26
Within-Group Changes in Fat Mass After 3 and 6 Months of Treatment with Eutropin™ INJ (Group A)

Fat Mass (kg) (mean ± SD) ITT w/ LOCF[#]	Group A Eutropin™ INJ (n=31)
Baseline	21.9 ± 6.0
Month 3	**20.2 ± 6.3* ^**
Month 6	**19.6 ± 5.7* #**

*p<0.0001 within-group change from baseline by paired t-test
^Δ = -1.7 kg; #Δ = -2.3 kg if one carries forward the 3 month value for the 1 patient (Subject #15003) who did not have a FM determination at Month 6.

Table 27 - Study HGCL-001
Within-Group Changes in Fat Mass After 3 Months of Treatment Across the 3 Treatment Groups

Mean ± SD in kg	Treatment Group					
	Group A (E→E)		**Group B (E→P)**		**Group C (P→E)**	
ITT Population**	n		n		n	
Baseline (Mean ± SD)	31	21.9 ± 6.0	27	24.2 ± 9.2	31	19.9 ± 3.7
Month 3 (Mean ± SD)	31	20.2 ± 6.3	27	23.5 ± 8.8	31	20.0 ± 3.5
Paired t-test p-value		**<0.0001***		**0.1201**		0.5476
PP1 Population	n		n		n	
Baseline (Mean ± SD)	24	21.8 ± 6.5	22	24.5 ± 9.5	27	20.0 ± 3.8
Month 3 (Mean ± SD)	24	20.1 ± 6.7	22	23.5 ± 9.4	27	20.2 ± 3.4
Paired t-test p-value		**0.0004***		**0.0167***		0.4007

*Statistically significant within-group change from baseline to Month 3 (p<0.05).

****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward.**
E = Eutropin™ INJ; P = Placebo

Table 28 – Study HGCL-001
Within-Group Changes in Fat Mass Between Month 3 and Month 6
Across the 3 Treatment Groups

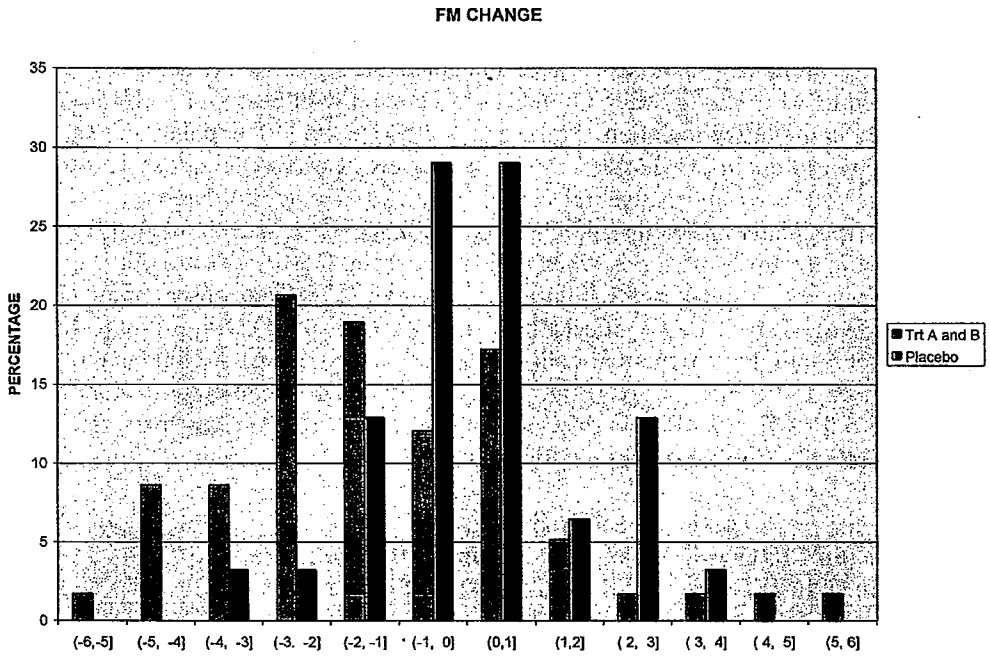
Mean ± SD in kg	Treatment Group					
		Group A (E→E)		**Group B (E→P)**		**Group C (P→E)**
ITT Population**	n		n		n	
Month 3 (Mean ± SD)	31	**20.2 ± 6.3**	26	23.6 ± 9.0	30	**20.2 ± 3.5**
Month 6 (Mean ± SD)	31	**19.6 ± 5.7**	26	24.0 ± 8.1	30	**19.0 ± 3.6**
Paired t-test p-value		**ns***		ns		**0.0019***

*Statistically significant within-group change from Month 3 to Month 6 ($p<0.05$).
****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward; also, the 3 month value was not carried forward for 1 subject in Group B and 1 subject in Group C who did not have a FM determination at Month 6; however, the 3 month value for the 1 patient (Subject #15003) in Group A who did not have a FM determination at Month 6 was carried forward.**
E = Eutropin™ INJ; P = Placebo

6.3.4.4.1.1 FM - Distribution of Response

As seen in Figure 9, ~70% of patients (Groups A and B combined) responded to 3 months of treatment with Eutropin™ INJ, i.e. change in FM was negative. **In ~60% of patients, the decrease in FM was >1 kg. On the other hand, ~30% of treated patients did not respond!**

Figure 9 - Study HGCL-001



6.3.4.4.1.2 Covariate Analyses for the Primary Efficacy Endpoint - Change in FM after 3 Months of Treatment with Eutropin™ INJ vs. Placebo

None of the covariates were significant, including FM value at baseline.

6.3.4.4.1.3 Subgroup Analyses for the Primary Efficacy Endpoint

6.3.4.4.1.3.1 Gender

Neither the Division's Statistical Reviewer or the sponsor detected any differences in the decrease in FM between men, hypogonadal/menopausal women treated with oral ERT, and hypogonadal/menopausal women not treated with oral ERT (data not shown).

6.3.4.4.1.3.2 CO vs. AO Adult GHD

Only 6 patients had CO adult GHD; therefore, subgroup analysis was not possible.

6.3.4.4.2 Secondary Efficacy Variables

6.3.4.4.2.1 Change in LBM

Change in LBM was the primary efficacy variable. The results obtained for changes (increases) in LBM are presented in Tables 29-31. As seen in Table 29, after 3 months of treatment with Eutropin™ INJ vs. placebo, there was a significant (p=0.026) between-group treatment difference for the change in LBM (**+0.88 kg**). Table 30 depicts the significant (p=0.0018) within-group change in LBM (**+0.9 kg**) after 3 months of treatment with Eutropin™ INJ for groups A+B combined in the ITT population. For group A alone in the ITT population, the significant within-group change in LBM after 3 months of treatment was **+1.0 kg** (see Table 31). 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 (p=0.06 in each population; data not shown). During treatment period 2, when patients in group C were crossed over to Eutropin™ INJ from placebo, a significant within-group change in LBM was observed as well (**+1.4 kg**; data not shown). Table 31 also reflects the significant (p<0.0001) within-group change in LBM (**+2.1 kg**) after 6 months of treatment with Eutropin™ INJ for group A alone in the ITT population. Furthermore, the within-group change in LBM between the beginning of Month 4 and the end of Month 6 for group A alone in the ITT population was **+1.1 kg; however, this change was not statistically significant (as per the sponsor).**

Table 29 - Study HGCL-001
Between-Group Changes in LBM after 3 Months of Treatment with Eutropin™ INJ (Groups A+B Combined) vs. Placebo (Group C)

LBM expressed in kg	Groups A and B Combined (n=58)	Group C (n=31)
ANCOVA* in ITT Population**	Eutropin™ INJ	Placebo
Baseline (Mean ± SD)	40.1 ± 10.8	38.0 ± 8.8
Change from Baseline to Month 3 (Mean ± SD)	0.94 ± 2.19	-0.24 ± 1.33
Change from Baseline to Month 3 (Adjusted Mean ± SE)	0.94 ± 0.22	+0.06 ± 0.32
Treatment Difference (95% CI)	**0.88** (1.65, 0.11) p=0.026	

*The adjusted LS means were obtained using the sponsor's ANCOVA model, where baseline FM, age and country were the covariates.
****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward.**

Table 30 - Study HGCL-001
Within-Group Changes in LBM After 3 Months of Treatment
(Groups A+B Combined Compared With Group C)

LBM expressed in kg	Group A+B Combined EutropinTM INJ		Group C Placebo	
ITT Population**	n		n	
Baseline (Mean ± SD)	58	40.1±10.8	31	38.0±8.8
Month 3 (Mean ± SD)	58	41.0±10.5	31	37.8±8.6
Paired t-test p-value		**0.0018***		0.3124

*Statistically significant within-group change from baseline at Month 3 ($p<0.05$).
****Three subjects (Subject 11015 in Group B and Subjects 12001 and 14010 in Group C) were not included because post-treatment values at Month 3 were not obtained, i.e. baseline values were not carried forward.**

Table 31
Within-Group Changes in LBM
After 3 and 6 Months of Treatment
with Eutropin™ INJ (Group A)

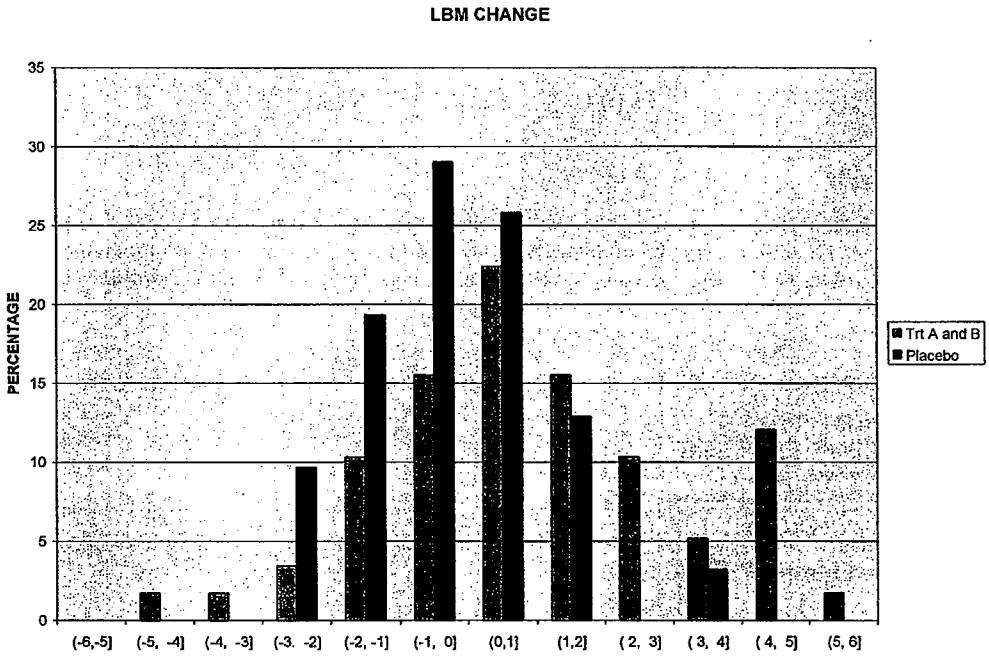
Fat Mass (kg) (mean ± SD) ITT w/ LOCF#	Group A Eutropin™ INJ (n=31)
Baseline	39.3 ± 9.8 kg
Month 3	40.3 ± 9.4 kg* ^
Month 6	41.4 ± 9.5 kg* #

*$p<0.0001$ within-group change from baseline by paired t-test
^Δ = +1.0 kg; #Δ = +2.1 kg if one carries forward the 3 month value for the 1 patient (Subject #15003) who did not have a LBM determination at Month 6.

6.3.4.4.2.1 LBM - Distribution of Response

As seen in Figure 10 (as was the case with FM), ~70% of patients (Groups A and B combined) responded to 3 months of treatment with Eutropin™ INJ, i.e. change in LBM was positive. **In ~45% of patients, the increase in LBM was >1 kg. On the other hand, ~30% of treated patients did not respond!**

Figure 10 - Study HGCL-001



6.3.4.4.2.2 Other Secondary Efficacy Endpoints

6.3.4.4.1.2.1 WHR/BMI

No significant within-group or between group changes were observed.

6.3.4.4.1.2.2 Lipids, Osteocalcin

Total and LDL cholesterol levels trended downward across the groups, but these changes rarely reached statistical significance. Serum osteocalcin did in fact increase significantly after the administration of Eutropin™ INJ (a well established effect of rhGH in adult GHD patients).

6.3.4.4.1.2.3 Serum IGF-1 and IGF-1 SDS

As seen in Table 32, 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 correlation between the within-group increase in serum IGF-1 and the within-group decrease in FM 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.

Please see the Integrated Summary of Safety regarding further analysis of the serum IGF-1 response.

Table 32 - Study HGCL-001
Serum IGF-1 Levels Before and After Treatment with Eutropin™ INJ

	Treatment Group					
	Group A (E→E)[a]		Group B (E→P)[a]		Group C (P→E)[a]	
Intend to Treat (ITT) Subset	N		N		N	
Visit 0 (Mean ± SD)	31	141.4 ± 79.1	28	134.4 ± 79.9	33	133.5 ± 63.1
Visit 3 (Mean ± SD)	31	313.5 ± 126.3	27	266.6 ± 103.3	31	144.9 ± 55.6
Visit 6 (Mean ± SD)	25	314.6 ± 102.6	25	133.1 ± 70.0	25	340.4 ± 200.5
Paired t-test p-value	V0 V3	<0.0001* 0.66		<0.0001* <0.0001**		0.40 <0.0001**

*Statistically significant difference for change from baseline (Visit 0) to Month 3 (Visit 3) within group.
**Statistically significant difference for change from Month 3 (Visit 3) to Month 6 (Visit 6) within group.
a: E = Eutropin; P = Placebo
Note: Data are given as Mean ± SD in kg.

6.3.5 Efficacy Summary/Discussion, Conclusions and Recommendations

6.3.5.1 Efficacy Summary/Discussion

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.

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.

In order to further assess the validity of the significant between-group and within-group changes in FM and LBM after treatment with 3-6 months of Eutropin™ INJ during Study HGCL-001 summarized in the preceding 3 paragraphs, it is important to compare these findings with published short-term studies wherein adult GHD patients were treated with other approved formulations of rhGH.

Table 33 (see 3 pages ahead) compares the 3 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 with the within-group results in a selection of 5 published studies of 3 months duration (85-89). 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 (85). In both of these studies, non-weight-based doses of rhGH were uptitrated 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 [85]). As seen in rows 1 and 2 of Table 35, **the decrease in FM was 1.7 kg in both studies, and the increases in LBM were similar**. Davies et al (86) and Orme et al (87) also administered more or less similar amounts of rhGH in open-label studies, and observed very similar decreases in FM, but more robust increases in LBM (see rows 5 and 6 of Table 35). The weight-based amounts of rhGH administered by Verhelst et al (88) and Christ et al (89) were more than twice that administered during Study HGCL-001 (~0.012 mg/kg/day vs. ~0.005 mg/kg/day, respectively) which may explain why the FM and LBM responses were more substantial (see rows 3 and 4 of Table 35).

Table 34 (see 4 pages ahead) compares the 6 month within-group changes from baseline in FM and LBM in Group A in Study HGCL-001 with the within-group results in a selection of 4 published studies of 6 months duration (insert references here and in table). 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 (90). In both of these studies, non-weight-based doses of rhGH were uptitrated 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 [90]). As seen in rows 1 and 2 of Table 36, **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 (90); and the increase in LBM (men and women combined) was identical in both studies (2.1 kg). Furthermore, although Ezzat et al administered twice the dose of rhGH administered during Study HGCL-001, the FM and LBM responses were almost identical (91; see row 4 of Table 36).** The weight-based amounts of rhGH administered by Attanasio et al (92) and

Hoffman et al (93; a different publication from the one referenced earlier in this paragraph) were more than twice that administered during Study HGCL-001 (~0.0125 mg/kg/day vs. ~0.005 mg/kg/day, respectively) which may explain why the FM and LBM responses were more substantial (see rows 3 and 5 of Table 35).

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 (-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). Furthermore, although the within-group increase in LBM between the beginning of Month 4 and the end of Month 6 for group A alone in the ITT population was more substantial **(+1.1 kg), this change also was not statistically significant. 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** (88; also see row 3 in Table 35). In contrast, another very large 6 month open-label study (94) 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 (54).

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** (88).

Table 33 - Study HGCL-001
Comparison of Within-Group Changes in FM and LBM
After 3 months of Treatment with Somatropin in Adults with GHD

Study	Product	Study design	Dose regimen	Final dose	Drt	N	LBM/FFM (kg) Mean ± SD		FM (kg) Mean ± SD	
							Baseline	Post-TRT (Change)	Baseline	Post-TRT (Change)
HGCL-001 Group A*	**Valtropin**	db, rnd, pc	Starting dose 0.33 mg/d (6/w) Titrated up to 0.67 mg/d (6/w)	**0.35 mg/d (6/w)**	3 m	31	**39.3 ± 9.8**	**40.3 ± 9.4 (+1.0)**	**21.9 ± 6.0**	**20.2 ± 6.3 (-1.7)**
Ahmad[85] 2001	**Genotropin or Humatrope**	open	Starting dose 0.13/0.15 mg/d (7/w) Titrated up to 0.27 mg/d	**0.27 mg/d (7/w)**	3 m	46	**55.9 ± 11.1**	**57.6 ± 11.5 (+1.7)**	**32.8 ± 13.6**	**31.1 ± 13.6 (-1.7)**
Verhelst[88] 1997	Genotropin	db, rnd, pc	0.006 mg/kg/d (7/w) for 1 m 0.012 mg/kg/d for 5 m	0.011 mg/kg/d	3 m	71	55.4	N/A **(+2.9 ± 4.6)**	21.2	N/A **(-2.5 ± 4.6)**
Christ[89] 2004	Genotropin	db, rnd, pc	0.006 mg/kg/d (7/w) for 1 m 0.012 mg/kg/d thereafter	0.012 mg/kg/d	3 m	7	48.5 ± 3.9	51.5 ± 4.4 **(+2.0)**	26.3 ± 2.7	22.8 ± 2.5 **(-3.5)**
Davies[86] 2000	Humatrope	open	M: 0.0033 mg/kg/d (7/w) for 1m 0.005 mg/kg/d for 2 m (n= 20) F: 0.0067 mg/kg/d (7/w) for 1 m 0.0083 mg/kg/d for 2 m (n=19)	M: 0.005 mg/kg/d (7/w) F: 0.0083 mg/kg/d (7/w)	3 m	39	50.2 ± 13.7	52.4 ± 13.9 **(+2.2)**	31.6 ± 16.7	29.8 ± 16.6 **(-1.8)**
Orme[87] 1992	Norditropin	open	0.44 mg (3/w)	0.44 mg (3/w)	8 w	8	48.7	51.3 **(+2.6)**	23.3	21.4 **(-1.9)**

Note: Drt - duration; LBM - lean body mass; FFM - fat free mass; FM - fat mass;
db – double-blind; rnd - randomized; pc – placebo-controlled; w - week, d - day; m - month; TRT - treatment; M - male; F – female.
*Group A received Eutropin™ INJ for 3 consecutive months.

Table 34 - Study HGCL-001
Comparison of Within-Group Changes in FM and LBM
After 6 months of Treatment with Somatropin in Adults with GHD

Study	Product	Study design	Dose regimen	Final dose	Drt	N	LBM/FFM (kg) Mean ± SD		FM (kg/%) Mean ± SD	
							Baseline	Post-TRT (Change)	Baseline	Post-TRT (Change)
HGCL-001* Group A	**Valtropin**	db, rnd, pc	Starting dose 0.33 mg/d (6d/w) Titrated up to 0.67 mg/d (6d/w)	**0.35 mg/d (6d/w)**	6 m	31	**39.3 ± 9.8**	**41.4 ± 9.5 (+2.1)**	**21.9 ± 6.0**	**19.6 ± 5.7 (-2.3)**
Hoffman[90] 2004**	**Humatrope**	open, rnd	Starting dose 0.2 mg/d Titrated up to 0.8 mg/d	N/A	8 m	M 109	**54.2 ± 11.2**	**N/A (+2.8 ± 2.8)**	**N/A**	**(-1.8 ± 2.5)**
						F 78	**40.0 ± 9.0**	**N/A (+1.1 ± 2.6)**	**N/A**	**(-2.0 ± 3.8)**
				0.54 mg/d (7d/w)		M & F	**48.1 ± 12.4**	**N/A (+2.1 ± 2.9)**	**N/A**	**N/A**
Attanasio[92] et al. 1997	Humatope	db, rnd, pc	0.00625 mg/kg/d for 1 m 0.0125 mg/kg/d thereafter	0.0125 mg/kg/d (7/w)	6 m	AO 52	57.9 ± 14.9	N/A **(+3.5 ± 8.5)**	29.5 ± 13.8%	N/A **(-4.9 ± 12.3%)**
						CO 32	43.5 ± 9.5	N/A **(+3.7 ± 4.1)**	32.2 ± 10.5%	N/A **(-5.5 ± 6.2%)**
Ezzat[91] et al. 2002	Saizen	db, rnd, pc	0.005 mg/kg/d for 1 m 0.010 mg/kg/d for 5 m	0.010 mg/kg/d (7/w)	6 m	52	49.1 ± 11.7	N/A **(+1.9 ± 2.2)**	27.7 ± 10.7	N/A **(-2.3 ± 2.7)**
Hoffman[93] et al. 2004	Humatrope	db, rnd, pc	0.0125 mg/kg/d for 1 m Titrated up to 0.025 mg/kg/d for 11 m	0.0125 mg/kg/d (79%)	12 m+	M 34	54.4 ± 6.8	58.5±7.1 **(+4.1 ± 3.2)**	27.5 ± 6.5%	22.9 ± 6.9% **(-4.6 ± 3.4%)**
						F 26	37.8 ± 5.9	39.8±5.8 **(+2.0 ± 1.7)**	44.0 ± 9.3%	41.6±10.5% **(-2.4 ± 3.7%)**

Note: Drt - duration; LBM - lean body mass; FFM - fat free mass; FM - fat mass; N/A - The Post-TRT values were not presented in the literature.
db - double-blind; rnd - randomized; pc – placebo-controlled; w - week, d - day; m - month; TRT - treatment; M - male; F - female; AO - Adult Onset; CO - Childhood Onset.
*Group A received Eutropin™ INJ for 6 consecutive months; ****Only results of non-weight based dosing shown.**
+No significant difference in LBM and FM between 6 and 12 months were observed.

6.3.5.2 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.

6.3.5.3 Efficacy Recommendations

- 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 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 [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 for the [redacted] section of the Valtropin Package Insert describing [redacted] was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential edits

b(4)

[redacted] 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.

7 INTEGRATED SUMMARY OF SAFETY

7.1 Indication Number 1 – Pediatric GHD

7.1.1. Methods and Findings

A thorough safety analysis of the clinical trial data from Study BP-EU-003 was performed. In addition, clinical trial data from Study BP-EU-003-RO (rollover) contained in the Safety Update submitted by the sponsor on 28Apr06 was reviewed. Given the vast experience with previously approved rhGH formulations over the last 20 years in children with GHD, **this review of safety is focused on the well known clinical and laboratory adverse events (AEs) associated with exposure to rhGH products in pediatric GHD patients** (which are clearly reflected in the Contraindications, Warnings, Precautions and Adverse Reactions sections of the Package Inserts of formulations of rhGH previously approved for the treatment of children with GHD).

7.1.1.1 Deaths

None.

7.1.1.2 Other Serious Adverse Events (SAEs)

Only 1 of the 7 SAEs reported in the Valtropin group was potentially related to the drug, i.e urticarial rash/pruritis following injection of the drug which resulted in study discontinuation. Neither of the 2 SAEs reported in the Humatrope arm was related to the drug. One patient developed acute lymphoblastic leukemia very soon after Humatrope therapy was initiated, and was immediately discontinued from the study.

7.1.1.3 Discontinuations

Two patients in the Valtropin group withdrew from the study due to AEs: 1) the patient described in Section 7.1.1.2 with a hypersensitivity reaction, and 2) another patient who was found to have a pituitary microadenoma (an exclusion criteria). One patient in the Humatrope group withdrew from the study because of the sudden emergence of acute lymphoblastic leukemia.

7.1.1.5 Non-Serious Adverse Events (AEs) (see Section 7.1.1.7.3 regarding Thyroid Dysfunction and Section 7.1.1.7.4 re Adrenal Dysfunction)

In a clinical study in which Valtropin (vs. an active somatropin control) was administered to GHD children for 12 months, the AEs that were seen most frequently (≥5.0% in either treatment group) are listed in Table 35. The incidence of all of these AEs were similar in the 2 treatment groups and reflect very common pediatric illnesses.

Table 35
Adverse Events Observed In Children With GHD Treated with Valtropin vs. an Active Somatropin Comparator for 12 Months

Adverse events (Incidence ≥5.0%)	Valtropin (n=98)	Comparator (n=49)
Headache	10 (10.2%)	8 (16.3%)
Pyrexia	9 (9.2%)	8 (16.3%)
Cough	5 (5.1%)	3 (6.1%)
Respiratory tract infection (NOS)*	5 (5.1%)	1 (2.0%)
Diarrhea	3 (3.1%)	4 (8.2%)
Vomiting	4 (4.1%)	4 (8.2%)
Pharyngitis	3 (3.1%)	4 (8.2%)

n = number of patients
* = not otherwise specified

7.1.1.7 Laboratory Findings

During Study BP-EU-003, mean values of standard laboratory parameters and electrocardiogram measurements did not change significantly, and there were no significant outliers.

7.1.1.7.1 Measures of Glucose Tolerance

7.1.1.7.1.1 Standard Analyses

Patients with preexisting diabetes mellitus were excluded. As summarized in Table 36, mean fasting blood glucose (FBG) and Hb_{A1c} values remained stable in children in both treatment arms throughout the study period. In addition, there were no significant differences between treatment groups at any time point.

Table 36 - BP-EU-003
Summary of Mean FBG and Hb_{A1c} Values Over Time

FBG (mg/dL) Hb_{A1c} (%)	Valtropin		Humatrope	
	FBG	Hb_{A1c}	FBG	Hb_{A1c}
Baseline	85.9 ± 13.6 (n=98)	5.3 ± 0.4 (n=95)	89.2 ± 12.9 (n=49)	5.3 ± 0.4 (n=49)
Month 6	89.1 ± 9.8 (n=96)	5.3 ± 0.3 (n=95)	90.7 ± 8.0 (n=46)	5.30 ± 0.3 (n=45)
Month 12	87.8 ± 11.6 (n=94)	5.4 ± 0.3 (n=93)	88.7 ± 8.3 (n=45)	5.29 ± 0.3 (n=46)

7.1.1.7.1.2 Analyses Focused on Shifts from Normal to Abnormal

The distribution of FBG values over time (see Table 37) demonstrates that ~80-90% of patients in both treatment groups maintained FBG levels below 100 mg/dL, and ~7-12% of patients in both treatment groups maintained FBG levels between 100 and 126 mg/dL. The number of patients in each treatment group with FBG values between 100 and 126 mg/dL did not change meaningfully over time.

Table 37 - BP-EU-003
Distribution of FBG Values Over Time by Patients (n[%])

	Valtropin (n=98)			Humatrope (n=49)		
FBG (mg/dL)	<100	100-126	>126	<100	100-126	>126
Baseline	88 (89.8)	9 (9.2)	1 (1.0)*	42 (85.7)	6 (12.2)	1 (2.0)**
Month 6^	86 (87.8)	10 (10.2)	0 (0.0)	40 (81.6)	6 (12.2)	0 (0.0)
Month 12#	87 (88.8)	7 (7.1)	0 (0.0)	41 (83.7)	4 (8.2)	0 (0.0)

*Patient #2079: FBG at screening was 91.8 mg/dL (vs. 127.8 mg/dL at baseline).
**Patient #2085 was discontinued from the study after ~1 month because of new onset acute lymphoblastic leukemia.
^Data missing for 2 patients in the Valtropin group and 3 patients in the Humatrope group.
#Data missing for 4 patients in the Valtropin group and 4 patients in the Humatrope group.

Table 38 demonstrates that treatment with Valtropin or Humatrope shifted FBG levels from "normal" (<100 mg/dL) at baseline to the "impaired fasting glucose" (IFG) range (100-126 mg/dL) in 5.7% and 7.1% of patients in the Valtropin and Humatrope groups, respectively, at Month 12. **Of note, no patients in either group shifted from normal at baseline to overt diabetes mellitus (>126 mg/dL) at Month 12.**

Table 38 - BP-EU-003
Shift Table for Patients with Normal FBG (<100 mg/dL) at Baseline (n[%])

	Valtropin (n=88)			Humatrope (n=42)		
FBG (mg/dL)	<100	100-126	>126	<100	100-126	>126
Baseline	88 (100)	-	-	42 (100)	-	-
Month 6	77 (87.5)	9 (10.2)	0 (0.0)	35 (83.3)	5 (11.9)	0 (0.0)
Month 12	79 (89.8)	**5 (5.7)**	0 (0.0)	36 (85.7)	**3 (7.1)**	0 (0.0)

Table 39 demonstrates that 7 out of the 9 patients in the Valtropin group, and 5 out of the 6 patients in the Humatrope group, with IFG at baseline had normal FBGs at Month 12, and **no patients in either group shifted from IFG at baseline to overt diabetes mellitus (>126 mg/dL) at Month 12.** Furthermore, the 1 patient in the Valtropin group with a FBG >126 mg/dL at baseline had normal FBGs at Months 6 and 12 (not shown in this table).

Table 39 - BP-EU-003
Shift Table for Patients with IFG (100-126 mg/dL) at Baseline (n[%])

	Valtropin			Humatrope		
FBS (mg/dl)	<100	100~126	>126	<100	100~126	>126
Baseline	-	9 (100.0)	-	-	6 (100.0)	-
Month 6	8 (88.9)	1 (11.1)	0 (0.0)	5 (83.3)	1 (16.7)	0 (0.0)
Month 12	7 (77.8)	2 (22.2)	0 (0.0)	5 (83.3)	1 (16.7)	0 (0.0)

Two patients in the Valtropin group (and 3 patients in the Humatrope group) **with normal FBG values at baseline had 2 or more consecutive FBG values between 100-126 mg/dL while on-study**, and 2 patients in the Valtropin group (and 2 patients in the Humatrope group) with IFG at baseline had 2 or more consecutive FBG values between 100-126 mg/dL while on-study.

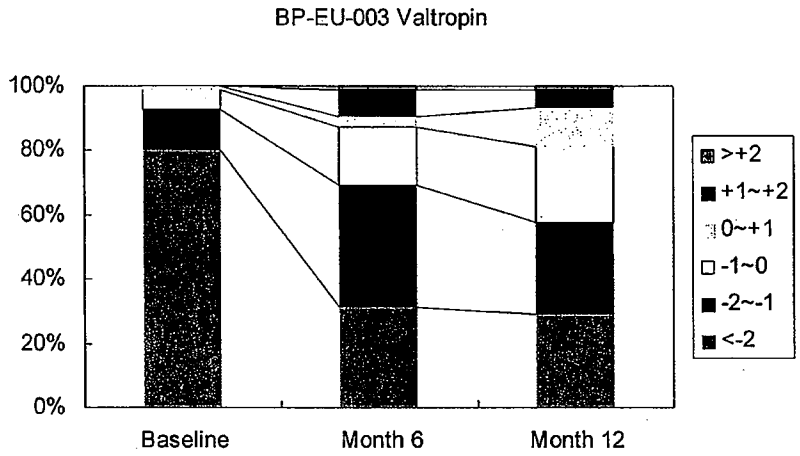
7.1.1.7.2 Serum IGF-1 and IGF-1 SDS responses

As the pattern observed was very similar between groups, this Medical Officer will focus his comments on the Valtropin group. See Tables 10 and 11 in Section 6.1.4.4.2.2.1 in the Integrated Summary of Efficacy for mean absolute values of serum IGF-1 and IGF-1 SDS before and after treatment. As seen in Table 40 and Figure 11, ~70% of children in the Valtropin arm had serum IGF-1 SDS <-2 at baseline (mean value = -3.21). After 12 months of Valtropin treatment, only 30% had serum IGF-1 levels <-2. Many had shifted into the 0 to -2 range, and 16 patients were now in the 0 to +2 range (at baseline there had been 1!). Only 1 patient had a serum IGF-1 SDS >+2 at Month 12. This is the expected pattern of response of GHD children after treatment with somatropin.

Table 40 – BP-EU-003
Distribution of Serum IGF-1 SDS Values by Percentage of Patients

Patients n (%)	Valtropin						Comparator					
IGF-1 SDS	<-2	-2~-1	-1~0	0~1	1~2	>2	<-2	-2~-1	-1~0	0~1	1~2	>2
Baseline	**70 (71.4)**	**11 (11.0)**	**5 (5.1)**	1 (1.0)			**32 (65.3)**	**11 (22.4)**	**3 (6.1)**			
Month 6	30 (30.6)	36 (36.7)	17 (17.3)	3 (3.0)	8 (8.2)	1 (1.0)	14 (28.6)	12 (24.5)	12 (24.5)	6 (12.2)	1 (2.0)	1 (2.0)
Month 12	**27 (27.6)**	26 (26.5)	**22 (22.4)**	**11 (11.2)**	**5 (5.1)**	**1 (1.0)**	10 (20.4)	12 (24.5)	**12 (24.5)**	**5 (10.2)**	**5 (10.2)**	**1 (2.0)**

Figure 11
Stacked Bar Graph Demonstrating the Distribution of the Serum IGF-1 SDS Response



7.1.1.7.3 Measures of Thyroid Function (including clinical AEs)

Out of 98 patients with pediatric GHD randomized to treatment with Valtropin in the pivotal study described above, 26 (26.5%) had preexisting central hypothyroidism. Even though the vast majority of pediatric GHD patients enrolled in Study BP-EU-003 were classified as "idiopathic" GHD, a literature review reveals that 10-30% of such patients have central hypothyroidism (and 5-10% have central hypoadrenalism) in association with GHD - especially if a particular triad of abnormalities are all present on MRI scan (pituitary hypoplasia, interrupted stalk and posterior pituitary ectopia) (12-13). Exacerbation of this 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.

7.1.1.7.4 Measures of Adrenal Function (including clinical AEs)

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.

7.1.1.10 Immunogenicity

During the clinical trial described above, low titer anti-rhGH antibodies were reported in 3 patients treated with Valtropin (vs. 1 patient treated with the comparator), and low titer anti-host cell protein antibodies were observed in 2 patients treated with Valtropin. These antibodies appeared after 6 months of treatment, disappeared after 12 months of treatment, and did not attenuate the growth response of these children.

7.1.1.17 Postmarketing Experience

Eutropin™ INJ differs from Valtropin only with regard to the somatropin dose contained in a dispensed vial (1.33 mg = 4 IU in the case of Eutropin™ INJ and 5 mg = 15 IU in the case of Valtropin). Following its approval in Korea in 1992 pediatric GHD, Eutropin™ INJ has been approved for pediatric GHD in 12 other countries in South America, the Middle East, Southwest Asia, and the Orient over the last 13 years.

Between 1992 and 2004, an estimated total of ——— vials of Eutropin™ INJ have been sold worldwide (the vast majority for the treatment of pediatric GHD). Although detailed postmarketing surveillance data are not available, the sponsor claims that a satisfactory safety profile has been demonstrated. Furthermore, multiple previously approved formulations of somatropin have been safely administered to many thousands of pediatric GHD patients for multiple years per individual, i.e. many thousands of patient-years of exposure. b(4)

7.1.2 Safety Results from Study BP-EU-003-RO - Part of **Safety Update**

Safety update was briefly reviewed. There were no new unexpected AEs potentially related to Valtropin. Four patients developed persistent anti-GH antibodies and 4 patients manifested anti-S. Cerevisiae antibodies on 2 consecutive visits. However, the growth patterns of all of these patients were not different than antibody-negative patients. Central hypothyroidism was reported in 3 patients. There were no *de novo* cases of diabetes mellitus. Occasional patients were noted to have serum IGF-1 SDS >+2. **The safety update profile for the rollover period looks very much the same as what was observed during the first 12 months of treatment.**

7.1.3 Safety Summary/Discussion, Conclusions and Recommendations

7.1.3.1 Safety Summary Discussion

- 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 were 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.

7.1.3.2 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.

7.1.3.3 Safety Recommendations

No further further safety data is necessary to obtain the pediatric GHD indication.

7.2 Indication Number 2 - Turner Syndrome

7.2.1. Methods and Findings

A thorough safety analysis of the clinical trial data from Study BP-EU-002 and the Korean TS study was performed. In addition, clinical trial data from Study BP-EU-002-RO (rollover) contained in the Safety Update submitted by the sponsor on 28Apr06 was reviewed. Given the extensive experience with previously approved rhGH formulations over the last 20 years in children with TS, **this review of safety is focused on the well known clinical and laboratory AEs associated with exposure to rhGH products in TS patients** (which are clearly reflected in the Contraindications, Warnings, Precautions and Adverse Reactions Sections of the Package Inserts of formulations of rhGH previously approved for the treatment of children with short stature associated with TS).

The 2 TS studies will be discussed together.

7.2.1.1 Deaths

None.

7.2.1.2 Other Serious Adverse Events (SAEs)

None.

7.2.1.3 Discontinuations

No patients were discontinued from either study because of an adverse reaction,

7.2.1.5 Non-Serious Adverse Events (AEs)

TS children with short stature were treated with 0.37 mg/kg/week of Valtropin (5 mg = 15 IU formulation) (n=30) and 0.33 mg/kg/week of Eutropin™ INJ (1.33 mg = 4 IU formulation qualitatively identical to Valtropin) (n=60) during Study BP-EU-002 and the Korean TS study, respectively. AEs were reported by 10 (33.3%) children during Study BP-EU-002. Most of these AEs reflect very common pediatric illnesses, mostly infectious in nature. The most frequently (≥1.0%) reported AEs were respiratory tract infections and **ear infections** (see Table 41). Turner syndrome patients are more prone to ear disorders and treatment with somatropin may increase the occurrence of these problems. During the Korean TS study, apparently, safety evaluations revealed no clinically relevant abnormalities that were considered to be related to Eutropin™ INJ treatment (the study report provided by the sponsor was rather abbreviated). Of interest, there were no reports in either study of benign intracranial hypertension, aggravation of preexisting scoliosis, slipped capital femoral epiphysis and hypertension. Somatropin-induced glucose intolerance will be discussed separately in the next paragraph. Immunogenicity will be discussed in Section 7.2.1.10.

Table 41 - Study BP-EU-002
Adverse Events Observed In Children
With Turner Syndrome Treated with Valtropin® for 12 Months

Adverse Events (Incidence ≥1.0%)	**Valtropin®** (n=30)	
	n	**%**
Anti-rhGH antibody positive	**1**	3.3
Anti-yeast antibody positive	**1**	3.3
Ear infection (NOS)*	**2**	6.7
Otitis media (NOS)*	**1**	3.3
Respiratory tract infection (NOS)*	**4**	**13.3**
Respiratory tract infection viral (NOS)*	1	3.3
Rhinitis NOS*	1	3.3
Sinusitis NOS*	1	3.3
Influenza	1	3.3
Injection site pain	1	3.3
Edema peripheral	**1**	**3.3**
Pyrexia	1	3,3

n = number of patients
*NOS = not otherwise specified

7.2.1.7 Laboratory Findings

During Study BP-EU-002 and the Korean TS study, mean values of standard laboratory parameters, electrocardiograms (Study BP-EU-002), chest Xrays (Korean TS study) did not change significantly, and there were no significant outliers.

7.2.1.7.1 Measures of Glucose Tolerance

7.2.1.7.1.1 Study BP-EU-002

7.2.1.7.1.1.1 Standard Analyses

Patients with preexisting diabetes mellitus were excluded.

As summarized in Table 42, **mean FBG increased ~5 mg/dL from baseline to Month 12, but remained within the normal range.** Mean Hb_{A1c} levels increased very slightly in TS children during the study period.

Table 42 - BP-EU-002
Summary of Mean FBG and Hb_{A1c} Values Over Time

FBG (mg/dL) Hb_{A1c} (%)	Valtropin	
	FBS	Hb_{A1c}
Baseline	88.4 ± 9.7 (n=30)	5.1 ± 0.4 (n=30)
Month 6	92.2 ± 10.6 (n=30)	5.2 ± 0.3 (n=30)
Month 12	93.8 ± 9.5 (n=29)	5.3 ± 0.3 (n=29)

7.2.1.7.1.1.2 Analyses Focused on Shifts from Normal to Abnormal

As per the exclusion criteria for Study BP-EU-002, there were no patients with FBGs compatible with overt diabetes mellitus at baseline. The distribution of FBG values over time (Table 43) demonstrates that 70% of patients (n=21) had normal FBG levels after 12 months of treatment with Valtropin compared with 83.3% (n=25) at baseline, **while the number of patients with IFG increased from 16.7% (n=5) at baseline to 26.7% (n=8) at Month 12.**

Table 43 - BP-EU-002
Distribution of FBG Values Over Time by Patients (n[%])

	Valtropin (n=30)		
FBG (mg/dL)	<100	100-126	>126
Baseline	25 (83.3)	5 (16.7)	0 (0.0)
Month 6	25 (83.3)	5 (16.7)	0 (0.0)
Month 12*	21 (70.0)	8 (26.7)	0 (0.0)

*Data missing for 1 patient.

Table 44 demonstrates that **treatment with Valtropin shifted FBG levels from normal at baseline to the IFG range in 5 patients (20%) at Month 12. Of note, no patients shifted from normal at baseline to overt diabetes mellitus (>126 mg/dL) at Month 12.**

Table 44 - BP-EU-002
Shift Table for Patients
with Normal FBG (<100 mg/dL) at Baseline (n[%])

	Valtropin (n=25)		
FBG (mg/dl)	<100	100-126	>126
Baseline	25 (100.0)		
Month 6	24 (96.0)	1 (4.0)	0 (0.0)
Month 12	19 (76.0)	5 (20.0)	0 (0.0)

Table 45 demonstrates that 2 out of the 5 patients with IFG at baseline had normal FBGs at Month 12, while 3 out of the 5 patients with IFG at baseline continued to have FBGs in the IFG range at Month 12. **No patients shifted from IFG at baseline to overt diabetes mellitus (>126 mg/dL) at Month 12.**

Table 45 - BP-EU-002
Shift Table for Patients
with IFG (100-126 mg/dL) at Baseline (n[%])

	Valtropin (n=5)		
FBG (mg/dl)	<100	100~126	>126
Baseline		5 (100)	
Month 6	1 (20.0)	4 (80.0)	0 (0.0)
Month 12	2 (40.0)	3 (60.0)	0 (0.0)

After 3 months of treatment with Valtropin 0.053 mg/kg/day, FBG was 149.4 mg/dL (**increased from a baseline value of 82.8 mg/dL**) in Patient #25 (age 3.5 yrs). At Month 6, FBG had returned to normal (91.8 mg/dL), but the patient's guardians withdrew consent for unknown reasons, and she was discontinued from the study.

One patient with a normal FBG at baseline had 2 or more consecutive FBGs between 100-126 mg/dL while on-study, and 4 patients with IFG at baseline had 2 or more consecutive FBGs between 100-126 mg/dL while on-study.

7.2.1.7.1.2 Korean TS Study

7.2.1.7.1.2.1 Standard Analyses

Patients with preexisting "endocrine disease" were excluded (presumably including diabetes mellitus).

As summarized in Tables 46, **mean FBG increased ~5 mg/dL from baseline to Month 12, but remained within the normal range.** Hb_{A1c} levels were not measured.

Table 46 – Korean TS Study
Summary of Mean FBG Values and
Changes from Baseline Over Time

FBG mg/dL	FBG	Changes from Baseline
Baseline	92.0 ± 16.3 (n=57)	-
Month 6	100.6 ± 15.4 (n=57)	+ 8.7 ± 21.2 (n=54)
Month 12	97.0 ± 16.9 (n=51)	+ 3.9 ± 23.3 (n=49)

7.2.1.7.1.2.2 Analyses Focused on Shifts from Normal to Abnormal

As per the exclusion criteria for the Korean TS Study, there were no patients with FBGs compatible with overt diabetes mellitus at baseline. The distribution of FBG values over time (Table 47) demonstrates that **46.6% of patients (n=28) had normal FBG levels after 12 months of treatment with Eutropin™ INJ compared with 68.3% (n=41) at baseline, while the number of patients with IFG increased from 26.7% (n=16) at baseline to 33.3% (n=20) at Month 12.**

Of note, 3 patients had FBG values >126 mg/dL at Month 12 (compared with none at baseline). These patients will be discussed at the end of this section.

Table 47 – Korean TS Study
Distribution of FBG Values Over Time by Patients (n[%])

	Eutropin™ INJ (n=60)		
FBG (mg/dl)	<100	100-126	>126
Baseline*	41 (68.3)	16 (26.7)	0 (0.0)
Month 6*	31 (51.7)	21 (35.0)	5 (8.3)
Month 12**	28 (46.6)	20 (33.3)	3 (5.0)

*Data missing for 3 patients at Baseline and Month 6.
**Data missing for 9 patients at Month 12.

Table 48 demonstrates that treatment with Eutropin™ INJ shifted FBG levels from normal at baseline to the IFG range in 16 patients (39%) at Month 12. Of note, 2 patients shifted from normal at baseline to FBG >126 mg/dL at Month 12 (see end of this section for comment).

Table 48 - Korean TS Study
Shift Table for Patients with
Normal FBG (<100 mg/dL) at Baseline (n[%])

	EutropinTM INJ (n=41)		
FBG (mg/dL)	<100	100-126	>126
Baseline	41 (100.0)	-	-
Month 6*	21 (51.2)	14 (34.1)	3 (7.3)
Month 12**	17 (41.5)	**16 (39.0)**	**2 (4.9)**

*Data missing for 3 patients at Month 6.
**Data missing for 6 patients at Month 12.

Table 49 demonstrates that 10 out of the 16 patients with IFG at baseline had normal FBG values at Month 12, while 3 out of the 16 patients with IFG at baseline continued to have FBG values in the IFG range at Month 12. **Of note, 1 patient shifted from IFG at baseline to >126 mg/dL at Month 12 (see end of this section for comment).**

Table 49 - Korean TS Study
Shift Table for Patients with
IFG (100-126 mg/dL) at Baseline (n[%])

	EutropinTM INJ (n=16)		
FBS (mg/dl)	<100	100~126	>126
Baseline	-	16 (100)	-
Month 6	7 (43.8)	7 (43.8)	2 (12.5)
Month 12	10 (62.5)	3 (18.8)	**1 (6.3)**

As noted earlier in this section, 3 patients (rows 1 through 3 in Table 50 below) had FBG values >126 mg/dL at Month 12 (compared with none at baseline), 2 of whom also had FBG values >126 mg/dL at other post-treatment time points. Two of these 3 patients began the study with normal FBG values (Patients #B4 and #Y7 in rows 1 and 2 of Table 50 below), and 1 of these 3 patients began the study with IFG (Patient #S11 in row 3 of Table 50 below). The sponsor could not provide detailed narratives or blood glucose values subsequent to drug discontinuation/study termination. It is therefore possible that these patients developed new onset diabetes mellitus after treatment with Eutropin™ INJ.

In addition, as seen in Table 50 below, there were a) **3 patients** (rows 4 through 6) **whose baseline FBG values were normal, and who had 1 post-treatment FBG value >126 mg/dL, as well as FBG values between 100-126 mg/dL at other post-treatment time points including Month 12**; b) **2 patients** (rows 7 and 8) **whose baseline FBG values were normal, and who had 1 FBG value >126 mg/dL, as well as 1 FBG value between 100-126 mg/dL at another post-treatment time point but not at Month 12**; and c) **2 patients who had IFG at baseline and 1 post-treatment FBG value >126 mg/dL** but not at Month 12.

Table 50 - Korean TS Study
Table Showing Serial FBG Values for Patients
Who Had At Least 1 FBG Value >126 mg/dL While On-Study

Site	ID	Baseline	3 months	6 months	9 months	12 months
B	**4**	**90**	**134**	**128**	**123**	**130**
Y	**7**	**84**	**89**	**106**	**99**	**145**
S	**11**	**121**	**92**	**142**	**134**	**134**
Y	20	88	118	137	116	N/A.
Y	14	85	134	92	112	124
S	1	69	91	87	131	109
S	3	74	86	142	120	94
Y	13	59	85	102	137	80
C	9	115	98	113	130	91
S	5	105	89	136	93	92

As seen in Table 51 below, there were a) **8 patients** (rows 1 through 8) **with a normal FBG value at baseline who had 2 or more consecutive post-treatment FBG values between 100-126 mg/dL while on-study, including Month 12**; b) **2 patients** (rows 9 and 10) **with a normal FBG value at baseline who had 2 or more consecutive post-treatment FBG values between 100-126 mg/dL while on-study, not including Month 12**; c) 3 patients (rows 11 through 13) with IFG at baseline who had 2 or more consecutive post-treatment FBG values between 100-126 mg/dL while on-study, including Month 12; and d) 4 patients (rows 14 through 17) with IFG at baseline who had 2 or more consecutive post-treatment FBG values between 100-126 mg/dL while on-study, not including Month 12

Table 51 - Korean TS Study
Table Showing Serial FBG Values for Patients Who Had 2 or More Consecutive FBG Values Between 100-126 mg/dL While On-Study

Site	ID	Baseline	3 months	6 months	9 months	12 months
B	1	87	111	101	112	101
Y	11	55	120	117	121	101
C	6	88	93	103	110	105
C	8	89	99	94	107	108
Y	15	92	100	94	103	117
Y	18	92	98	92	103	101
Y	10	95	107	103	90	102
S	8	94	122	102	93	103
Y	19	97	100	106	94	90
B	6	79	122	100	89	100
B	8	101	110	106	113	102
S	6	111	124	94	108	111
C	2	113	106	117	124	N/A
C	5	114	98	116	112	84
S	10	104	96	103	116	72
S	16	107	107	117	107	76
C	10	103	116	97	101	N/A

7.2.1.7.1.2.3 Commentary About Glucose Tolerance in the 2 TS Studies

It is therefore clear that the Korean TS Study was associated with a much greater amount of apparent somatropin-induced glucose intolerance than Study BP-EU-002.

During Study BP-EU-002, a modest degree of glucose intolerance was observed in the 30 patients treated with Eutropin™ INJ for 12 months. No *de novo* cases of overt diabetes mellitus were diagnosed. On the other hand, during the Korean TS study, a much greater amount of glucose intolerance was observed: a) 3 patients (with normal FBG values at baseline [<100 mg/dL]) had FBG values between 130 and 145 mg/dL at Month 12 as well as other study time points and (absent follow-up data after study termination) may have

developed somatropin-induced *de novo* diabetes mellitus; and b) 16 out of 41 patients (with normal fasting blood glucose values) at baseline had fasting blood glucose values between 100-126 mg/dL at Month 12 (and 3 of these 16 patients had fasting blood sugars >126 mg/dL transiently during the study). Since the amount of somatropin administered in the Korean TS study (0.34 mg/kg/week) was slightly less than the amount administered in Study BP-EU-002 (0.37 mg/kg/week), these findings are difficult to interpret. It may be that some of this "glucose intolerance" is related to the fact that these children were not necessarily fasting when blood sugars were obtained during the study (see Section 6.2.3.2.4 in the Integrated Summary of Efficacy). However, one must also note what was recently class labeled in the General subsection of the Precautions section of the Package Inserts of all rhGH formulations regarding the well known potential of somatropin drug products to cause glucose intolerance, especially in patients at greater inherent risk for diabetes mellitus, i.e. patients with Turner syndrome.

7.2.1.7.2 Serum IGF-1 and IGF-1 SDS responses

Study BP-EU-002 and the Korean TS Study will be discussed together.

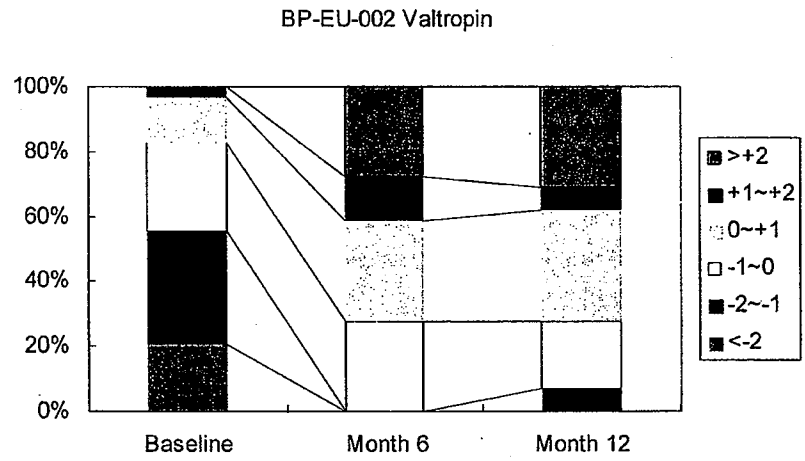
See Tables 17 and 18 (Study BP-EU-002) and Table 19 (the Korean TS study) in Section 6.2.4.4.2 of the Integrated Summary of Efficacy for the mean values of serum IGF-1 and IGF-1 SDS at baseline, Month 6 and Month 12. Table 52 and Figure 12 below describe the distribution of response for serum IGF-1 SDS values at Month 6 and Month 12 in Study BP-EU-002. At baseline, **curiously**, most patients had lowish to clearly low serum IGF-1 SDS between 0 and -2 (mean = -1.16). Nonetheless, it is clear that the number of patients with serum IGF-1 SDS values >+2 went from 0 to 8 (27.6%) and 9 (31%) at Month 6 and Month 12, respectively. As noted earlier, serum IGF-1 SDS could not be calculated for the Korean TS study. However, the Month 12 values presented in Table 19 of Section 6.2.4.4.2 of the Integrated Summary of Efficacy were substantially increased from baseline (mean = 423!!), and tend to substantiate the observations during Study BP-EU-002.

Compared with the serum IGF-1 and IGF-1 SDS responses in GHD children (see Sections 6.1.4.4.2.2.1 and 7.1.1.7.2), the IGF-1 responses observed during Study BP-EU-002 and the Korean TS study were much more robust. These observations are not surprising given that the amount of Valtropin (0.053 mg/kg/day; BP-EU-002) and Eutropin™ INJ (0.048 mg/kg/day; Korean TS study) administered to TS patients during the TS studies was ~1.5X the amount of Valtropin (0.033 mg/kg/day) administered to GHD children in Study BP-EU-003. **However, the fact that 31% of TS patients in Study BP-EU-003 manifested a serum IGF-1 SDS >+2 at Month 12 (i.e., greater than the theoretically desirable upper threshold of response) is a bit concerning. The long-term consequences/significance of serum IGF-1 SDS >+2 during an extended period of rhGH treatment are unknown.**

Table 52 - BP-EU-002
Distribution of Serum IGF-1 SDS Values
by Percentage of Patients

Patient n (%)	Valtropin					
IGF-1 SDS	<-2	-2~-1	-1~0	0~1	1~2	> 2
Baseline	6 (20.7)	10 (34.5)	8 (27.6)	4 (13.8)	1 (3.4)	
Month 6			8 (27.6)	9 (31.0)	4 (13.8)	8 (27.6)
Month 12		2 (6.9)	6 (20.7)	10 (34.5)	2 (6.9)	9 (31.0)

Figure 12 - Study BP-EU-002
Stacked Bar Graph Demonstrating the
Distribution of the Serum IGF-1 SDS Response



7.2.1.10 Immunogenicity

In Study BP-EU-002, 1 patient developed low titer antibodies to rhGH, and 1 other patient developed low titer anti-yeast antibodies at Month 6; these titers had disappeared at Month 12. These antibodies did not attenuate the growth response of these 2 children. During the Korean TS study, 2 patients developed low titer antibodies to rhGH at Month 12, and 4 patients developed transient antibodies to S. Cerevisiae..

7.2.1.17 Postmarketing Experience

Eutropin™ INJ differs from Valtropin only with regard to the somatropin dose contained in a dispensed vial (1.33 mg = 4 IU in the case of Eutropin™ INJ and 5 mg = 15 IU in the case of Valtropin). As discussed in detail in Sections xxx and xxx earlier, following its approval in Korea in 1998 for TS children with short stature, Eutropin™ INJ has been approved for use in 9 other countries in South America, the Middle East, Southwest Asia, and the Orient over the last 8 years for TS children.

Between 1992 and 2004, an estimated total of ——— ials of Eutropin™ INJ have been sold worldwide (the vast majority for the treatment of pediatric GHD, but a substantial minority for the treatment of TS children). Although detailed postmarketing surveillance data are not available, the sponsor claims that a satisfactory safety profile has been demonstrated. Furthermore, multiple previously approved formulations of somatropin have been safely administered to substantial numbers of TS children for multiple years per individual, i.e. many patient-years of exposure.

b(4)

7.2.2 Safety Results from Study BP-EU-003-RO - Part of **Safety Update**

Safety update was reviewed briefly. There is very little to report. On patient developed what was thought to be somatropin-related edema, 1 patient had an injection site reaction and several patients manifested transient antibodies to GH (n=1) and S. Cerevisiae (n=4).transient antibodies. There were no reports of diabetes mellitus or other untoward adverse reactions.

7.2.3 Safety Summary/Discussion, Conclusions and Recommendations

7.2.3.1 Safety Summary/Discussion/Conclusions

- 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 in Korea, so I guess we will never know). TS patients are predisposed to type 2 diabetes mellitus (20-21) and somatropin certainly can unmask latent diabetes mellitus (95-96). 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 the 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. This is certainly not an issue unique to Valtropin.**

7.3 Indication Number 3 – Adult GHD

7.3.1. Methods and Findings

A thorough safety analysis of the clinical trial data from Study HGCL-001 was performed. The patients who completed this clinical trial were **not** "rolled over" into an open-label extension study. Given the extensive experience with previously approved rhGH formulations over the last 10 years in adults with GHD, **this review of safety is focused on the well known clinical and laboratory AEs associated with exposure to rhGH products in adult GHD patients** (which are clearly reflected in the Contraindications, Warnings, Precautions and Adverse Reactions Sections of the Package Inserts of formulations of rhGH previously approved for the treatment of adults with GHD).

7.3.1.1 Deaths

None.

7.3.1.2 Other Serious Adverse Events (SAEs)

There were 3 SAEs unrelated to Eutropin™ INJ administration – 1 patient with a cerebrovascular accident, 1 patient who for some reason discontinued his glucocorticoid and thyroid replacement therapies thereby incurring a hypopituitary crisis – for which he was hospitalized and recovered and continued with the trial, and 1 patient with preexisting diabetes mellitus who had a **hyperglycemic decompensation about 1 ½ months after being started on placebo** in Group C.

7.3.1.3 Discontinuations

The 2 patients described in Section 7.3.1.2 with 1) cerebrovascular accident and 2) diabetic decompensation were discontinued prematurely from the study.

7.3.1.5 Non-Serious Adverse Events (AEs)

Adult GHD patients were treated with Eutropin™ INJ (1.33 mg = 4 IU formulation; qualitatively identical to Valtropin, a 5 mg = 15 IU formulation) vs. placebo during the pivotal clinical study. Ninety two patients received at least 3 months of treatment with Eutropin™ INJ (31 of these patients were treated with Eutropin™ INJ for an additional 3 months), and 61 patients received 3 months of treatment with placebo. AEs with an incidence of ≥5.0% are presented in Table 53. The most frequent AE during treatment with **Eutropin™ INJ** was edema which was reported more frequently than during placebo treatment. **In some of these patients, edema resulted in down-titration of the dose of Eutropin™ INJ as per protocol.** Myalgia was reported by 2 patients receiving Eutropin™ INJ and 2 patients treated with placebo. **Arthralgia was reported by 2 patients receiving Eutropin™ INJ.** There were no reports of carpal tunnel syndrome. These types of AEs are thought to be related to the fluid accumulating effects of somatropin. Most adverse events reported during the study were mild in severity.

Table 53
Adverse Events Observed In Adults With GHD Treated With Eutropin™ INJ vs. Placebo for 3 Months

Adverse events (Incidence ≥5.0%) n = number of patients	Eutropin™ INJ (n=92 for 3 months & n=31 for an additional 6 months)		Placebo (n=61 for 3 months)	
	n	%	n	%
Edema	**11**	**12.0**	**5**	**8.2**
Myalgia	**2**	**2.2**	**2**	**3.3**
Back pain	**4**	**4.3**	**0**	**0**
Headache	**3**	**3.3**	**2**	**3.3**
Upper respiratory tract infection	6	6.5	1	1.6
Urticaria	3	3.3	4	6.6

7.3.1.7 Laboratory Findings

During Study HGCL-001, mean values of standard laboratory parameters did not change significantly, and there were no significant outliers.

7.3.1.7.1 Measures of Glucose Tolerance

7.3.1.7.1.1 Standard Analyses

The protocol allowed inclusion of diabetics as long as they did not have proliferative or progressive retinopathy (and, in fact, 8 patients with diabetes mellitus were included).

In spite of the inclusion of 8 subjects with preexisting diabetes mellitus, mean FBG and Hb_{A1c} levels were normal at all timepoints for all groups. Only data for Group A, the group that received Eutropin™ INJ continuously for 6 months, are shown in Table 54.

Table 54 – HGCL-001
Summary of Mean FBG and Hb_{A1c} Values Over Time

FBG (mg/dL) Hb_{A1c} (%)	Group A - Eutropin™ INJ x 6 Months	
	FBG	Hb_{A1c}
Baseline	91.8 ± 15.1 (n=31)	5.6 ± 0.6 (n=31)
Month 3	94.3 ± 16.0 (n=31)	5.9 ± 0.9 (n=31)
Month 6	87.2 ± 12.0 (n=30)	5.8 ± 0.6 (n=30)

7.3.1.7.1.2 Analyses Focused on Shifts from Normal to Abnormal

Table 55 demonstrates distribution of FBGs at different timepoints. The 3 patients (2 in Group B and 1 in Group C) with FBG >126 mg/dL at baseline were amongst the 8 included diabetics; 5 of the included diabetics had normal FBG levels at baseline. In addition, the 1 patient in Group A with FBG >126 mg/dL at Month 6 was also one of the included diabetics. Also of note is the fact that 8 of the 10 patients in the IFG range at baseline in Group A finished the study with normal FBG levels. Lastly, the **2 patients in Group C with FBG >126 mg/dL at Month 6 (who had just completed a 3 month course of Eutropin™ INJ) may be cases of somatropin-induced *de novo* diabetes mellitus - no followup blood glucose values after study termination was provided.**

Table 55 - HGCL-001
Distribution of FBG Values Over Time by Patients (n[%])

	*A (rhGH>rhGH) (n=31)			*B (rhGH>placebo) (n=28)			*C (placebo>rhGH) (n=33)		
FBG (mg/dl)	<100	100-126	>126	<100	100-126	>126	<100	100-126	>126
Baseline	**21 (67.7)**	**10 (32.3)**	0 (0.0)	23 (82.1)	3 (10.7)	2 (7.1)	26 (78.8)	6 (18.2)	1 (3.0)
Month 3	**21 (67.7)**	**8 (25.8)**	2 (6.5)	22 (78.6)	4 (14.3)	1 (3.6)	25 (75.8)	5 (15.2)	1 (3.0)
Month 6	**27 (87.1)**	**2 (6.5)**	1 (3.2)	21 (75.0)	6 (21.4)	0 (0.0)	21 (63.6)	7 (21.2)	**2 (6.1)**

*Note: Group A (rhGH for 6 consecutive months); Group B (rhGH for 3 months crossed over to placebo for 3 months); Group C (placebo for 3 months crossed over to rhGH for 3 months)

Table 56 demonstrates some very strange findings in Group B where 18 out of 23 patients with normal FBG at baseline had FBGs in the IFG range after 3 months of treatment with Eutropin™ INJ which persisted at Month 6 even after receiving placebo for 3 months. Group A stands in contrast to Group B. In spite of continuous Eutropin™ INJ treatment for 6 months, all 21 began the study with normal FBGs and all 21 ended the study with normal FBG levels.

On the other hand, 2 out of 26 patients in Group C with normal FBG at baseline had FBG >126 mg/dL after 3 months of treatment with Eutropin™ INJ during Period 2 , and 4 out of 26 had FBG in the IFG range at Month 6.

Table 56 - HGCL-001
Shift Table for Patients with Normal FBG (<100 mg/dL) at Baseline (n[%])

	*A (rhGH>rhGH) (n=21)			*B (rhGH>placebo) (n=23)			*C (placebo>rhGH) (n=26)		
FBS (mg/dl)	<100	100-126	>126	<100	100-126	>126	<100	100-126	>126
Baseline	21 (100.0)	-	-	23 (100.0)	-	-	26 (100.0)	-	-
Month 3	18 (85.7)	3 (14.3)	0 (0.0)	4 (17.4)	**19 (82.6)**	0 (0.0)	24 (92.3)	2 (7.7)	0 (0.0)
Month 6	21 (100.0)	0 (0.0)	0 (0.0)	4 (17.4)	**18 (78.3)**	0 (0.0)	19 (73.1)	**4 (15.4)**	**2 (7.7)**

*Note: Group A (rhGH for 6 consecutive months); Group B (rhGH for 3 months crossed over to placebo 3 months); Group C (placebo for 3 months crossed over to rhGH for 3 months)

Table 7 demonstrates that most patients who began the study with FBG in the IFG range had normal FBG levels at Month 6.

Table 57 – HGCL-001
Shift Table for Patients with IFG (100-126 mg/dL) at Baseline (n[%])

	*A (rhGH>rhGH) (n=10)			*B (rhGH>placebo) (n=3)			*C (placebo>rhGH) (n=6)		
FBS (mg/dl)	<100	100-126	>126	<100	100-126	>126	<100	100-126	>126
Baseline	-	10 (100.0)	-	-	3 (100.0)	-	-	6 (100.0)	-
Month 3	4 (40.0)	4 (40.0)	2 (20.0)	3 (100.0)	0 (0.0)	0 (0.0)	1 (16.7)	3 (50.0)	0 (0.0)
Month 6	6 (60.0)	2 (20.0)	1 (10.0)	2 (66.7)	1 (33.3)	0 (0.0)	2 (33.3)	2 (33.3)	0 (0.0)

*Note: Group A (rhGH for 6 consecutive months); Group B (rhGH for 3 months crossed over to placebo 3 months); Group C (placebo for 3 months crossed over to rhGH for 3 months)

With regard to the 8 patients with preexisting diabetes mellitus: 3 were taking oral agents, 3 were on no medications, and 2 were diagnosed at study entry with elevated FBG; 3 of the 8 had FBG >126 mg/dL at baseline (2 in Group B and 1 in Group C) but 5 did not including 2 receiving oral agent combination therapy; one in Group A had a FBG >126 mg/dL at Month 12. In general, the diabetics did well on-study with no post-rhGH treatment FBG >164 mg/dL - except for the 1 patient in Group C receiving placebo for 1 ½ months who was then admitted with hyperglycemic crisis and discontinued.

Two patients (without known preexisting diabetes mellitus) in Group C who had FBG >126 mg/dL at Month 6 (after completing a 3 month course of Eutropin™ INJ) may be cases of somatropin-induced *de novo* diabetes mellitus – no followup blood glucose values after drug discontinuation/study termination were obtainable by the sponsor.

7.3.1.7.2 Serum IGF-1 and IGF-1 SDS responses

Please see Table 34 in Section 6.3.4.4.1.2.3 in the Integrated Summary of Efficacy for a tabular depiction of the significant increases in serum IGF-1 levels after 3 months of treatment with Eutropin™ INJ. The assay-derived means and SDs of the serum IGF-1 values referenced for age and gender were not available for the kit used to measure serum IGF-1 levels in Study HGCL-001 (i.e., only the age- and gender-referenced normal ranges were available). Therefore, the sponsor could not calculate serum IGF-1 SDS values. However, it is clear that mean levels of serum IGF-1 were lowish at baseline and at the high end of normal (>300 ng/mL) after 3 months of treatment with Eutropin™ INJ (referring to the normal reference range for men and women aged 45-55 - the approximate mean age of the adult GHD patients enrolled in the study). In Group A, the high normal mean serum IGF-1 level observed at Month 3 was more or less the same as the mean value observed at Month 6, i.e. it did not increase further. Although, as stated above, serum IGF-1 SDS could not be calculated for this study, it would appear that a significant number of patients had post-treatment serum IGF-1 SDS >+2. **In that it is generally recommended to avoid sustained serum IGF-1 SDS >+2 because of the theoretical but unproven long-term risk of oncogenic adverse effects, this finding is a bit disturbing.**

7.3.1.7.3 Measures of Thyroid Function (including clinical AEs)

Seventy five out of the 92 adult GHD patients in the pivotal study (~81%) had preexisting central hypothyroidism and most of them were being treated with thyroxine replacement therapy, usually in conjunction with panhypopituitarism. None of these patients manifested clinical signs/symptoms of exacerbated central hypothyroidism (serial thyroid function tests were not obtained per protocol) during treatment with Eutropin™ INJ, i.e. there were no changes in maintenance thyroxine dose nor adverse events related to the thyroid during Eutropin™ INJ therapy. Furthermore, none of the remaining 17 patients enrolled in this study manifested clinical evidence of *de novo* central hypothyroidism.

7.3.1.7.4 Measures of Adrenal Function (including clinical AEs)

Seventy five out of the 92 adult GHD patients in the pivotal study (~81%) also had preexisting central hypoadrenalism and most of them were being treated with glucocorticoid replacement therapy. None of these patients demonstrated convincing clinical evidence of an exacerbation of preexisting central hypoadrenalism; 2 patients required an increase in hydrocortisone replacement dosages while they were taking placebo approximately 2 months removed from treatment with Eutropin™ INJ. Furthermore, none of the remaining 17 patients enrolled in this study manifested clinical evidence of *de novo* central hypoadrenalism.

7.3.1.10 Immunogenicity

Not performed.

7.3.1.17 Postmarketing Experience

Eutropin™ INJ differs from Valtropin only with regard to the somatropin dose contained in a dispensed vial (1.33 mg = 4 IU in the case of Eutropin™ INJ and 5 mg = 15 IU in the case of Valtropin). Following its approval in Korea in 2004 for patients with adult GHD, Eutropin™ INJ has been approved for use in 2 other countries for adult GHD (Egypt and Indonesia).

Between 1992 and 2004, an estimated total of ——— vials of Eutropin™ INJ have been sold worldwide (the vast majority for the treatment of pediatric GHD and short stature associated with TS, and, obviously, a much smaller amount for the treatment of adult GHD). Although detailed postmarketing surveillance data are not available, the sponsor claims that a satisfactory safety profile has been demonstrated. Furthermore, multiple previously approved formulations of somatropin have been safely administered to substantial numbers of adult GHD patients for multiple years per individual, i.e. many patient-years of exposure. b(4)

7.3.2 Safety Summary/Discussion, Conclusions and Recommendations

7.3.2.1 Safety Summary/Discussion

- 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.

9 LABELING REVIEW - PACKAGE INSERT (PI)

The **Clinical Pharmacology section** (except for the **Pharmacokinetics** and **Special Populations** subsections - containing edits by the Division's Biopharmaceutical Reviewers and incorporated in this review), [redacted], **Indications And Usage section***, **Contraindications section***, **Warnings section***, **Precautions section*** (except for the **Carcinogenesis, Mutagenesis and Fertility**, and **Pregnancy** subsections - containing edits by the Division's Toxicology Reviewers and incorporated in this review)*, **Adverse Reactions section***, **Overdosage section**, **Dosage*** subsection of the **Dosage And Administration section**, and the **Administration** subsection of the **Dosage And Administration/Stability And Storage/How Supplied sections** (primarily edited by the Division's CMC Reviewers with input from this Medical Officer and DMETS) **of the proposed Valtropin® PI were very carefully reviewed and edited by this Medical Officer (* = essentially rewritten). <u>These edits/rewrites were submitted to the sponsor who agreed completely with all of the changes proposed by this Medical Officer</u>. The <u>untracked</u> version of the language mutually agreed to follows below.**

b(4)

Note: Edits by the Division's CMC Reviewers in the **Description**^ section of the proposed Valtropin® PI were provided to the sponsor by the Division's Project Manager and are not incorporated in this review (^ = incorporating edits by the Division's CMC Reviewers).

CLINICAL PHARMACOLOGY

General

In vitro, preclinical and clinical testing have demonstrated that somatropin is therapeutically equivalent to pituitary-derived human growth hormone (pit-hGH). Clinical studies in normal adults also demonstrated equivalent pharmacokinetics.

a. Tissue Growth

The primary and most intensively studied action of somatropin is the stimulation of linear growth. This effect is demonstrated in children with somatropin deficiency.

1. Skeletal growth – the measurable increase in bone length after administration of somatropin results from its effect on the cartilaginous growth areas of long bones. Studies *in vitro* have shown that the incorporation of sulfate into proteoglycans is not due to a direct effect of somatropin, but rather is mediated by the somatomedins or insulin-like growth factors (IGF). The somatomedins, among them IGF-1, are polypeptide hormones which are synthesized in the liver, kidney, and various other tissues. IGF-1 levels are low in the serum of growth hormone deficient children with short stature and hypophysectomized humans or animals, but its presence can be demonstrated after treatment with somatropin.

25 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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