Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Somatropin

Proprietary Product Name: Humatrope

Sponsor: Eli Lilly Australia Pty Ltd

January 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	22 June 2012
Active ingredient:	Somatropin
Product Name:	Humatrope
Sponsor's Name and Address:	Eli Lilly Australia Pty Ltd
Dose form	Powder for injection
Strengths:	6 mg (18 IU), 12 mg (36 IU) and 24 mg (72 IU)
Containers:	Cartridge (containing powder) and syringe (containing diluent)
Pack sizes:	One
Approved Therapeutic use:	*Humatrope is also indicated for the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years. [See Clinical Trials].*
Route(s) of administration:	SC injection
Dosage:	The [abridged] recommended dosage is 0.033 to 0.067 mg/kg body weight per day (see approved Product Information for full dosage recommendations).
ARTG Numbers:	53364, 53365, 52423

Product background

Somatropin is a polypeptide hormone of recombinant deoxyribonucleic acid (rDNA) origin. It has 191 amino acid residues and a molecular weight of about 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (GH) of pituitary origin. Somatropin is synthesised in a strain of *Escherichia coli* that has been modified by the addition of the gene for human GH. The biological effects of somatropin are equivalent to human GH of pituitary origin.

Humatrope is a sterile, white, lyophilised powder intended for subcutaneous (SC) or intramuscular (IM) administration after reconstitution. It is currently indicated for growth disturbance due to GH deficiency, including in Prader-Willi syndrome, chronic renal insufficiency and Turner Syndrome.

This AusPAR describes the application by Eli Lilly (the sponsor) to extend the indications for Humatrope to include the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years. The use of Humatrope for the proposed indication was granted orphan drug designation on the 13 June 2002.

Eli Lilly previously submitted an application to the TGA to register Humatrope for the use in SGA but withdrew it in 2003 after the TGA's Australian Drug Evaluation Committee (ADEC) agreed with the Delegate that the application should be rejected on the grounds of inadequate data to support efficacy for the proposed indication.

The earlier application was supported by one uncontrolled clinical trial, B9R-FP-0908. Since then the sponsor has completed a 2 year controlled clinical study, B9R-EW–GDGB (OPTIMA) and is undertaking a Phase IV observational study B9R-EW-GDFC (The *Genetics and Neuroendocrinology of Short Stature International Study*; GeNeSIS) evaluating the long-term efficacy and safety of Humatrope. Data from all three studies and a thorough review of the literature were provided in support of the current submission.

Published references referred to in this AusPAR have been listed at the end of the document (see References).

Regulatory status

Humatrope was first registered in the Australian Register of Therapeutic Goods (ARTG) on 24 October 1995.

The sponsor indicates that somatropin is registered in about 40 overseas countries, including the USA (since March 2009), UK (October 2006) and Canada (July 2010); however, it is not clear if all of these approvals include treatment of SGA. In the sponsor's letter of application it is stated that *"Lilly and company submitted the SGA indication in the EU between November 2001 and December 2008, US on the 17 January 2008 and Canada on the 25 June 2008. Approval was received in the EU between October 2002 and December 2009 and in the US on the 12 March 2009."*

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Small for gestational age (SGA)

The most common definition of SGA refers to a weight below the tenth percentile for gestational age. However, this definition does not make a distinction among infants who are constitutionally small, growth-restricted and small, and not small but growth-restricted relative to their potential. As an example, as many as 70% of fetuses who weigh below the tenth percentile for gestational age are small simply because of constitutional factors such as female sex or maternal ethnicity, parity or body mass index. Small for gestational age birth is preceded in many cases by intrauterine growth retardation (IUGR), which is defined by prenatal determination of delayed *in utero* growth.

In some literature, the term IUGR has been used interchangeably with SGA on this subject; however, for the purpose of this evaluation, the term SGA will be used to encompass all births meeting the above definition without regard to whether or not IUGR was formally documented during pregnancy.

Physical growth

SGA infants have different patterns of growth depending upon the aetiology and the severity of growth restriction. In moderately affected infants, growth during the first 6 to 12 months after birth may be accelerated, resulting in attainment of normal size in most children. In one study, for example, 87% of 3650 term infants with birth length more than two standard deviations (SD) below the mean had normal height at one year of age. However, in a report of national survey data, SGA infants appeared to catch up in weight in the first six months, but maintained a deficit in height of approximately 0.75 SD units through 47 months compared to appropriate for gestational age (AGA) infants. In comparison, severely affected SGA infants frequently weigh less and are shorter than AGA infants throughout childhood and adolescence. In one report, for example, body measurements at age 17 years in adolescents who had birth weight less than the third percentile were compared to those who were AGA. The average height, in centimetres (cm), was significantly less in the SGA group (169 versus 175 cm and 159 versus 163 cm, for boys and girls respectively). In addition, the adolescent height of SGA newborns was more likely to be less than the tenth percentile (odds ratio (OR) 4.13 and 3.32, for boys and girls respectively).

The sponsor included the following information in their submission:

> *For the majority of SGA births, the etiology remains unknown despite thorough investigation (Lee et al., 2003). The average adult height of individuals who were born SGA is close to 1 SD (approximately 6 centimetres) below the average height of individuals born appropriate for gestational age (AGA). Prevalence of being born SGA in a population depends on the cut-off level used for its definition. The most commonly used cut-off for children born SGA is a weight and/or length less than -2 SD (Clayton et al., 2007). A subpopulation of children born SGA who remain short (height below -2 SD scores [SDS]) at 2 years of age (estimated to be 8% to 15%), will remain short as adults (Albertsson-Wikland et al., 1993; Karlberg and Albertsson-Wikland 1993; Albertsson-Wikland and Karlberg 1994; Hokken-Koelega et al., 1995; Karlberg and Albertsson-Wikland 1995; Leger et al., 1997; Albertsson-Wikland et al., 1998; Karlberg et al., 2002). Furthermore, the relative risk of adult short stature following short stature at 2 years of age is 7-fold greater for SGA than for AGA births. Thus, the age of 2 years is an appropriate [as a lower cut-off age for growth failure].*

Neurodevelopment

SGA infants appear to be at increased risk for neurodevelopmental abnormalities and decreased cognitive performance, although the data are conflicting. Most of the early studies of outcome are difficult to interpret because of small sample sizes and inclusion of infants with underlying conditions and neonatal complications that affect outcome. Affected children with neonatal complications had significantly lower intelligence quotient (IQ) scores and poorer neurodevelopmental outcome at three years than did those with uncomplicated courses. When complications such as birth asphyxia were excluded in another report, term SGA infants had a good prognosis for cognitive and neurologic development at 13 to 19 years.

IUGR appears to effect neurodevelopment and behaviour in adolescents and young adults, as demonstrated by the following studies:

- In one study, adolescents born at term with severe IUGR (≤ third percentile) had intelligence test scores comparable to those born AGA but affected males were significantly more likely to have less than 12 years of schooling or attend a vocational school (OR 2.4).
- In another report, adolescents born SGA (≤ third percentile) at term were more likely to have learning difficulties (32% versus 18%) compared to those born AGA, although cognitive ability was not affected. Learning difficulties were related to the severity of growth restriction but not symmetry. Attentional problems were more frequent in the SGA girls but not boys.
- In a population-based cohort study of young adult Swedish males evaluated at the time of military conscription, multiple logistic regression analysis demonstrated low intellectual performance scores were associated with birth weight <2 SDS below the mean (OR 1.22, 95% confidence interval [CI] 1.13 to 1.33), birth length <2 SDS below the mean (OR 1.33, 95% CI 1.22 to 1.46) and birth head circumference <2 SDS below the mean (OR 1.28, 95% 1.20 to 1.37).

Problem statement

Adults who are short (< 3 SDS) are thought to be disadvantaged in our society. The use of medicines to increase height in children with growth failure is now widespread in Australia. Current use includes children who have growth failure secondary to GH deficiency and other inherited disorders such as Turner Syndrome. The psychosocial benefits of treatment have been assumed in this dossier and are not addressed in detail by the evaluator (other than highlighting them as an issue for consideration). The other long-term consequences of SGA, such as diabetes and cardiovascular risk, are unlikely to be addressed by increase in height through medical intervention. These issues have not been addressed in the dossier either. It could be that GH treatment affects these other risks (either improved or worsened) however, only very long-term follow-up studies could be expected to address this. Short term changes in surrogates such as the development of insulin resistance or changes in lipid profile may give an indication of potential alterations in these risk factors.

The aim of the treatment of growth failure secondary to SGA is to increase final height into the normal range, preferably within 2 SDS. Interim improvements in linear growth in childhood that do not translate into improved final height are of much lesser importance. The sponsor contends that treatment with Humatrope does result in the improvements in final height warranted to justify its use. It should be noted that the use of GH is onerous with daily injections, potentially for years as well as the stigma for the child; of being labelled as “different” by the need to take a daily medicine.

The clinical data consisting of 4 volumes containing the clinical study reports as well as supporting literature. While the literature supplied included studies for the proposed application, the sponsor did not use these in a way to inform the application or the proposed PI.

The dossier presentation was clear, the pages were legible and tables were well presented.

Pharmacokinetics

No specific studies on pharmacokinetics were conduced.

Pharmacodynamics

No specific studies on pharmacodynamics were conduced.

Efficacy

Two studies were submitted by the sponsor investigated efficacy parameters. Neither of these studies had an untreated control arm and there were no other placebo controlled studies included in the dossier. The primary justification was that the regimen involved daily SC injections for up to several years duration and that it was unethical to include a blinded placebo group under such circumstances. The evaluator believes that a placebo arm receiving daily injections would be unethical, however, an untreated control group of some description would have been helpful.

Study B9R-EW-GD-GB

Study B9R-EW-GDGB was a multicentre, open-label, multi-dose study of Humatrope in children aged more than 3 years with growth failure secondary to SGA (Table 1). This Phase III study investigated the efficacy and safety of Humatrope over two years, comparing two similar regiments of Humatrope; a fixed dose (so called fixed high dose (FHD)) of 0.067 mg/kg/day with an individually adjusted dose (IAD) based upon response to a lower dose of 0.035 mg/kg/day. In the IAD arm, the dose was escalated up to 0.067 mg/kg/day if the patient failed to respond to the lower dose (see Figure 1). It was designed as a non-inferiority study between the two arms with the primary outcome measures being height SD score (SDS), change in height SDS and HV at 12 and 24 months. The study also estimated the target height from the mid parental height, baseline predicted height and the final predicted height using a sex matched population's height SD. Bone age was determined by radiography of the left wrist.

Table 1. Study B9R-EW-GDGB: Summary.

Study ID (B9R)	Study Design	Patient Baseline Characteristics (N, mean ± SD)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Treatment Dose and Regimen	Outcome Variables
EW-GDGB	Phase 3b, randomized 2-arm, open-label, multicenter w/extension	FAS: N=193 m=91 f=102 Age: 6.8 ± 2.4 yr Height SDS: -3.9 ± 0.7	SGA (birth weight <10th percentile and/or birth length <-2 SD for gest age); height ≤-3 SDS; age ≥3 yr; prepubertal; bone age ≤9 yr (f) or 10 yr (m) at Visit 1	Periods I and II (IAD versus FHD): 12 mo Period III (extension): 12 mo	Humatrope 0.067 mg/kg/day (FHD) or 0.035 mg/kg/day (starting dose for IAD group). After 3 mo, a portion of IAD group ↑ dose to 0.067 mg/kg/day if predicted 1-yr change in height SDS <0.75. After 1 yr, a portion of pts in IAD low dose group ↑ dose to 0.067 mg/kg/day if 1-yr change in height SDS <0.75.	**Efficacy**: Height SDS at yr 1 and yr 2, change in height SDS baseline to yr 1 and yr 2, absolute HV at yr 1 and yr 2. **Safety**: AEs, vital signs, clinical laboratory assessments (IGF-I, glucose, insulin, lipids, thyroid function, OGTT [yr 2]).

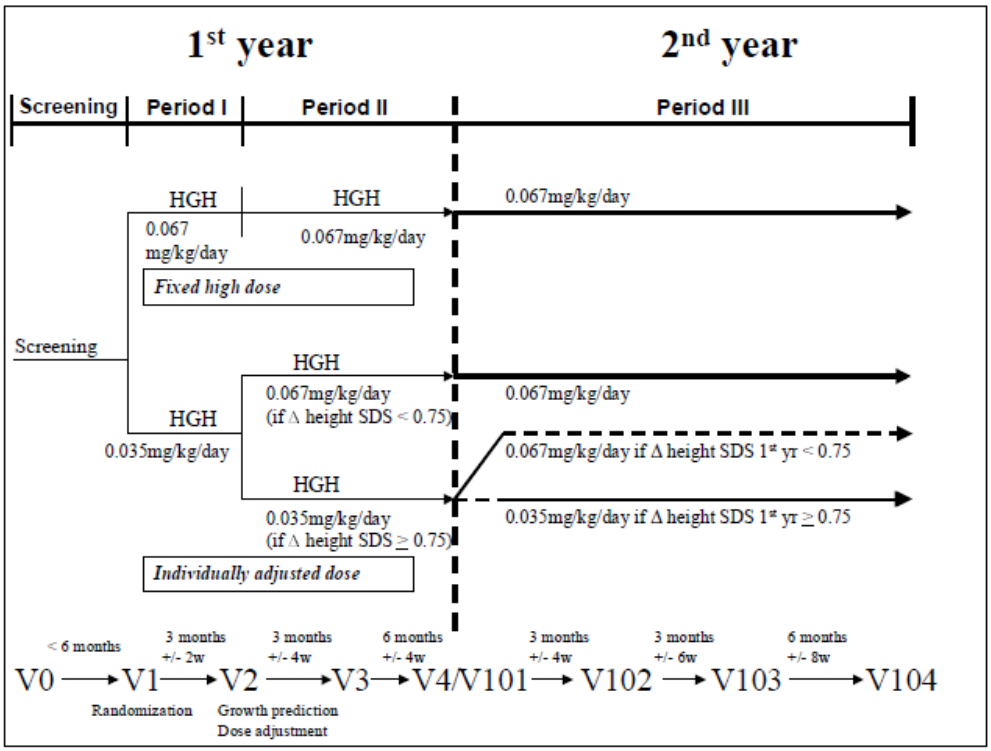
Abbreviations: AEs = adverse events; f = female; FAS = full analysis set; FHD = fixed high dose; gest = gestational; GH = growth hormone; HV = height velocity; IA = individually adjusted; IAD = individually adjusted dose; IGF-I = insulin-like growth factor I; m = male; Mat = maternal; mo = month(s); N = number of patients; OGTT = oral glucose tolerance test; Pat = paternal; pts = patients; SD = standard deviation; SDS = standard deviation score; SGA = small for gestational age; tx = treated/treatment; wk = week(s); yr = year(s).

a SGA also referred to as intrauterine growth retardation.

b Bioavailability: 1 IU = 2.7 mg prior to 1995 (0.2 IU/kg/day = 0.52 mg/kg/wk). 1 IU = 3 mg from 1995 forward (0.2 IU/kg/day = 0.47 mg/kg/wk).

The study enrolled 193 patients with 184 included in the "restricted full analysis set" (baseline height and at least one height after visit 2). There were 169 patients in the per protocol analysis at 12 months and 150 patients at 24 months. The inclusion criteria included SGA, height < -3 SDS; age > 3 years; bone age < 9 years for girls and < 10 years for boys.

Figure 1. Study B9R-EW-GDGB: Design.



Abbreviations: Δ height SDS = change in height standard deviation score; HGH = human growth hormone (Humatrope); V = visit; w = weeks; yr = year.

- If the predicted first year change in height SDS was ≥ 0.75 then the patient remained on 0.035 mg/kg/day or
- If the patient's first year change in height SDS was < 0.75, the patient HGH dose was increased to 0.067 mg/kg/day

Results

The mean baseline age of the patient population as a whole was 6.8 ± 2.4 years (range: 3 to 12 years) and similar for each group. Mean baseline height SDS was -3.9 ± 0.7. Mean Humatrope doses during the first 3 months of treatment were 0.035 and 0.067 mg/kg/day for the IAD and FHD groups, respectively. The FHD group maintained a mean dose of 0.067 mg/kg/day for the remainder of the first year. During the extension period, the mean dose in the FHD group was 0.064 mg/kg/day (n=88). The primary outcome measures are shown in Table 2 below.

Table 2. Primary outcome measures.

	N	Dose (mg/kg/week) Mean	Baseline Height SDS Mean ± SD	1-Year Height SDS Mean ± SD	2-Year Height SDS Mean ± SD	Final Height SDS Mean ± SD	Gain in Height SDS[a, b] Mean ± SD (p-value)
Study GDGB							
FHD Group							
Full Analysis Set	96		-3.9 ± 0.6	-2.7 ± 0.7	-2.2 ± 0.7	N/A	1.7 ± 0.6
Per Protocol	89	0.47	-3.9 ± 0.5	-2.8 ± 0.7	-2.2 ± 0.7	N/A	1.7 ± 0.6
IAD Group							
Full Analysis Set	88	0.24[d]	-3.9 ± 0.6	-3.0 ± 0.7	-2.5 ± 0.8	N/A	1.4 ± 0.5
Per Protocol	80	0.24 [d]	-3.8 ± 0.6	-3.0 ± 0.7	-2.4 ± 0.8	N/A	1.4 ± 0.5
IA low-low Dose							
Months 4 through 12	48	0.24	-3.9 ± 0.6	-2.9 ± 0.6	-	-	-
Months 13 through 24	32	0.25	-	-	-2.5 ± 0.6	N/A	1.5 ± 0.4

Height

The mean gain in height across the study SDS was 1.7 ± 0.6 for the FHD group and 1.4 ± 0.6 for the IAD group. This corresponded to an average increase in height of 18.3 ± 2.7 cm in the FHD group and 17.4 ± 2.4 cm in the IAD group during the 2 years of the study. While there is no control group in this study, the average height gain per year for a group of prepubertal Australian children above the age of 3 years would be approximately 5-7 cm per year, corresponding to a gain of 10-14 cm over a 2 year period[1].

The 1-year change in height SDS in the IAD group was non-inferior compared to the FHD group, based on the predefined non-inferiority margin. The treatment group difference (IAD minus FHD, least squares mean) was -0.24 (95% CI:-0.35 to -0.12) at Year 1, and thus well above the non-inferiority margin of -0.5. This difference corresponds to a mean difference in height gain of approximately 1 cm for the first year of treatment in favour of the FHD group. At Year 2, the treatment group difference (IAD minus FHD, LS mean) was -0.25 (95% CI: -0.42 to -0.08), which remained above the -0.05 SDS margin assigned a-priori as the definition of non-inferiority.

Height velocity

At 2 years (n=150) in the per protocol analysis, patients in the FHD group had a mean increase in HV from baseline to the second year of 2.7 ± 0.2 cm per year (mean HV 7.9 ± 0.2 cm per year; mean HV SDS 2.1 ± 0.2). Patients in the IAD group had a mean increase from baseline of 2.5 ± 0.2 cm per year (mean HV 7.7 ± 0.2 cm per year; mean HV SDS 1.7 ± 0.2).

Height SDS minus target height SDS

After 2 years in the per protocol analysis, the LS mean differences between height SDS and target height SDS were -0.5 ± 0.1 and -0.7 ± 0.1 in the FHD and IAD groups, respectively. The between-group difference for baseline to 2-year change (IAD-FHD) was -0.2 ± 0.1 SDS (p=0.005). Both groups showed catch-up towards target height SDS during both Year 1 and Year 2, such that by the end of Year 2 both groups were on average less than 1.0 SDS

[1] see Centre for Disease Control (CDC) dataset at http://www.cdc.gov/growthcharts/clinical_charts.htm#Set1

below their target height SDS. Overall, the FHD group had a statistically significant greater catch-up by 0.23 ± 0.08 SDS.

Bone age and bone age delay

At baseline in the per protocol analysis, the mean bone age for the study population was 4.7 ± 2.3 years for the FHD group and 4.8 years ± 2.2 for the IAD group. At Year 1, bone age had increased to 6.3 ± 2.3 years in the FHD group and to 6.3 ± 2.5 years in the combined IA low and IA high group. At Year 2, bone age had increased to 7.6 ± 2.6 years in the FHD group and to 7.7 ± 2.6 years in the IAD group.

Summary

In summary, study B9R-EW-GDGB provides evidence of short-term clinical efficacy for Humatrope in the children with growth failure secondary to SGA. While there was no control group, there was evidence of a significant increase in HV over the 2 years of the study compared to pre-study. Furthermore, the increase in HV was higher than expected from historical data and Australian child HV standards. There was also a suggestion of a dose response with the higher dose in the FHD group having a trend to greater catch-up growth than the IAD group. While the primary aim of the study was to demonstrate non-inferiority of the IAD dosing compared to FHD dosing, this is of limited interest in the context of the current application.

Study B9R-FP-0908

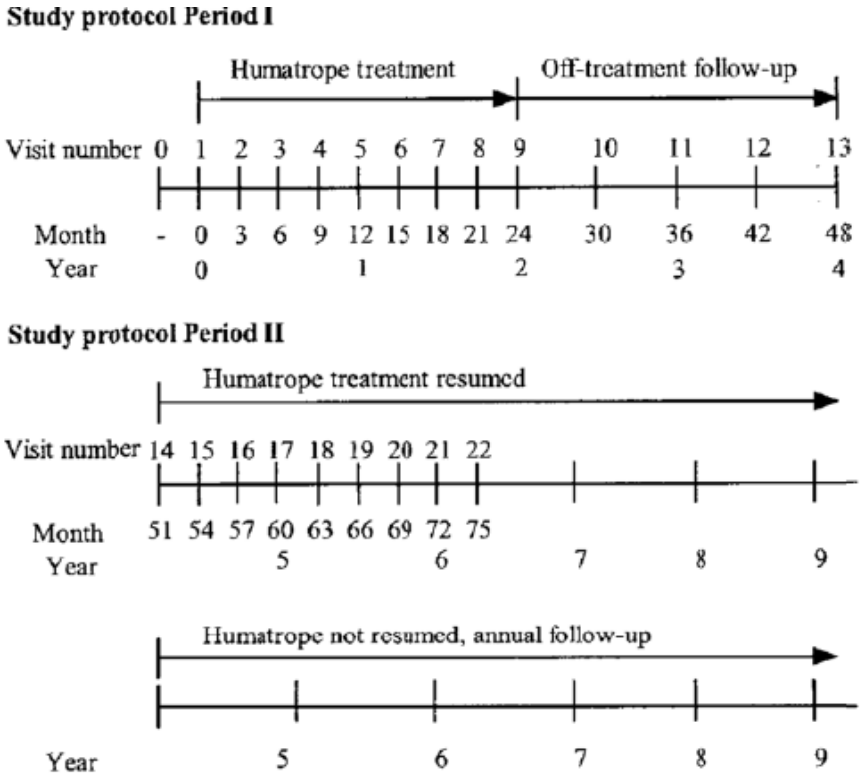
Study B9R-FP-0908 was a Phase III, open-label, single arm, multi-centre, multi-dose efficacy and safety study of Humatrope in children aged >7 years with growth failure secondary to SGA (see Table 3). This Phase III study investigated the efficacy and safety of Humatrope treatment over two years with follow-up for up to 7 years post initial treatment to investigate the final height achieved. The study was divided into 2 periods; I and II (see Figure 2).

Thirty-five patients received 2 years of Humatrope treatment; 29 of these patients completed the 2 year off-treatment follow-up in Period I. During Period II, patients could be restarted on Humatrope (Treatment Restarted - TR) or remain off Humatrope (Treatment Not Restarted - TNR). At the end of Period II, 20 patients attained their final height (4 TR and 16 NTR). The primary endpoints included actual height; changes from baseline for height SDS and HV; final height SDS and change in height SDS from baseline to final height.

Table 3. Study B9R-FP-0908: Summary.

Study ID (B9R)	Study Design	Patient Baseline Characteristics (N, mean ± SD)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Treatment Dose and Regimen	Outcome Variables
FP-0908	Phase 3, open-label, multicenter	Enrolled in Period I: N=35 m=24 f=11 Age: 9.3 ± 0.9 yr Height SDS: -2.7 ± 0.5	SGA[a] (birth length <-2 SD for gest age); pregnancy duration >36 wk; height <-2 SDS; age ≥7 and <9 yr (f), ≥9 and <11 yr (m); Pat height ≥160 cm; Mat height ≥147 cm; normal response to GH stimulation test	Period I: tx ~2 yr; monitored off tx x 2 yr (total = 4 yr) Period II: end of Period I until final height (n=20) Mean duration (yr): Period I: 2.3±0.1 Period II: 1.6±0.8	Humatrope 0.2 IU/kg/day (0.47 mg/kg/wk)[b]	**Efficacy**: Height SDS, HV, final height. Primary Efficacy Endpoint: 2-year height SDS and HV. **Safety**: AEs, clinical laboratory tests, bone age retardation.

Figure 2. Study B9R-FP-0908: Design.



Results

The mean chronological age at baseline was 9.3 ± 0.9 years and the mean bone age was 7.7 ± 1.3 years. The height SDS at baseline was below the normal range (<-2.0 SDS) for all patients with a mean baseline height SDS of -2.7 ± 0.5. The average prescribed Humatrope dose was 0.07 mg/kg/day (0.49 mg/kg/week) for patients who completed Period I (N=29) and Period II (TR Group) (n=7). The other patients (TNR) in Period II did not receive ongoing doses of Humatrope. The primary outcome measures are shown in Table 4 below.

Table 4. Primary outcome measures.

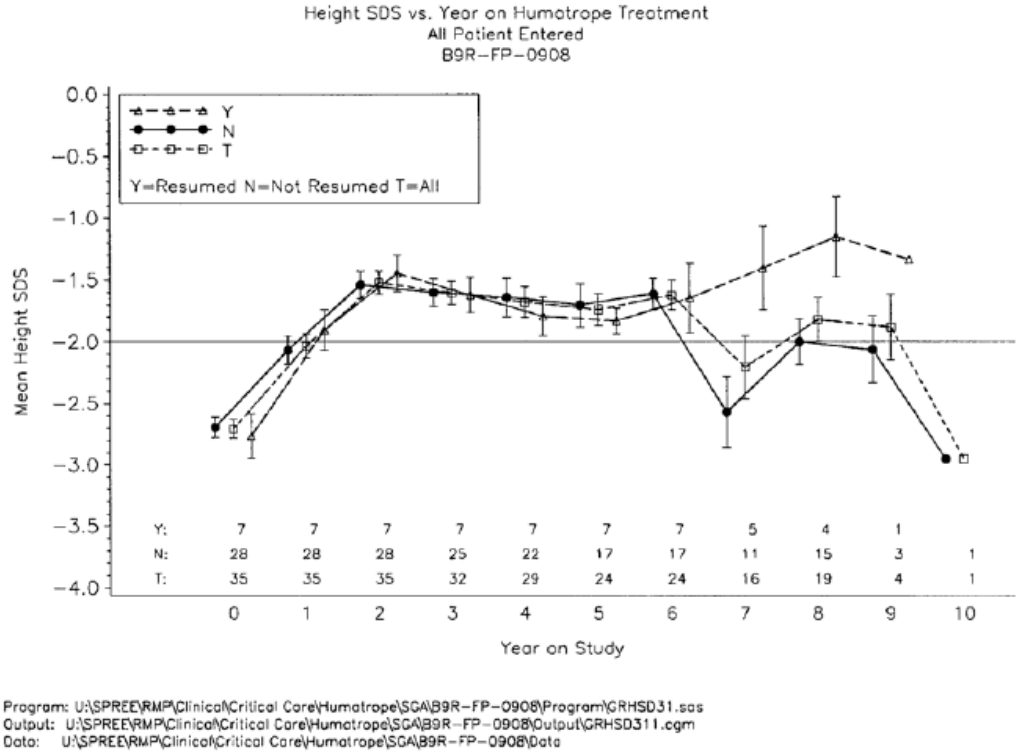
	Treatment Not Resumed	Treatment Resumed	Total
Chronological age at baseline (years)	9.4 ± 0.7 (16)	9.5 ± 1.5 (4)	9.4 ± 0.9 (20)
Height at baseline (SDS)	-2.7 ± 0.4 (16)	-2.6 ± 0.5 (4)	-2.7 ± 0.4 (20)
Height SDS--Period I at end of 2 Years (Treatment)	-1.4 ± 0.5 (16)	-1.4 ± 0.4 (4)	-1.4 ± 0.5 (20)
Height SDS--Period I at end of 4 Years (2 Years Off Treatment)	-1.5 ± 0.6 (13)	-1.8 ± 0.6 (4)	-1.6 ± 0.6 (17)
Target height (SDS)	-1.4 ± 1.0 (15)	-1.2 ± 0.3 (4)	-1.4 ± 0.9 (19)
Period II			
Bone age at Year 5	13.8 ± 0.7 (17)	12.3 ± 3.9 (2)	13.6 ± 1.3 (19)
Height SDS	-1.5 ± 0.6 (13)	-1.8 ± 0.6 (4)	-1.6 ± 0.6 (17)
Target height (SDS)	-1.4 ± 1.0 (15)	-1.2 ± 0.3 (4)	-1.4 ± 0.9 (19)
Final height (SDS)	-2.0 ± 0.7 (16)	-1.9 ± 1.1 (4)	-2.0 ± 0.8 (20)
Target – Baseline height	1.2 ± 1.2 (15)	1.5 ± 0.4 (4)	1.3 ± 1.1 (19)
Final height – Baseline height	0.7 ± 0.6 (16)	0.7 ± 1.5 (4)	0.7 ± 0.8 (20)
Final height – Target height	-0.6 ± 1.2 (15)	-0.7 ± 1.1 (4)	-0.6 ± 1.2 (19)
Age at final height (years)	17.4 ± 1.4 (16)	16.5 ± 1.0 (4)	17.3 ± 1.3 (20)

Abbreviations: n = number of patients; SD = standard deviation; SDS = standard deviation score.

Height

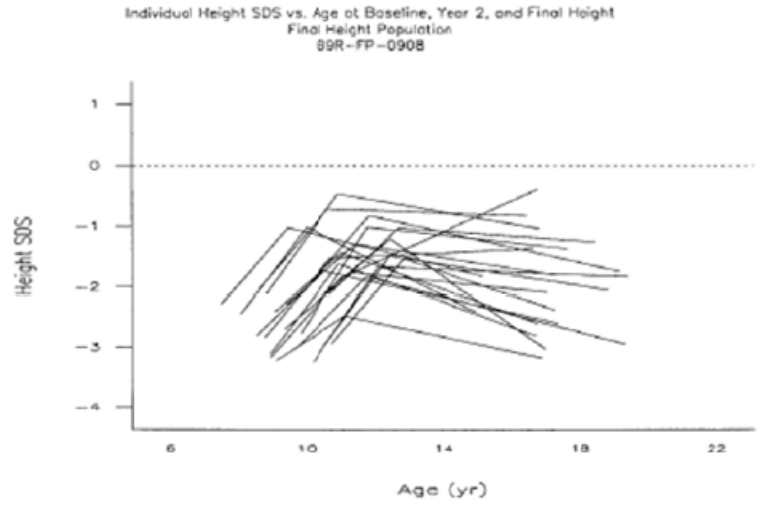
The mean gain in height SDS across the study was 0.7 ± 0.8 for the full group, 0.7 ± 1.5 in the TR group and 0.7 ± 0.6 in the TNR group. Most of the gains were made during the first 2 years of the study and some of this gain was lost later (see Figure 3). The final height SDS was -2.0 ± 0.8. The estimated gain in final height (n=20), based upon the change in SDS, was sex dependent. The estimated gain in final height for males was -0.88 ± 5.3 cm. In girls, the mean final height was 5.4 ± 6.5 cm above the predicted height. The sponsor claims that for boys the increase was less favourable because the method used for final height predictions tends to over-predict final height in boys compared with girls.

Figure 3. Height SDS versus year of Humatrope treatment.



In those who took the longest to achieve final height, there did seem to be some advantage in the group that restarted Humatrope treatment (TR) after the 2 years. However, treatment was not randomised at the end of Year 2 and the numbers were small in the TR group (n=7), so any conclusions based upon these data are tentative. The sponsor points out that these results are consistent with several other studies in the literature, which showed that part of the height SD gain at 2 or 3 years of treatment was lost at final height SD (see Figure 3). Height SDS was above -2.0 after 1 year of Humatrope treatment for 18 (55%) patients and was above -2.0 SDS for 29 (83%) patients after 2 years of treatment. After 2 years off treatment, 22 (76%) patients remaining in the study maintained their height above -2.0 SDS. At the end of the study, 28 of the original 35 (80%) patients maintained their height above -2.0 SDS (see Figure 4).

Figure 4. Individual height SDS: Year 2 and final height.



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Data: U:\SPREE\RWP\Clinical\Critical Care\Humatrope\SGA\89R-FP-0908\Data

Abbreviations: SDS = standard deviation score; yr = year.

Height velocity

In the study (n=35), the patients had a HV at baseline of 4.7 ± 0.7 cm. This increased to 8.1 ± 1.5 cm in the first year and 7.7 ± 0.9 cm in the second year. Height velocity declined by the end of the second year off treatment (Year 4) to 5.5 ± 2.0 cm per year. Height Velocity SDS increased from -1.2 ± 1.3 at baseline, to 4.4 ± 2.5 after 1 year, and 2.5 ± 1.4 after 2 years. Height velocity SDS declined to -1.1 ± 1.2 after the first year off treatment and-1.0 ± 1.3 after 2 years off treatment.

Height SDS minus target height SDS

The difference between all patients' target height SDS and patients' height SDS was 1.3 ± 1.0 at baseline and 0.5 ± 1.2 at the end of the study. This is commensurate with the estimated gain in height SD of 0.7 ± 0.8.

Height SDS minus baseline predicted height SDS

After 1 year of treatment the mean height SDS was 0.6 ± 0.9 above baseline predicted height SDS and by 2 years on treatment the mean height SDS exceeded predicted baseline height SDS by 1.1 ± 1.0. This difference at 2 years off treatment was 1.1 ± 0.9 SDS. As mentioned above, this was gender-dependent. The predicted versus observed heights at different points are shown in Table 5.

Table 5. Study B9R-FP-0908. Predicted final height [cm] at baseline and at various time points in patients followed up until final height.

	Treatment Not Resumed		Treatment Resumed		Total	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Predicted height at baseline[a] (cm)						
Boys	9	160.3 ± 5.3	1	163.4	10	160.6 ± 5.1
Girls	6	146.5 ± 4.1	2	149.0 ± 2.6	8	147.1 ± 3.7
Predicted height at 2 years (cm)						
Boys	9	169.3 ± 4.0	1	158.5	10	169.2 ± 3.7
Girls	7	153.3 ± 4.1	2	156.5 ± 2.3	9	154.7 ± 3.7
Predicted height at 4 years (cm)						
Boys	4	166.6 ± 4.5	1	166.1	5	166.5 ± 3.9
Girls	4	150.5 ± 4.3	1	150.4	5	150.5 ± 3.7
Final height – predicted height at baseline (cm)						
Boys	9	1.4 ± 5.3	1	-3.9	10	0.88 ± 5.3
Girls	6	4.9 + 6.4	2	6.9 + 6.3	8	5.4 ± 6.5
Final height (cm)						
Boys	10	161.9 ± 3.5	2	157.4 ± 3.0	12	161.2 ± 3.7
Girls	6	151.4 ± 5.9	2	155.9 ± 6.7	8	152.5 ± 5.9

Abbreviations: N = number of patients; SD = standard deviation.

[a] According to the Bayley Pinneau method (Bayley and Pinneau 1952)

Bone age and bone age delay

The mean bone age at baseline was 7.7 ± 1.3 years. This was delayed by 1.7 ± 1.1 years relative to the patients' chronological age (9.3 ± 0.9 years). After 2 years of Humatrope treatment, bone age increased to 10.0 ± 1.5 years, remaining 1.6 ± 1.3 years behind chronological age. After 2 years off treatment (Year 4), bone age increased to 12.5 ± 1.6 years, remaining 0.9 ± 1.2 years behind chronological age of 13.4 ± 1.0. As expected, by the end of the study, the bone age had reached maturity in those patients who reached this point.

Summary

In summary, Study B9R-FP-0908 provides some evidence of clinical efficacy for Humatrope in the children with growth failure secondary to SGA. This was a small study of 2 years treatment duration. Over that time, there was a significant increase in growth velocity and the height SD. Some of this height SD increase was maintained at 2 years off therapy (Year 4). Of those 20 subjects who reached their final height, there was some evidence that this growth advantage continued. This was much more marked for girls (+5.4 cm) compared with boys (+0.8 cm). The study design was unable to demonstrate whether restarting therapy 2 years post initial therapy was an advantage in this group. Overall, the gains in final height were modest, especially in boys, despite early growth acceleration for the 2 years of initial therapy.

Overall efficacy summary

The sponsor has submitted two studies in support of the use of Humatrope for the treatment of growth failure in children born with SGA. Both studies support the short term acceleration of linear growth during a 2 year treatment period. Only one study (B9R-FP-0908) investigated final adult height in this population. Much of the gains made during the 2 year treatment period were subsequently lost. There appeared to be a gender difference in final height attained in this study with boys having a much smaller increment in final height compared to girls. The sponsor submits that the small increment in final height in boys is because the formula used to predict final height in the population produces an over-estimate. This could have been addressed by a control group, either

contemporaneous or historical. The ultimate endpoint for the use of Humatrope in this population is to increase final height into the normal ranges (> -2 SDS). Height at 2 years therapy and growth velocity are surrogates which, based upon the presented data, do not fully predict the final outcome in this population. Finally, the sponsor did not submit a study which included continuous use of Humatrope up to the time of final height, although this is how the product is intended to be used in this population. This is a deficiency. The sponsor should supply further data (not necessarily new data) and analysis to further clarify the final height using Humatrope in the way proposed in the updated product information.

Safety

Human GH has a long experience of use in children with growth failure due to a variety of causes. The sponsor has included the two efficacy studies (B9R-FP-0908 and B9R-EW-GDGB) and a third safety study (B9R-EW-GDFC) for this analysis with an exposure of approximately 1265 patient-years. The sponsor also refers to clinical trial experience as of February 2006, exposure to Humatrope during clinical trials exceeding 7700 patient-years for all paediatric patient populations. Details of this are not included in the current dossier. A summary of the submitted studies is included in Table 6.

Table 6. Safety summary.

Study	Number of Patients	Total Patient Years	Entry/Eligibility Criteria	Design	Dosage and Regimen[a]
B9R-FP-0908	Enrolled: N=35 Safety Pop: N=35	90.2	SGA[b] (birth length below –2 SD for gestational age); age ≥7 years and <9 years (f), ≥9 years and <11 years (m); duration of pregnancy >36 weeks; height <-2 SD; paternal height ≥160 cm, maternal height ≥147 cm; normal response to GH stimulation test. Safety Population: All patients who entered the study	Phase 3, open label, multicenter	0.067 mg/kg/day (0.47 mg/kg/wk)
B9R-EW-GDGB	Enrolled: N=194 Safety Pop: N=193 (yr 1) N=175 (yr 2)	352.5	SGA (birth weight <10th percentile and/or birth length <-2 SD for gestational age); height ≤-3 SDS; age ≥3 years; prepubertal; bone age ≤9 years (f) or ≤10 (m) years at Visit 1. Safety Population: All patients who received ≥1 dose of Humatrope.	Phase 3b, randomized, 2-arm, open label, multicenter with extension	FHD: 0.067 mg/kg/day; IAD: IA low-low: 0.035 mg/kg/day, IA high: 0.035 mg/kg/day x 3 mo followed by 0.067 mg/kg/day x up to 24 mo, IA low-high: 0.035 mg/kg/day x 12 mo followed by 0.067 mg/kg/day x up to 24 mo.
B9R-EW-GDFC	Enrolled: N=429 Safety Pop: N=340	987.4	SGA, including IUGR (unknown cause, Russell-Silver syndrome or investigator-reported known cause). Safety Population: All enrolled patients who were treated and had at least 1 posthaseline visit.	Phase 4, open label, obs. multicenter, multinational, PM	At discretion of treating physician; mean dose = 0.29 mg/kg/wk (range=0.01-0.59 mg/kg/wk)

Abbreviations: f = female; FHD = fixed high-dose group; GH = growth hormone; IAD = individually adjusted dose; IU = International Unit; IUGR = intrauterine growth retardation; m = male; mo = months; N = number of patients; obs = observational; PM = postmarketing; Pop = population; SD = standard deviation; SDS = standard deviation score; SGA = small for gestational age; wk = week.

a Somatropin administered as single daily subcutaneous injection in all studies. Bioavailability 1 IU = 2.7 mg prior to 1995 (0.2 IU/kg/day = 0.52 mg/kg/wk). 1 IU = 3 mg from 1995 forward (0.2 IU/kg/day = 0.47 mg/kg/wk).

b SGA also referred to as IUGR.

A total of 658 patients were enrolled in the 3 studies. Of these, 568 were stated to be assessable for safety. This is primarily because in Study B9R-EW-GDFC 89 patients did not meet the criteria of at least 1 post-baseline assessment. Studies B9R-FP-0908 and B9R-EW-GDGB were described above; Study B9R-EW-GDFC is described below:

Study B9R-EW-GDFC

Study B9R-EW-GDFC (*GeNeSIS - An Interim Analysis of the Safety of Humatrope Treatment in Pediatric Patients Born Small for Gestational Age)*. This is a Phase IV post marketing observational study based upon data from 169 centres in 26 countries. The study has been ongoing since 1990. The current report is an interim analysis from September 2006.

The entry criteria were broad and included any child who was born SGA from any cause and were found to have poor linear growth (although this is not clearly defined). The patients had a height SDS at baseline of -2.7 ± 1.08 with a range from -7.65 to 0.32. The third quartile had a height SDS of -2.1 which indicated that up to 25% of the enrolled patients were within the normal range (+2 SDS) for height. The study included patients with Turner Syndrome and other known genetic causes of short stature (such as short stature homeobox-containing gene (SHOX) deficiency and Leri-Weill syndrome) which further confounds the analysis. The poor quality of the data is further emphasised by the need to exclude large amounts of "impossible data". As noted above, 89 patients were excluded from the analysis as they had not had any evaluations post-baseline.

Evaluator comment: In summary, this observational study is of poor quality and the reliability of the data is questionable. Based on the data presented, it is unlikely that this study would be found to comply with Good Clinical Practice (GCP) guidelines. It may well be that the study under-reports the rate and types of adverse events (AEs).

Deaths

The study included 1 death and 6 non-fatal serious adverse events (SAEs). The single death was in a 15 year old boy with previous history of hydrocephalus and renal aplasia. The sponsor stated that it seemed likely that the child died a cardio-respiratory death due to ventriculoperitoneal shunt malfunction and resultant raised intracranial pressure; and assessed the event as unrelated to treatment. However the study investigator did not provide an opinion on the relatedness of this event to Humatrope treatment.

Serious adverse events

Of the 6 non-fatal SAEs, 2 were considered as possibly related to treatment by the investigators.

- A 10 year old girl with Russell-Silver syndrome developed non-insulin dependent diabetes mellitus after approximately 2.9 years of somatropin treatment. The diabetes was reported by the investigator to be persistent at 11 months after treatment discontinuation; however, all laboratory parameters (including haemoglobin A1c (glycated haemoglobin) were normal and the child was receiving no antihyperglycaemic medications.
- An 11 year old girl developed carpal tunnel syndrome (confirmed on electromyography) approximately 2 weeks after initiation of treatment. This child had a positive family history of carpal tunnel syndrome as well as short stature.

The sponsor also highlighted a third SAE in a 14 year old boy with a history of Arnold-Chiari malformation who was diagnosed with scoliosis after approximately 1 year of somatropin treatment. He underwent surgical procedure to correct worsened scoliosis (ascribed to noncompliance with brace treatment) after about 5.8 years of somatropin treatment. The study investigator determined the events to be unrelated to somatropin treatment. However, the sponsor considered that the events may be possibly related to treatment, as some cases of scoliosis have been reported to worsen during periods of rapid growth, such as those induced by somatropin treatment.

Adverse events

Non-serious treatment-emergent AEs were reported in 71 (21%) patients. The most commonly reported events were hypothyroidism (11 [3%] patients), precocious puberty (4 [1%] patients) and scoliosis (4 [1%]) patients). The majority of the other reported treatment-emergent AEs were typical childhood illnesses (such as infections).

Proposed changes to the Product Information

The evaluator commented on changes to the AE section of the PI as a result of the above findings; however, details regarding PI revisions are beyond the scope of this AusPAR.

Safety population

The safety population demographics are summarised in Table 7:

Table 7. Baseline demographics for the safety population.

Baseline (Mean ± SD)	Study 0908 All Patients Entered N=35[b]	Study GDGB Full Analysis Set[a] N=193[b]	Study GDFC Safety N=340
Chronological age (years)	9.3 ± 0.9	6.8 ± 2.4	9.3 ± 3.8
Bone age (years)	7.7 ± 1.3	4.7 ± 2.2	8.1 ± 3.8
Male (n, %)	24 (69)	91 (47)	193 (57)
Female (n, %)	11 (31)	102 (53)	147 (43)
Height SDS	-2.7 ± 0.5	-3.9 ± 0.7	-2.7 ± 1.1
Birth weight SDS	-1.7 ± 0.9	-2.1 ± 0.8	-2.2 ± 1.3
Fasting glucose (mg/dL)	86.0 ± 10.7	77.5 ± 10.9	83.0 ± 13.4
IGF-I SDS	-0.9 ± 1.4	-1.1 ± 1.4	-1.4 ± 1.5

Abbreviations: N = number of patients; n = number of patients in subgroup; IGF-I = insulin-like growth factor I; SD = standard deviation; SDS = standard deviation score.

a The Full Analysis Set includes all patients who received at least 1 dose of Humatrope (also known as the Safety Population).

Adverse events

The sponsor states that AEs in the clinical study report (CSR) for Study B9R-FP-0908 were coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. To maintain consistency with the other studies in this submission, AE terms have been-recoded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events in Studies B9R-EW-GDGB and B9R-EW-GDFC were coded using MedDRA[2]. A listing of the clinically significant AEs can be found in Table 8.

[2] **MedDRA=the Medical Dictionary for Regulatory Activities;** a standard set medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (such as medical devices and vaccines).

Table 8. Comparison of adverse events of relevance in GH-treated patients.

	Patient Population (n, %)						
	0908	GDGB	GDFC	SGA Total[a]	ISS[b]	GHD[b]	TS[b]
Total Number of patients	35	193	333	561	276	333	304
Total patient-years of GH exposure	90.2	352.5	987.4	1430	1212	1232	1219
Death	1 (2.9)	0 (0.0)	1 (0.3)	2 (0.3)	1 (0.4)	3 (0.1)	0 (0.0)
Otitis media	1 (2.9)	8 (4.6)	2 (0.6)	11 (2.0)	22 (8.0)	95 (28.5)	133 (43.8)
Scoliosis	0 (0.0)	0 (0.0)	5 (1.5)	5 (0.8)	8 (2.9)	5 (1.5)	1 (0.3)
Hypothyroidism	2 (5.7)	4 (2.3)	14 (4.1)	20 (3.6)	2 (0.7)	78 (23.4)	50 (16.4)
Alteration in carbohydrate metabolism	0 (0.0)	15 (7.7)	1 (0.3)	16 (2.9)	2 (0.7)	1 (0.3)	1 (0.3)
Hypertension	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.4)	1 (0.3)	15(4.9)
Slipped capital femoral epiphysis	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.4)	1 (0.3)	0 (0.0)
Benign intracranial hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Edema	0 (0.0)	2 (1.0)	1 (0.3)	3 (0.5)	0 (0.0)	5 (1.5)	6 (2.0)
Pubertal or prepubertal gynecomastia	3 (12.5)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: GH = growth hormone; GHD = growth hormone deficiency; ISS = idiopathic short stature; n = number of patients; SGA = small for gestational age; TS = Turner syndrome.

[a] SGA Total is the total values for the SGA studies (0908, GDGB, GDFC).

[b] Patient data from Quigley et al. 2005.

Discontinuations

Four patients discontinued due to AEs, all from Study B9R-EW-GDGB: One patient was discontinued from Humatrope treatment due to the development of focal glomerulosclerosis. The event was assessed as not related to study drug and the patient continued in the study for safety follow-up. Two patients in the FHD group were discontinued for impaired fasting glucose and mood alteration. These were assessed as possibly related to study drug by the investigators. One patient who complained of pain in extremity was assessed as not related to study drug.

Serious adverse events

The sponsor reported a total of 52 SAEs in 37 patients in the 3 submitted studies.

Study B9R-FP-0908

This study reported 18 SAEs in 13 of 35 patients (37%). Three accidental injuries were reported for 2 patients, 2 gastrointestinal events were reported for 2 patients and the remainder of events were reported once each (see Table 9).

Table 9. Serious adverse events in Study B9R-FP-0908.

Patient Number	Preferred Term	Related	Reason Serious	Severity	Drug DC	Time from Start of Humatrope Treatment
301-7002	Limb operation	No	HO	Mild	N/A	Off treatment; event occurred during follow-up
302-7007	Appendectomy	No	HO	UK	No	454 days
302-7008	Ear operation	No	HO	UK	No	229 days
302-7009	Wrist fracture	No	HO	UK	No	473 days
302-7010	Tooth extraction	No	HO	UK	No	614 days
302-7012	Anorexia	No	HO	Moderate	N/A	Off treatment; event occurred during follow-up
303-7021	Fall	No	HO	UK	No	381 days
	Head injury	No	HO	UK	No	381 days
	Vomiting	No	HO	UK	No	381 days
	Amnesia	No	HO	UK	No	381 days
303-7026	Depression	Yes	HO	Moderate	Yes	177 days in Period II.
305-7041	Paronychia	No	HO	Mild	No	472 days
305-7043	Death	No	DE	Severe	Yes	Off treatment
305-7046	Pyelonephritis	Yes	HO	Moderate	N/A	Off treatment; event occurred during follow-up
306-7055	Abdominal pain	No	HO	UK	No	150 days
	Injection site pain	No	HO	UK	No	150 days
	Appendicitis	No	HO	Moderate	N/A	Off treatment; event occurred during follow-up
307-7063	Otitis media	UK	HO	UK	N/A	Patient off somatropin when event occurred.

Abbreviations: DC = discontinued; DE = death; HO = hospitalization; N/A = not applicable; Period II = extension period to final height; UK = unknown.

Study B9R-EW-GDGB

Thirty-two SAEs were reported for 17 of 193 patients (8.8%; see Table 10). Of these, 4 SAEs reported for 3 patients were rated by the study investigator as possibly related to treatment with somatropin:

- 1 patient hospitalised for slipped capital femoral epiphysis ["epiphysiolysis capitis femoris"];
- 1 patient had adenoidal and tonsillar hypertrophy;
- 1 patient had adenoidal hypertrophy.

Table 10. Serious adverse events in Study B9R-EW–GDGB.

Patient Number	Treatment Group	Preferred Term	Related	Reason Serious	Severity	Drug DC	Days from Start of Treatment
201-2019	FHD	Headache	No	HO	Severe	No	126
201-2999	FHD	Tonsillar disorder	No	HO	Mild	No	242
		Arthritis	No	HO	Moderate		408
		Arthritis infective	No	HO	Mild		442
		Arthritis infective	No	HO	Moderate		476
306-3064	FHD	Vomiting	No	HO	Severe	No	192
400-4001	FHD	Asthma	No	HO	Severe	No	47
104-1040	FHD	Gastroenteritis	No	HO	Mild	No	602
107-1071	FHD	Pyrexia	No	HO	Severe	No	525
		Rash	No	HO	Severe	No	525
201-2016	FHD	Diarrhoea	No	HO	Moderate	No	420
		Influenza	No	HO	Moderate	No	420
		Pain in extremity	No	HO	Moderate	Yes	420
209-2091	FHD	Febrile infection	No	HO	Moderate	No	457
		Upper limb fracture	No	HO	Mild	No	483
400-4000	IAD (no prediction)[a]	Vomiting	No	HO	Severe	No	Ongoing[b]
		Pyrexia	No	HO	NA	No	23
		Staphylococcal sepsis (x 2)	No	HO, LT	NA	No	3 and 22
100-1001	IA high	Epiphysiolysis	Yes	HO	Severe	No	370
103-1031	IA high	Focal glomerulosclerosis	No	HO	Severe	Yes[c]	222
103-1030	IA low	Laryngitis	No	HO	Moderate	No	33
		Adenoidal hypertrophy	No	HO	Moderate	No	52
		Adenoidal hypertrophy (recurrence)	Yes	HO	Moderate	No	119
		Tonsillar hypertrophy	Yes	HO	Moderate	No	119
106-1062	IA low	Pneumonia (x 2)	No	HO	Severe	No	110
201-2011	IA low	Head injury	No	HO	Mild	No	303
		Skin laceration	No		Moderate	No	303
201-2015	IA low	Gastroenteritis salmonella	No	HO	Moderate	No	294
201-2060	IA low	Convulsion	No	HO	Moderate	No	286
103-1035	IA low-high	Adenoidal hypertrophy	Yes	HO	Moderate	No	605

Abbreviations: DC = discontinued; FHD = fixed high dose; HO = hospitalization; IAD = individually adjusted dose; IA high = 0.035 mg/kg/day for 3 months followed by 0.067 mg/kg/day for remainder of the study (Months 4 through 24); IA low = 0.035 mg/kg/day (0.25 mg/kg/week) for the entire study; IA low-high = 0.035 mg/kg/day for first 12 months of study followed by 0.067 mg/kg/day for remainder of study (Months 13 to 24); LT = life threatening; NA = not available.

[a] Low dose was administered to this patient during study participation. Subject discontinued prior to assignment to IA low or IA high dose groups.

[b] This event was listed as ongoing for Patient 400-4000 at the end of Year 1.

[c] Humatrope discontinued, but patient continued in the study off treatment.

Study B9R-EW-GDFC

SAEs were reported in 7 patients (see Table 11). Two of the SAEs were considered by the study investigators to be possibly related to Humatrope treatment.

- Carpal tunnel syndrome was reported in an 11 year old girl 2 weeks after onset of therapy;
- A 10 year old girl with Russell-Silver syndrome was hospitalisation for non-insulin dependent diabetes.

A third event of hospitalisation and surgery (spinal fusion) for scoliosis was considered by the sponsor to be possibly related to treatment.

Table 11. Serious adverse events in Study B9R-EW-GDFC.

Patient Number	Preferred Term	Related	Reason Serious	Severity	Drug DC	Days from Start of Somatropin Treatment
3403-34026	Cardiovascular disorder	N/A	DE	Severe	Yes	4267
2015-20285	Carpal tunnel syndrome	Yes	HO	Severe	No	13
2056-21962	Congenital aplastic anemia	No	CO[a]	Severe	No	735
3455-34618	Inguinal hernia	No	HO	Mild	No	3783
4436-44302	Ulna fracture	No	HO	Severe	No	82
6073-60736	Diabetes mellitus non-insulin-dependent	Yes	HO	Severe	Yes	1047
976-92701	Arnold-Chiari malformation Spinal fusion surgery	No [b]	HO	Moderate	No	1955

Abbreviations: CO = congenital anomaly; DC = discontinued; DE = death; HO = hospitalization; N/A = not applicable.

[a] Incorrectly coded by the investigator. Actual cause should be recorded as HO.

[b] Considered by Lilly physician as possibly drug-related.

SAEs from the Literature

The sponsor identified SAEs in 27 patients in published data from clinical trials and observational studies (Chatelain *et al.,* 1994; Butenandt and Lang 1997; Darendeliler *et al.,* 2002; Carel *et al.,* 2003; Wilton, 2007). The sponsor's summary of these is reproduced below.

> *The reported SAEs include 3 cases of malignancy. In the first case (Belgian-French study), a suprahypothalamic dysgerminoma was identified in an 11 year old boy on the basis of a workup for raised intracranial pressure 23 months after starting somatropin (Chatelain et al., 1994). A baseline computerised tomography (CT) scan had not been performed. The second case of malignancy was an osteosarcoma, identified at an undisclosed time after treatment in a 9.9 year old girl was discontinued (Darendeliler et al., 2002). The third case was that of a patient reported in the 20-year update of the Kabi International Growth Study (KIGS). Acute myeloblastic leukemia was reported in a patient who had received 4.7 years of somatropin treatment (Wilton, 2007). Two additional SAEs were reported as possibly related to somatropin treatment: slipped femoral capital epiphyses in*

1 patient and seizure in 1 patient (Carel et al., 2003). The remaining 23 SAEs were reported as unrelated to somatropin treatment.

Deaths

There were 2 death reported in the safety population:

Study B9R-EW-GDFC: A 15 year old boy died from cardiovascular failure and is described in detail above.

Study B9R-FP-0908: A 17 year old male patient who left the study and was lost to follow up committed suicide more than 4 years after discontinuation of Humatrope. His suicide was considered unrelated to study drug treatment.

Specific adverse events

Diabetes

There was only one case of diabetes reported in the submitted studies as was discussed above in the section on SAEs from Study B9R-EW-GDFC. Blood sugar measurements were included as part of Studies B9R-FP-0908 and B9R-EW–GDGB. Study B9R-EW-GDFC did not measure blood sugar routinely. Insulin levels were not included in any of the studies and so potential insulin resistance would not be recognised.

Lipids

Lipid measurements were included in Study B9R-EW-GDGB with no clinically significant changes identified.

Insulin-Like Growth Factor I (IGF-1) and Insulin-Like Growth Factor-Binding Protein 3 (IGFBP-3)

All three studies included measurements of IGF-I and IGFBP-3. Levels at baseline were generally low to normal and there was a variable response to therapy. Study B9R-EW-GDGB included a dose reduction strategy for increasing levels of IGF-I and low levels of IGFBP-3. Actual dose reductions occurred for 8 patients in the FHD group and 2 of the IAD group.

Thyroid function

All three studies included measurements of thyroid function.

- Studies B9R-FP-0908 did not report significant changes in thyroid function.
- Study B9R-EW-GDGB identified 4 patients with significant alterations in thyroid function.
- Study B9R-EW-GDFC identified 1 patient with significant alterations in thyroid function.

The sponsor reported that only one patient received thyroxin for their abnormal thyroid function. However, 11 patients (3%) were reported to have hypothyroidism in the study report and this should be clarified.

Carcinogenicity

There were no reports of neoplasia or malignancy in the submitted studies. However, 3 cases are reported in the literature: an 11 year old boy was diagnosed with a suprahypothalamic dysgerminoma after 23 months of somatropin treatment (Chatelain *et al.,* 1994), an osteosarcoma was diagnosed in a 9.9 year old girl (Darendeliler *et al.,* 2002) and acute myeloblastic leukemia was reported 4.7 years after initiation of therapy (Wilton, 2007).

Summary

Overall, the reported safety from the three studies is consistent with the known adverse event profile of Humatrope. The main deficiency in the data was the conduct of Study B9R-EW-GDFC. As stated previously, this observational study is of poor quality and the reliability of the data is questionable. It may well be that the study under-reports the rate and types of AEs. Also hypothyroidism was reported inconsistently through the dossier and the sponsor should clarify the rate and severity of hypothyroidism in the submitted studies.

Post marketing surveillance

Other than Study B9R-EW-GDFC, no other post-marketing data were presented.

List of questions

The questions TGA posed to the sponsor re described under *Issues addressed, Supplementary Clinical Evaluation*, below.

Clinical summary and conclusions

Overall, the dossier was of mixed quality. The data supporting the use of Humatrope in growth failure secondary to being born SGA had some deficiencies; these are listed below.

- There were no controlled studies with a placebo or untreated comparator group.
- There is a lack of final height data. The final height data that are presented are from an open label study and includes only 20 patients who reached this endpoint. Furthermore the potential height gains described in the study were modest in girls (5.7 cm) and insignificant in boys (0.8 cm). No comparator group was included.
- The safety study was poorly conducted with many errors in data. The evaluator doubts that the study was performed in compliance to GCP and believes that it may have significantly underestimated the rate and severity of AEs.
- The data relating to thyroid function is confusing and should be addressed.

Initial recommendation

Because of the concerns raised above, the evaluator could not recommend the extension of indication requested by the sponsor. It was recommended the deficiencies could be addressed by clarifying the potential final height and the safety data.

The evaluator recommended that the sponsor supply further data (not necessarily new data) and analysis to further clarify the final height achieved using Humatrope in the way proposed in the PI.

Supplementary clinical evaluation

The sponsor's response to eleven questions raised by the TGA (see *Issues addressed*, below), were evaluated in a *Supplementary Clinical Evaluation* report. The response (titled *Response to the Clinical Evaluation Report for Humatrope (Somatropin) Treatment of Growth Failure in Children Born Small for Gestational Age (SGA))* included a detailed reply, including supplementary clinical data, to these questions as well as a response to six questions posed by the European Medicines Agency (EMA) in response to the findings from *The Sante Adulte GH Enfant* (SAGhE) study. The latter does not address the Australian

PI directly or the issues raised in the initial TGA evaluation report. Its purpose was summarised by the sponsor as follows:

> *"This communication is in response to the 6 questions in the List of Questions (LoQ) from the European Medicines Agency (EMA) regarding information on Humatrope® (somatropin, LY137998) dated 14 January 2011.*
>
> *These questions had been provided to the Marketing Authorisation Holder (MAH) on 20 December 2010 during a procedure under Article 107 of Directive 2001/83/EC, as amended. This procedure has been initiated following a Rapid Alert in Pharmacovigilance from Agence francaise de securite sanitaire des produits de sante (AFSSAPS) dated 09 December 2010 in regards to results from The Santo Adulte GH Enfant (SAGhE) study[3]. The SAGhE study, part of a broader European retrospective observational study entitled "Safety and Appropriateness of' Growth hormone treatments in Europe," suggested an increased risk of mortality in a young adult population previously treated with somatropin products during childhood compared to the French general population."*

The clinical evaluator only presented data from this report when relevant to the current application. Also the sponsor included a large number of literature reports on the use of somatropin; the evaluator presented data from these when directly relevant to the application.

Issues addressed

Issue 1: No study included a placebo arm

This issue was raised because no placebo or other control groups were included in any of the submitted studies. This was a deficiency. The evaluator recommended that the sponsor supply further data, including control subject data (not necessarily new data) and analysis to further clarify *the final height* achieved using Humatrope in the way proposed in the PI.

Sponsor's response

The sponsor stated that although desirable, the inclusion of an untreated control arm into Study B9R-FP-0908 was not feasible. Long-term studies in children are difficult to conduct, especially when the follow-up lasts 7 years or more and if only auxological measurements are performed but no somatropin treatment is provided. Patient enrolment would have been problematic and discontinuation rates in the untreated control group would have been high.

The sponsor reiterated the 2 year data presented in the original dossier. In Study B9R-FP-0908, 20 of 35 patients remained available for follow-up until final height. The sponsor concluded that the inclusion of an untreated control arm for the initial 2 year treatment phase might have been feasible but no additional information would have been gained regarding final height. Study B9R-EW-GDGB did not include any final height data.

The sponsor concluded that although the two Lilly studies did not include untreated control groups, growth responses after 2 years of somatropin treatment and final height data of Study B9R-FP-0908 were in the same range as in published studies of comparable patient populations and similar treatment regimens and gain in height was consistently higher than reported for untreated controls in published studies.

The sponsor included a further four published studies which included final height data (see Table 12 below), two of which included the use of somatropin at the proposed dose of 0.47 mg/kg per week. As the sponsor stated, in the Carel *et al*., 2003 study a mean gain in

[3] See Official Website of the SAGhe study. Accessed at: http://saghe.aphp.fr/site/spip.php?rubrique40, on 30 April 2011.

height of +1.1 ± 0.9 SDS was achieved after a mean treatment duration of 2.7 ± 0.6 years in patients older than those in Study B9R-FP-0908. In the study by van Pareren *et al*., 2003, the 0.47 mg/kg per week dose group had mean final height that was -0.9 ± 0.8 SDS, which was significantly higher than the mean final height of -2.3 ± 0.7 SDS observed in 15 untreated children who served as an historical control group; however this included children with GH deficiency (although the study found that the mean height gain SDS of the non-GH deficient children was 2.1 ± 0.8 compared with 2.2 ± 0.6 for group B in the partially GH deficient children. The adult height SDS as well as the height gain SDS were not significantly different between the non-GH deficient and the partially-GH deficient SGA children).

Table 12. Studies reporting final height data.

Reference	Study design	Treatment Duration [years]	Indication	Treatment Group/Dose [mg/kg/wk][a]	N	Age at Baseline, mean±SD[b] [years]	Baseline Height SDS, mean±SD[b]	Growth Response, mean±SD[b]
van Pareren et al. 2003a	Randomized, controlled, double-blind for GH vs. historical control	GH: 7.8±1.7 (mean±SD)	SGA, 17 of 54 treated children partially GHD	Historical control GH 0.23 GH 0.47	15 28 26	7.8±1.7 7.9±1.9 8.2±1.9	–2.6±0.5 –2.9±0.8 –3.0±0.7	*Final height SDS / Gain:* –2.3±0.7 / +0.3±0.7 –1.1±0.7 / +1.8±0.7 –0.9±0.8 / +2.1±0.8 (significant treatment group differences vs. historical control)
Dahlgren and Albertsson-Wikland 2005	Observational	-	SGA, broad range of GH secretory capacity	Untreated control GH 0.23	34 77	8.3±0.6 10.7±2.5	–2.2±0.5 –2.8±0.7	*Final height SDS / Gain* –2.0±0.8 –1.2±0.7 / +1.7±0.7; –1.6±0.8 / +0.9±0.7 (GH for > 2 / < 2 prepubertal yrs)
Lilly Study 0908	Single-arm	≥ 2, dis-continuous	SGA, no GHD	GH 0.47	20	9.4±0.9	–2.7±0.4	*Final height SDS / Gain:* –2.0±0.8 / +0.7±0.8
Zucchini et al. 2001	Non-randomized	3–7 (range)	SGA, GHD (treated), or SGA, no GHD (untreated)	Untreated control GH 0.24	20 29	10.7±0.6 10.9±0.4	–2.0±0.1 –2.3±0.1	*Final height SDS:* –1.9±0.2[d] –1.8±0.2[d]
Carel et al. 2003	Randomized, controlled, open-label	2.7±0.6 (mean±SD)	SGA, no GHD	Untreated control GH 0.47	33 91	12.9±1.4 12.6±1.5	–3.2±0.6 –3.2±0.6	*Final height SDS / Gain:* –2.7±0.9 / +0.5±0.8 –2.0±1.0 / +1.1±0.9 (p=0.002 for gain in height SDS)

Evaluator's comment: The sponsor had provided some additional commentary based upon two published studies supporting the contention that the proposed dose of somatropin may increase the final height. However the small number of patients enrolled in Study B9R-FP-0908 did not show the gains in height seen in the published studies (see Table 12).

Issue 2: Studies also included those patients who were GH deficient.

Patients with GH deficiency were not specifically identified in the efficacy studies. However, patients in the efficacy studies did have IGF-I and IGFBP-3 measured. It is likely that approximately 10% of patients in the efficacy studies were GH deficient and would have qualified for GH replacement under the current TGA indications.

Sponsor's response

In Study B9R-FP-0908, the inclusion criteria specified that only patients who had a normal response to GH stimulation tests were included in the study and there were no protocol violations regarding this inclusion criterion.

In Study B9R-EW-GDGB, patients with known GH deficiency or any significant signs of disproportion or underlying genetically based syndromal disease (investigator opinion) were excluded from the study. Based on the protocol, the study investigator had to confirm on the case report form that the patient was not GH deficient according to criteria of consensus guidelines of the *Growth Hormone Research Society* (2000). In 2 patients, excluded syndromal conditions were identified after the start of treatment (Turner

syndrome; suspected mitochondrial disease) but no patient with known GH deficiency was enrolled. Therefore, all patients enrolled into Studies B9R-FP-0908 and B9R-EW-GDGB had to be confirmed as non-GH deficient by the study investigator.

Study B9R-EW-GDFC aims to collect routine care information on patients with short stature for all approved indications. Based on the reported information and the described diagnosis definition structure, a patient could fall under various diagnostic spectrums, for example, SGA with GH deficiency or SGA without GH deficiency. Therefore, children with short stature born SGA and GH deficient were allowed to be included in the study.

Evaluator's comment: The evaluator accepts that Study B9R-FP-0908 excluded patients with GH deficiency. Study B9R-EW-GDGB did not exclude biochemical GH deficiency. The sponsor relied upon the exclusion of patients with syndromal and phenotypic GH deficiency on clinical grounds. The evaluator cannot confidently identify that some patients with GH deficiency were not included in this study. Therefore, there may be some patients included in the study population who had concomitant GH deficiency and would have been eligible for somatropin under current indications.

Issue 3: Ensure that those patients included in the studies were those who had severe growth retardation and who did not achieve catch-up growth by 2 to 4 years, as this is the proposed indication.

In the efficacy studies, SGA was defined as a birth weight < -2 SDS which is consistent with the literature. In Study B9R-EW-GDGB, growth failure was defined as a height of < -3 SDS by the age of 3 to 4 years, while Study B9R-FP-0908 used a definition of a height < -2 SDS by the age > 7 years.

Sponsor's response

The population studied in trial B9R-FP-0908 had been chosen according to standards at the time when the trial was started and performed. As the study was designed to evaluate the effects of treatment on final height, the age at baseline was chosen to reflect a still prepubertal status but being closer to puberty; actual ages ranged from 6.7 to10.8 years.

Study B9R-FP-0908 was designed to generate final height data and therefore needed to limit enrolment to older but still prepubertal patients to obtain final height data within a reasonable time frame. Patients enrolled in Study B9R-FP-0908 had to have a baseline height of < -2 SDS at the age of ≥ 7 to < 9 years for girls and ≥ 9 to < 11 years for boys. The actual overall mean age at baseline was 9.3 years, ranging from 6.7 to 10.8 years.

Evaluator's comment: The evaluator agrees with the sponsor's assertion that both studies (B9R-EW-GDGB and B9R-FP-0908) have enrolled patients who can be considered to have "severe growth failure" and who did not achieve catch-up growth by at least 2 to 4 years, as shown by the presence of persistent growth failure at the age of inclusion into the study. This does however mean that patients with less severe SGA, who were included not in these two studies, who are included in the Indication in the proposed PI.

Issue 4: Please discuss the primary efficacy endpoint and its relevance (height velocity in some studies and height SDS in others).

The studies used either HV or height SDS as primary outcome measures. As stated in the evaluation, it is the final height achieved that is the most important outcome, rather than intermediate heights or height growth velocity without a significant increase in final height.

Sponsor's response

Because the majority of gain in height SDS occurs during the initial treatment years and because final height can be predicted based on the first-year growth response, the first and second year changes in height SDS and/or HV SDS can be considered as appropriate primary endpoints to evaluate the efficacy of somatropin in short children born SGA.

It was agree that final height is a key outcome after somatropin treatment, to clarify if the genetic target height range has been achieved. Primary outcome data should therefore be supported by actual final height data wherever possible. Final height has been analysed for 20 children in Study B9R-FP-0908; these data illustrate that there was a clinically relevant gain in height SDS which was suboptimal due to the discontinuous treatment regimen used and the start of treatment at a more advanced age. Two years of somatropin treatment at a dosage of 0.47 mg/kg per week (with an additional 2 years of treatment in 4 of these 20 children) resulted in an increase in final height of approximately 4.2 cm; 50% of patients achieved a final height within the normal range (> -2 SDS). Following optimised treatment regimens, as many as 85% of patients may attain final height within the normal range (van Pareren *et al*., 2003). Additional final height data from the ongoing post-marketing surveillance study B9R-EW-GDFC (GeNeSIS) have been submitted as supplementary data, showing that more than 75% of patients born SGA reached a final height within the normal range (> –2 SDS) in an observational setting.

Evaluator's comment: The sponsor is arguing that the height after 1 and 2 years of treatment with somatropin are valid surrogate markers for the final height attained in children who are SGA. Data to support this assertion in the original submission are lacking. The sponsor does present some recently published data to support this, for example in Ranke et al., 2010. However the Ranke study did include children with Silver-Russell syndrome. The evaluator accepts that HV or height SDS after 1 to 2 years of treatment with somatropin, for children with SGA, may be appropriate endpoints where final height data are lacking.

Issue 5: Please ensure that the efficacy analysis is provided on the intention-to-treat (ITT) population.

The important primary outcome measures, including final height were not presented for an ITT analysis.

Sponsor's response

Study B9R-FP-0908 was a non-comparative study and height analyses included all entered patients with an available final height measurement. Thus, this population can be considered as close as possible to following the ITT principle in this kind of study design, without introducing any bias.

In Study B9R-EW-GDGB, the Full Analysis Set included all randomised subjects receiving at least 1 dose of study drug. Subjects were therefore analysed according to the treatment design they were assigned to (= ITT population, see Gillings and Koch, 1991). One patient with an unintended assignment error that had occurred at random and had no impact on clinical outcome was allowed to be analysed according to the dose the patient actually received (Gillings and Koch 1991). In order to avoid extreme growth data extrapolation while evaluating the robustness of the primary efficacy analysis, the restricted Full Analysis Set was used.

Evaluator's comment: The sponsor has not performed a true ITT analysis. However, the Full Analysis Set is sufficiently close to an ITT set that it is unlikely that ITT analyses of these studies would have changed the conclusions of the evaluation.

Issue 6: There are some final height data - please comment on these figures (for example, how do they compare to what is considered "normal" height"; are there enough subjects included; comment on the variance around the mean values, and so on).

The evaluator considered that the final height data are inadequate and that the presented data show an insufficient increase in height.

Sponsor's response

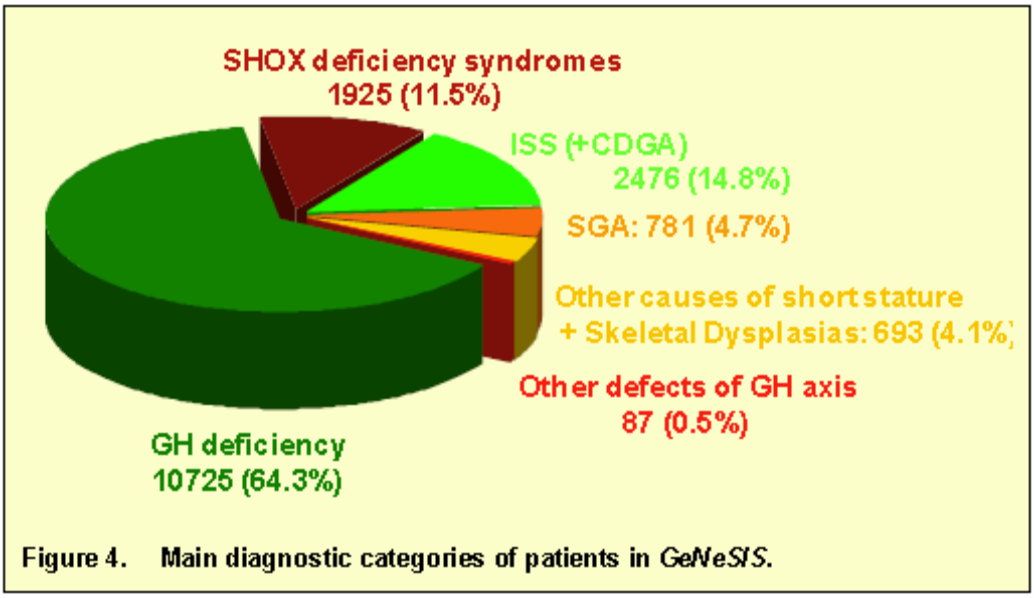
Study B9R-FP-0908; the sponsor agreed that the number of patients with final height data for Humatrope within a clinical trial setting is small. Additional final height data are now available for patients from Lilly Study B9R-EW-GDFC (GeNeSIS), which have been added as supplementary data. The sponsor also presented data from other manufacturers of somatropin and claim that these data are now sufficient to demonstrate that somatropin reduced the final height deficit when compared to non-treated controls:

- Final height data from 20 patients after discontinuous treatment with Humatrope in Study B9R-FP-0908 [reported in the original clinical evaluation report];
- Final height data from 110 children (70 non-GH deficient) after treatment with Humatrope based on supplementary data from Study B9R-EW-GDFC [described below];
- Published meta-analysis of 4 randomised studies, including data from 270 patients treated with somatropin at doses of 0.033–0.067 mg/kg per day, revealing a significant gain in height SDS at final height when compared to untreated controls (Maiorana and Cianfarani, 2009);
- Meta-analysis of 56 patients treated with somatropin, showing a gain in height SDS at final height in both treatment groups (0.033 mg/kg per day and 0.067 mg/kg per day), considered sufficient final height information for approval of somatropin in short children born SGA by regulatory authorities in Europe (CPMP 2003a, CPMP 2003b);
- Final height gain reported for a group of 28 patients (0.033 mg/kg per day) and 26 patients (0.067 mg/kg per day) treated with somatropin (van Pareren *et al.*, 2003; a subgroup of these patients included in the meta-analyses above);
- Final height data from patients starting somatropin treatment close to or during early pubertal development (Carel *et al.*, 2003; patients included in meta-analysis by Maiorana and Cianfarani 2009).
- Final height data for 126 patients from other published studies vs. untreated controls (Coutant *et al.*, 1998, De Zegher i, 2000, Zucchini *et al.*, 2001).
- Final height data for 264 patients from published uncontrolled studies (Albanese *et al.*,1998, Bannink *et al.*, 2010, De Ridder *et al.*, 2008, Dunger 2007, Fjellestad-Paulsen *et al.*, 2004, Ranke and Lindberg 1996).

Study B9R-EW-GDFC

Study B9R-EW-GDFC (*"GeNeSIS - An Interim Analysis of the Safety of Humatrope Treatment in Pediatric Patients Born Small for Gestational Age"*). This is a Phase IV post marketing observational study based upon data from 17,191 patients from 765 sites in 30 countries. The study has been ongoing since 1999. The updated report is an interim analysis at February 2010. Of these 781 (4.7%) were treated for SGA (see Figure 5).

Figure 5. Diagnostic categories for Study B9R-EW-GDFC.



Unfortunately the update did not address the SGA patients in detail. However, a summary of final height data for patients treated for SGA was provided (Table 13).

Table 13. Final height data for Study B9R-EW-GDFC.

Parameter	GHD				SGA All				SGA, Non-GHD			
	N	Mean ± SD	Median Q1, Q3	95% CI for mean	N	Mean ± SD	Median Q1, Q3	95% CI	N	Mean ± SD	Median Q1, Q3	95% CI for mean
Baseline age	1873	11.35±3.43	11.99 (9.48, 13.81)	11.20; 11.51	110	11.05±3.19	11.67 (9.51, 13.23)	10.45; 11.66	70	11.00±3.17	11.67 (9.11, 13.41)	10.24; 11,75
Baseline height SDS	1873	–2.38±1.09	–2.36 (–2.86, –1.81)	–2.43; –2.33	110	–2.66±0.99	–2.50 (–3.14, –2.08)	–2.85; –2.48	70	–2.76±1.15	–2.65 (–3.18, –1.98)	–3.04; –2.49
Target height SDS	1709	–0.44±0.90	–0.44 –1.03, 0.14)	–0.49; –0.40	102	–0.69±0.89	–0.62 (–1.34, –0.10)	–0.86; –0.51	65	–0.70±0.88	–0.64 (–1.18, –0.10)	–0.91; –0.48
Height SDS – target height SDS	1709	–1.95±1.19	–1.86 (–2.61, –1.19)	–2.01; –1.89	102	–1.95±1.21	–1.93 (–2.56,–1.17)	–2.18; –1.71	65	–2.04±1.30	–1.93 (–2.79, –1.22)	–2.36; –1.72
Somatropin dose (mg/kg/wk)	1820	0.24±0.11	0.22 (0.18, 0.29)	0.24; 0.25	106	0.28±0.09	0.26 (0.23, 0.34)	0.26; 0.30	66	0.31±0.09	0.31 (0.24, 0.35)	0.28; 0.33
Years on therapy	1839	5.28±3.31	4.39 (3.02, 6.87)	5.13; 5.43	109	4.68±3.06	3.79 (2.59, 5.57)	4.09; 5.26	69	4.78±3.11	3.80 (2.56, 6.37)	4.03; 5.53
Age at final height	1873	16.75±1.79	16.73 (15.55, 17.79)	16.67; 16.84	110	15.95±1.46	15.95 (14.83,17.08)	15.67; 16.22	70	15.94±1.50	15.92 (14.83, 17.12)	15.58; 16.30
Final height SDS	1873	–1.02±1.19	–0.99 (–1.65, –0.32)	–1.07; –0.97	110	–1.52±0.75	–1.51 (–1.93,–1.06)	–1.66; –1.38	70	–1.62± 0.71	–1.54 (–2.04, –1.10)	–1.79; –1.45
Final height SDS – baseline height SDS	1870	1.37±1.15	1.32 (0.66, 2.01)	1.32; 1.43	110	1.14±1.04	1.14 (0.44,1.72)	0.94; 1.33	70	1.15±1.14	1.18 (0.32, 1.73)	0.88; 1.42
Final height SDS – target height SDS	1709	–0.57±1.14	–0.45 (–1.14, 0.14)	–0.62; –0.51	102	–0.83±0.87	–0.73 (–1.35,–0.25)	–1.00; –0.66	65	–0.91±0.92	–0.82 (–1.35, –0.28)	–1.14; –0.68

Source: 2011 SGA Efficacy Analysis; Section 5.3.5.2.1.5; Tables 4.13.4.3, 4.13.4.7a and 4.13.4.7b
Abbreviations: CI = confidence interval; GH = growth hormone; GHD = growth hormone deficient; N = number of patients; Q1, Q3 = 25% and 75% quartiles; SDS = standard deviation score; SGA = small for gestational age.
Note: Data are for Patient Population 4, including all patients treated (either naïve or already pretreated with GH at baseline) who were evaluable for efficacy and attained final height.

Discontinuations

The summary indicates that a significant number of SGA patients have discontinued from the study: 26.8% discontinued as they had reached their final height; of the other discontinuations, 21.2% were due to parental reasons and 12% were due to sponsor reasons. The other reasons for discontinuation are shown in Table 14.

Table 14. GeNeSIS Discontinuations. Percentage (% of N) of all causes of discontinuation by diagnostic category.

	All (N= 16741)	GHD (10538)	ISS (2457)	SGA (763)	SHOX-D (248)	TS (1500)	Other (839)
Final height attained	23.7	22.4	27.1	26.8	34.0	33.3	21.9
Patient/parent decision	17.6	14.2	17.7	21.2	19.1	15.9	16.4
Sponsor decision[1]	15.6	19.5	0.9	12.7	4.9	10.9	7.3
Unable to contact patient	11.8	11.1	21.9	11.0	6.6	6.3	11.9
Other	11.4	11.5	10.8	8.3	9.8	10.9	14.2
Physician decision	8.2	8.2	4.8	11.8	14.8	8.7	11.5
Patient moved	5.2	5.1	4.5	7.5	3.3	6.3	4.5
Third party required patient to change brand of somatropin	4.8	3.7	8.4	3.1	6.6	6.6	7.6
Patient has received another somatropin brand for >1 year[3]	0.6	0.4	1.3	0	1.6	0.3	2.1
Patient transferred to *HypoCCS*	0.5	0.7	0.1	0	0	0	0.3
Death[2]	0.4	0.4	0	0.4	0	0.2	1.5
Adverse event	0.2	0.3	0	0.4	0	0	0.6

[1] The high number of discontinuations due to sponsor decision is largely due to completion of an earlier study protocol in Japan. A new Japanese *GeNeSIS* protocol is now ongoing.
[2] See Section 10.5.
[3] Patients who changed somatropin brand were previously allowed to remain in the study for 1 year before discontinuation. However, protocol amendment (b) permits those who switch GH brand to remain in the study indefinitely.

Sponsors approach to the variability of growth response to somatropin

In Lilly Study B9R-FP-0908, the response to somatropin in terms of final height was highly variable, with individual final height values ranging between -0.4 and -3.2 SDS. Large inter-individual variability in final height has also been noted in the meta-analysis by Maiorana and Cianfarani (2009). Growth response to somatropin, both short- and long-term, is well known to be highly variable because multiple factors are involved (Jung *et al.,* 2008). Children born SGA are a heterogeneous group with regard to etiology and metabolic and endocrine status considerably varies between subjects. These factors are known to influence the growth pattern, although the specific mechanisms by which they affect the response to treatment are difficult to identify and under ongoing discussion (Jung *et al.,* 2008). Nevertheless, there is a need to identify as early as possible after start of somatropin treatment, which children can be expected to achieve a final height within the normal range > –2 SDS. It has been broadly reported that the first year treatment response to somatropin is strongly predictive for the responses in subsequent years of continuous somatropin treatment up to final height (Kriström *et al.,* 2009, de Zegher *et al.,* 2000).

Evaluator's comment: The sponsor has presented further data from Study B9R-EW-GDFC in support of an improvement in final height in children treated for short stature secondary to SGA.

Issue 7: Are there any "quality of life" (QoL) measures factored into claiming efficacy?

This is important as most of the children are treated for cosmetic reasons only. No quality of life data were presented in the dossier.

Sponsor's response

In children, QoL is difficult to evaluate in particular as specific measures need to address the developmental stage of different age groups. Because adult measures may fail to address the specific aspects of QoL that are important to the child, many different tools, both generic and disease-specific, have been developed to assess QoL in children; however, their quality in terms of psychometric properties often seems questionable (Trama and Dieci 2011). QoL evaluations have therefore not been included in any of the 3

submitted Lilly studies on Humatrope in children born SGA. After review of the literature, they conclude that, although solid data on the potential impact of somatropin treatment on patient QoL are still scarce and QoL in children is difficult to assess, there seem to be some evidence suggesting that children with short stature born SGA who received long-term somatropin treatment may experience relevant improvement in QoL and related psychosocial parameters either compared to baseline and/or compared to their peers.

Evaluator's comment: There are no QoL data to support the registration of Humatrope for use in children with SGA. As part of any ongoing use of somatropin for the treatment of SGA, the sponsor should address QoL as an important outcome measure. This is especially important as the primary aim of therapy is aesthetic rather than medical.

Issue 8: Is the minimum effective dose defined?

No dose escalation studies were included and the minimum effective dose was not defined in the dossier. The study doses chosen (0.035-0.067 mg/kg per day in Study B9R-EW GDGB and averaged 0.07 mg/kg per day in Study B9R-FP-0908) were higher than those currently recommended in the Australian PI for use in children who are GH deficient (0.177-0.255 mg/kg per week) or have Turner syndrome (0.3 mg/kg per week).

Sponsor's response

The Humatrope doses chosen for Studies B9R-FP-0908 and B9R-EW–GDGB were based on somatropin doses used in previous publications. Taken together, the results from published studies, the efficacy results from Studies B9R-FP-0908 and B9R-EW–GDGB, and the safety data presented in this application, provide data supporting the approval of Humatrope at a dose range from 0.033 up to 0.067 mg/kg per day (corresponding to 0.47 mg/kg per week) for children with short stature born SGA. The key efficacy results supporting this dose recommendation are summarised in the application. More recent published data have demonstrated that optimal final height gains were obtained using somatropin doses of 0.47-0.49 mg/kg per week, corresponding to 0.067 mg/kg per day (de Zegher *et al.,* 2000, van Pareren *et al.,* 2003, Fjellestad-Paulsen *et al.,* 2004, Dahlgren and Wikland 2005). However, as Study B9R-EW–GDGB shows, it may be sufficient for some patients to start on a lower dose of 0.035 mg/kg per day, for example in patients who start treatment at younger ages, without a clinically relevant loss in growth response. Finally, the proposed dose range for Humatrope is in line with current SGA consensus guidelines (Clayton *et al.,* 2007), which recommend that the somatropin starting dose should cover the range of 0.035-0.07 mg/kg per day, with higher doses used in children with more pronounced growth retardation.

Evaluator's comment: There are limited data to support the contention that the proposed dose is optimal. It could be that a lesser dose than recommended could result in an adequate increase in growth. Furthermore, the higher dose may result in increased AEs.

Issue 9: Most studies have included a relatively small number of children. Is this adequate to establish safety, especially safety of long term use? In your report please give a breakdown on the subjects by duration of treatment.

The efficacy studies are too small and, in the main, too short to establish long term safety with only 20 patients in Study B9R-FP-0908 being followed to final height. The safety Study B9R-EW-GDFC does include 340 evaluable patients and has been ongoing since 1990. However, the quality of these data is questionable. There were no long-term follow-up post maturity data; important long-term outcomes including the risks of diabetes, cardiovascular disease and neoplasia cannot be assessed. The data were not presented in a fashion that allowed the evaluator to determine whether there were significant trends in AEs as exposure to Humatrope increased. The sponsor was asked to reanalyse the data to clarify this.

Sponsors response

Safety data from Lilly Study B9R-EW–GDGB broken down by first and second year of treatment and the more recent safety data from Study B9R-EW-GDFC provided as supplementary data have not changed the current overall safety profile of Humatrope. Longer term safety data for patients treated with Humatrope up to final height are available for the 20 patients from Study B9R-FP-0908. These data are additionally supported by published long-term safety data on several hundred patients who have received longer term somatropin treatment and have been followed up to final height and in 1 study up to 6.5 years after discontinuation of childhood somatropin treatment (van Dijk *et al.,* 2007). The specific aspects of somatropin treatment in children born SGA, such as glucose metabolism and cardiovascular risk profiles, have been addressed through the published trials reported here. As only one study evaluated previously somatropin-treated children born SGA at a mean of 6.5 years after treatment discontinuation in early adulthood, the retrospective study on SAGhE has been initiated. The analysis of a subgroup of patients with idiopathic GH deficiency, idiopathic short stature (ISS) and short stature after being born SGA from France has suggested an increased risk of mortality after childhood somatropin treatment in particular if higher doses were used. While data from Study B9R-EW-GDFC have been requested and provided to support this European study, at the present time neither Study B9R-EW-GDFC nor another Lilly safety surveillance study "*B9R-MC-GDGA: Hypopituitary Control and Complications Study, HypoCCS*" can provide data addressing this hypothesis directly.

However, data analyses from both studies overall and in Study GDGA on an adult population with childhood onset GH deficiency provided information that mortality during somatropin treatment or GH replacement was well in line with the respective reference population.

In summary, the sponsor agreed that additional long-term follow-up safety data following somatropin treatment are needed for all indications but the current data available are sufficient to warrant the use of somatropin in short children born SGA.

Evaluator's comment: The sponsor has limited data on the long term outcome use of somatropin in children. A registration of Humatrope for the treatment of children with SGA should be contingent upon the ongoing evaluation and reporting of outcomes in this population.

Issue 10: The Phase IV study is a post-market study that has data on safety only. Please comment on the quality of the safety data.

The data in this study was of poor quality and there were many breaches of GCP described in the study report. The poor quality of the data is further emphasised by the need to exclude large amounts of "impossible" data. Based on the data presented, it is unlikely that the study would be found GCP compliant. It may well be that the study under-reports the rate and types of AEs.

Sponsor's response

Study B9R-EW-GDFC, as an ongoing multinational, multicenter, open-label non-interventional observational study, is conducted based on local laws and regulations. It has been accepted as the basis for reports to authorities fulfilling regulatory commitments and more than 10 peer-reviewed publications have been generated from this study to date. Following the primary objective, that is to evaluate safety and effectiveness of Humatrope treatment, the annual B9R-EW-GDFC interim analyses provide safety as well as effectiveness data for all patients and specific diagnostic subgroups, such as patients with short stature born SGA. The short to midterm efficacy data after 4 years of Humatrope treatment have shown that more than 75% of patients born SGA regardless of their GH-secretion status reach a height SDS within the normal range. The more recent

safety analysis for the group of patients born SGA treated with Humatrope (B9R-EW-GDFC 2009 SGA Report) has not changed the overall safety profile of Humatrope for this subgroup of patients.

Evaluator's comment: The evaluator accepts that this is a post marketing study and the rigor to which it is conducted may be less stringent than an earlier phase study. However, the sponsor should more fully address the apparent large number of "impossible data" and how this will be minimised in any ongoing safety studies.

Issue 11: In the context of safety, please mention the data (or lack thereof) on IGF-I monitoring, precocious puberty, bone age/chronological age, and glucose intolerance.

Of specific note, glucose tolerance and insulin resistance were not assessed. Also, hypothyroidism was reported inconsistently and the sponsor should clarify the rate and severity of hypothyroidism in the submitted studies.

Sponsor's response

Based on the known safety considerations for somatropin treatment, all Lilly studies presented data addressing glucose metabolism, growth factors (IGF-I and IGFBP-3), thyroid function, pubertal development as well as bone age in line with standard recommendations of care in such a paediatric population. Studies B9R-EW–GDGB and B9R-EW-GDFC specifically focused on enhancing the reporting of AEs known to be associated with somatropin treatment by proactively questioning for the occurrence of specific medical conditions. The data presented are in line with published information and confirm the consensus for monitoring patients born SGA, in particular patients at risk for evidence of disturbances in glucose metabolism, thyroid function, imbalances in growth factors and maturational development. In relation to these safety topics, previous and additional information presented here did not reveal new safety concerns in such a population of children born SGA. Therefore, the data support the currently established safety profile for Humatrope treatment in paediatric patients in general.

Glucose metabolism and risk of diabetes

The sponsor has included extra evidence about impaired glucose tolerance and the development of diabetes.

In Study B9R-EW-GDGB, after one and two years of treatment, there was evidence of impaired glucose tolerance in up to 9.5% of treated patients at 1 year (IAD group) and 4.4% at 2 years (FHD group). No patients in this study had developed diabetes at 2 years (see Table 15).

Table 15. Study B9R-EW-GDGB oral glucose tolerance testing results. Safety Analysis Set, second year analysis (N = 175).

		Number (%) of Patients	
		FHD Group (N=91)	IAD Group (N=84)
After first year	IGT or IFG	6 (6.6)	8 (9.5)
	Diabetes mellitus	0	0
	Missing data	7 (7.7)	5 (6.0)
After second year	IGT or IFG	4 (4.4)	1 (1.2)
	Diabetes mellitus	0	0
	Missing data	14 (15.4)	6 (7.1)
IGT or IFG both after first and second year		1 (1.1)	0

Abbreviations: IGT = impaired glucose tolerance; IFG = impaired fasting glucose; OGTT = oral glucose tolerance test.

In Study B9R-EW-GDFC, 1 case of diabetes among 340 patients born SGA was reported in the abbreviated CSR as of 2007. According to the more recent safety data for n=540 patients reported in the 2009 SGA Report including data up to September 2008 (B9R-EW GDFC 2009 SGA Report), 3 cases of diabetes (two Type 2 diabetes, one unspecified) were confirmed for patients born SGA.

Sponsors summary regarding diabetes

The sponsor concludes that submitted data for Humatrope, based on results from Lilly Studies B9R-EW–GDGB and B9R-EW-GDFC, are well in line with published data on the risk of insulin resistance and diabetes. However, all children born SGA who are treated with somatropin should be monitored for evidence of glucose intolerance or insulin insensitivity (Clayton *et al.,* 2007).

IGF-I and IGFBP-3 Levels

All 3 Lilly studies included measurements for IGF-I and/or for IGFBP-3, and summaries are included in the original evaluation. The sponsor has now submitted supplementary data in the B9R-EW-GDFC 2009 SGA Report. Of the 340 patients treated, 108 patients had at least 1 follow-up IGF-I SDS value available. Of those, 29 (26.9%) patients had 1 IGF-I value of > +2 SDS at any follow-up visit. Of the 70 patients with at least 2 follow-up IGF-I SDS values available, none had an IGF-I level of > +2 SDS more than once.

Hypothyroidism

The sponsor has clarified the thyroid function data.

Study B9R-FP-0908: This study did not report significant changes in thyroid function. Two patients (5.7%) had hypothyroidism reported as an AE.

Study B9R-EW-GDGB: During the first treatment year, 4 notable patients overall experienced increases in thyroid stimulating hormone (TSH) values and/or decreases in total thyroxine (T4) values that were rated as significantly above/below normal. During the second year, 4 additional patients had hypothyroidism or increased TSH values reported; one of them was a patient who had already had isolated increased TSH values in the first year. Thus overall for Study B9R-EW–GDGB during the first and second treatment year, 6 of 175 patients (3.4%) had AEs related to potential thyroid dysfunction.

Study B9R-EW-GDFC: In this study, primary hypothyroidism or secondary hypothyroidism was reported in 14 of 340 patients (4%) overall for the abbreviated interim report on patients born SGA as of 2007. This included 11 patients (2.8%) with a MedDRA coded preferred term of “hypothyroidism”, plus 3 additional patients with preferred terms of “primary hypothyroidism” or “secondary hypothyroidism”.

According to the more recent safety data for n=540 patients reported in the 2009 SGA Report, submitted as supplementary data, there are now 19 of 540 patients overall (3.5%) with hypothyroidism reported.

Precocious puberty

The sponsor clarified that the onset of pubertal development was within the normal time range and there were no cases of precocious puberty.

Bone age and chronological age

In Studies B9R-FP-0908 and B9R-EW-GDGB, the initial bone age retardation decreased over time during somatropin treatment. In Study B9R-FP-0908, children approached a bone age consistent with the chronological age while progressing through puberty and patients reaching final height displayed an adequate bone age. In Study B9R-EW-GDGB, bone age was only followed for 2 years. A summary of the results related to bone age for Study B9R-FP-0908 are presented in Table 16 and for Study B9R-EW-GDGB in Table 17.

Table 16. Study B9R-FP-0908: Bone age retardation over chronological age and time.

		Mean age/retardation (SD), years		
Years of treatment	N	Chronological age	Bone age	Bone age retardation
Baseline	31	9.3 (0.8)	7.7 (1.3)	1.7 (1.1)
2 years	32	11.5 (0.9)	10.0 (1.5)	1.6 (1.3)
3 years	20	12.5 (1.0)	11.6 (1.3)	0.9 (0.9)
4 years	17	13.4 (1.0)	12.5 (1.6)	0.9 (1.2)
5 years	19	14.4 (1.1)	13.6 (1.2)	0.8 (0.8)
6 years	17	15.4 (1.1)	14.9 (1.4)	0.5 (1.0)
7 years	10	16.1 (0.9)	15.4 (1.9)	0.8 (1.6)
8 years	11	17.2 (1.0)	17.1 (0.9)	0.1 (1.0)

Abbreviations: SD = standard deviation.
Bone age retardation calculated as follows: chronological age – bone age.

Table 17. Study B9R-EW-GDGB: Bone age retardation over chronological age and time.

		Mean age/retardation (SD), years		
Years of treatment	N	Chronological age	Bone age	Relative bone age retardation
FHD group				
Baseline	99	6.7 (2.4)	4.6 (2.4)	–0.33 (0.18)
1 year	91		6.2 (2.3)	–0.21 (0.15)
2 years	82		3.0 (0.9)	–0.13 (0.13)
IAD group				
Baseline	84	6.8 (2.5)	4.8 (2.2)	–0.29 (0.18)
1 year	80		6.3 (2.5)	–0.20 (0.16)
2 year	74		7.7 (2.6)	–0.14 (0.14)

Abbreviations: SD = standard deviation.
Relative bone age retardation calculated as follows: actual bone age minus chronological bone age, divided by chronological age.

Evaluator's comment: The sponsor has clarified the safety issues raised in the initial evaluation. The extra data provided since the original submission have clarified all points of concern, to the evaluator, in this question.

Conclusions and recommendations

The sponsor has adequately addressed some of the issues raised by the evaluator in the initial clinical evaluation report. However, the sponsor has been unable to adequately answer the following issues:

Issue 7

The sponsor has not demonstrated an improvement in quality of life in children with SGA treated with somatropin. There are no QoL data to support the registration of Humatrope for use in children with SGA. As part of any ongoing use of somatropin for the treatment of SGA, the sponsor should address QoL as an important outcome measure. This is especially important as the primary aim of therapy is aesthetic rather than medical.

Issue 8

The sponsor has failed to define the minimum effective dose. There are limited data to support the contention that the proposed dose is optimal. It could be that a lesser dose

than recommended could result in an adequate increase in growth. Furthermore, the higher dose may result in increased AEs.

Issue 9

The sponsor has supplied limited data on the long term outcome with somatropin in children. A registration of Humatrope for the treatment of children with SGA should be contingent upon the ongoing evaluation and reporting of outcomes in this population.

Issue 10

The evaluator accepts that this is a post marketing study and the rigor to which it is conducted may be less stringent than an earlier phase study. However, the sponsor should more fully address the apparent large number of "impossible data" and how this will be minimised in any ongoing safety studies.

Final recommendation

The evaluator, on balance, supports the registration of Humatrope for the treatment of growth failure in SGA subject to the following caveats:

- The sponsor support ongoing post marketing studies to investigate the final height, QoL and safety outcomes and report these results at regular intervals.
- Given the contention of the sponsor that growth at 2 years predicts final height (for which there is some support), ongoing treatment with Humatrope should be subject to adequate growth acceleration for the first 2 years of treatment; such that a particular patient's height is then within the "normal" height range for their age (> -2 SD).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR). Table 18 below shows a summary of the Ongoing Safety Concerns identified by the sponsor.

Table 18. Ongoing Safety Concerns

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks: BIH, Insulin resistance and impaired glucose tolerance (also in adults), Hypothyroidism in patients with hypopituitarism, SCFE, Edema/Peripheral edema, Arthralgia (also in adults), Myalgia, Carpal tunnel syndrome (only in adults), Paresthesias (only in adults), Second neoplasms in survivors of childhood cancer	Routine pharmacovigilance activities; Targeted surveillance terms activities; Surveillance activities	Routine risk minimization. Important identified risks were included in the PI as ADRs (Contraindication, and Special Warning, Special Precautions for Use, and Undesirable Effects sections).
Identified Potential Risks: Diabetes mellitus type 2 and Neoplasia	Routine pharmacovigilance activities; Targeted surveillance terms activities; Surveillance activities; Special Topics of Interest for Humatrope	Routine risk minimization. Identified potential risks were included in the PI (Contraindications [active neoplasm], and Special Precautions for Use, and Undesirable Effects [diabetes type 2] sections).

This was accepted.

Summary of recommendations

The evaluator considered that a RMP was not required unless a specific issue is identified by the Delegate.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Initial clinical data

Efficacy

Children born SGA, as defined by birth weight below the tenth percentile and/or birth length shorter than 2 SD below the mean for gestational age, based on local standards were eligible for inclusion in the clinical studies.

Study B9R-EW-GDGB was a Phase III, multicentre, open label study in children ≥ 3 years old with growth failure secondary to SGA; it was a 2 year study. There were two treatment arms: one was a FHD of 0.67 mg/kg/day; the other was an IAD based on the response to a lower dose of 0.035 mg/kg/day and increasing to 0.67 mg/kg/day if the patient failed to respond. It was designed as a non-inferiority study of the two dosing regimens. The primary outcome measures were SDS, change in height SDS and HV at 12 and 24 months. The inclusion criteria included SGA, height <-3 SDS; age > 3 years; bone age < 9 years for girls and < 10 years for boys. The baseline characteristics are shown in Table 19.

Table 19. Baseline characteristics (Full Analysis Set, first year (N=193).

	FHD Group (N=99)	IAD Group (N=94)
Age (male / female) (years)	6.7 ± 2.5 / 6.7 ± 2.3	6.9 ± 2.5 / 6.8 ± 2.5
Male /female (%)	55.6 / 44.4	50.0 / 50.0
Gestational age (weeks)	36.8 ± 4.0	37.4 ± 3.0
Birth weight SDS	-2.11 ± 0.90	-2.17 ± 0.73
Birth length SDS	-2.81 ± 1.27	-2.79± 1.22
Standing height (cm)	103.5 ± 12.4	103.9 ± 12.3
Height SDS	-3.89 ± 0.64	-3.91 ± 0.67
HV (cm/year)	5.3 ± 1.6	5.3 ± 1.8
HV SDS	-1.45 ± 1.91	-1.47 ± 2.25
Height SDS – target height SDS	-2.17 ± 1.18	-2.17 ± 1.23
Absolute bone age delay (years)	-2.1 ± 1.1	-1.9 ± 1.2

Abbreviations: FHD = fixed high dose of Humatrope; HV = height velocity; IAD = individually adjusted dose of Humatrope; N = number of patients with data available; SDS = standard deviation score.
Note: Data for continuous variables are presented as mean ± standard deviation.

The evaluator states that 193 patients were enrolled with 184 included in the "restricted full analysis set";169 were included in the "per protocol" analysis at 12 months and 150 patients at 24 months. The primary outcome measures are given in Tables 20 and 21.

Table 20. Summary of growth response after 12 months. Per Protocol population, first year (N=169).

	Baseline		Month 12		Change from Baseline	
	FHD Group (N=89)	IAD Group (N=80)	FHD Group (N=89)	IAD Group (N=80)	FHD Group (N=89)	IAD Group (N=80)
Ht (cm)	104.2 ± 12.3	103.8 ± 12.5	114.6 ± 11.8	113.2 ± 12.5	+10.4 ± 1.9	+9.4 ± 1.5
Ht SDS	-3.88 ± 0.54	-3.84 ± 0.62	-2.75 ± 0.65	-2.95 ± 0.68	+1.13 ±0.40	+0.89 ±0.34
HV (cm/year)	5.2 ± 1.5	5.4 ± 1.9	10.3 ± 1.9	9.3 ± 1.5	+5.2 ± 2.4	+3.9 ± 2.7
Ht SDS – target Ht SDS	-2.15 ± 1.15	-2.12 ± 1.11	-1.03 ± 1.15	-1.24 ± 1.11	+1.12 ±0.39	+0.89 ±0.35

Abbreviations: FHD = fixed high dose of Humatrope; Ht = height; HV = height velocity; IAD = individually adjusted dose of Humatrope; N = number of patients with data available; SDS = standard deviation score.

Note: Data are presented as mean ± standard deviation.

Table 21. Growth response after 24 months. Per Protocol population, second year (N=150).

	Baseline		Month 12		Month 24	
	FHD Group (N=78)	IAD Group (N=72)	FHD Group (N=78)	IAD Group (N=72)	FHD Group (N=78)	IAD Group (N=72)
Ht (cm)	103.5±12.2	104.7±12.8	113.8±11.6	114.1±12.7	121.8±11.5	122.0±13.1
Ht SDS	-3.90±0.55	-3.82±0.61	-2.77±0.66	-2.91±0.67	-2.22±0.74	-2.39±0.80
HV (cm/year)	5.1±1.4	5.2±1.5	10.3±1.9	9.3±1.5	7.9±1.3[a]	7.7±1.5[a]
Ht SDS – target Ht SDS	-2.12 ± 1.19	-2.06 ± 1.06	-1.01 ± 1.17	-1.16 ± 1.07	-0.46±1.16	-0.63±1.12

a HV Month 24 = HV during second year of treatment

Abbreviations: FHD = fixed high dose of Humatrope; Ht = height; HV = height velocity; IAD = individually adjusted dose of Humatrope; N = number of patients with data available; SDS = standard deviation score.

Note: Data are presented as mean ± standard deviation.

The evaluator mentions that "the increase in HV was higher than expected from historical data and Australian child HV standards". This study, however, showed non-inferiority of two dose regimens only. Since there was no control group, no further conclusions can be drawn.

Study **B9R-FP-0908** was a Phase III open label single arm multicentre study of Humatrope in children > 7 years with growth failure secondary to SGA. This study involved the administration of Humatrope for two years with a 7 year follow up to assess whether final height was achieved. There were two treatment periods in this study. In treatment Period I, 35 subjects received two years of Humatrope treatment; 29 subjects completed a further off-treatment follow up. In Period II, subjects could restart Humatrope treatment or continue without treatment. Four subjects who had repeat Humatrope and 16 subjects who did not have repeat Humatrope in this period reached final height. The primary outcome measures are given in Table 22.

Table 22. Primary outcome measures, Study B9R-FP-0908.

	Treatment Not Resumed	Treatment Resumed	Total
Chronological age at baseline (years)	9.4 ± 0.7 (16)	9.5 ± 1.5 (4)	9.4 ± 0.9 (20)
Height at baseline (SDS)	-2.7 ± 0.4 (16)	-2.6 ± 0.5 (4)	-2.7 ± 0.4 (20)
Height SDS--Period I at end of 2 Years (Treatment)	-1.4 ± 0.5 (16)	-1.4 ± 0.4 (4)	-1.4 ± 0.5 (20)
Height SDS--Period I at end of 4 Years (2 Years Off Treatment)	-1.5 ± 0.6 (13)	-1.8 ± 0.6 (4)	-1.6 ± 0.6 (17)
Target height (SDS)	-1.4 ± 1.0 (15)	-1.2 ± 0.3 (4)	-1.4 ± 0.9 (19)
Period II			
Bone age at Year 5	13.8 ± 0.7 (17)	12.3 ± 3.9 (2)	13.6 ± 1.3 (19)
Height SDS	-1.5 ± 0.6 (13)	-1.8 ± 0.6 (4)	-1.6 ± 0.6 (17)
Target height (SDS)	-1.4 ± 1.0 (15)	-1.2 ± 0.3 (4)	-1.4 ± 0.9 (19)
Final height (SDS)	-2.0 ± 0.7 (16)	-1.9 ± 1.1 (4)	-2.0 ± 0.8 (20)
Target – Baseline height	1.2 ± 1.2 (15)	1.5 ± 0.4 (4)	1.3 ± 1.1 (19)
Final height – Baseline height	0.7 ± 0.6 (16)	0.7 ± 1.5 (4)	0.7 ± 0.8 (20)
Final height – Target height	-0.6 ± 1.2 (15)	-0.7 ± 1.1 (4)	-0.6 ± 1.2 (19)
Age at final height (years)	17.4 ± 1.4 (16)	16.5 ± 1.0 (4)	17.3 ± 1.3 (20)

Abbreviations: n = number of patients; SD = standard deviation; SDS = standard deviation score.

The points to note are:

Height SDS: The final height SDS was -2.0 ± 0.8, whilst the baseline height SDS was -2.7 ± 0.4. The final height SDS was based on 20 subjects. The estimated gain in final height for males was -0.88 cm ± 5.3 and for girls was 5.4 cm ± 6.5. The evaluator mentions, *"the sponsor claims that, for boys, the increase was less favourable because the method used for final height predictions tends to over predict final height in boys compared with girls"*.

Height velocity results reflected the above changes.

Overall this was a small study where 2 years treatment with Humatrope showed "*significant increase in growth velocity and the height SD*". Some of this was maintained off treatment and whether restarting treatment was beneficial was difficult to assess as the study was small.

Overall efficacy conclusions

The evaluator discussed the deficiencies in the efficacy data. In essence, no study is submitted to support continuous use of Humatrope till final height is achieved as recommended in the draft PI.

Safety

The evaluator mentions the safety data from the two efficacy studies and the third Phase IV safety study. Overall subject inclusion was 568.

B9R-EW-GDFC was a Phase IV post marketing observational study in those enrolled with SGA. The evaluator mentions that this study was of poor quality and the *"reliability of the data is questionable"*.

Of note:

There was one report of non-insulin dependent diabetes in a 10 year old girl, another report of Carpal tunnel syndrome and a third report of scoliosis requiring surgery. There were six reports of precocious puberty.

There were five cases of scoliosis and one case of slipped upper femoral epiphysis. There were also 6 cases of precocious puberty.

The evaluator also discusses SAEs from published data. There were three cases of malignancies: 1. Suprahypothalamic dysgerminoma 2. Osteogenic sarcoma, and 3. acute myeloblastic leukemia. The duration of treatment was unreported in one case and ranged from 2-4.7 years in the others.

The evaluator mentions that overall the safety data are consistent with the AE profile of Humatrope.

Initial recommendation by evaluator

The evaluator mentions that the deficiencies are that there were no controlled studies with placebo or an untreated comparator group. There were no good quality final height data. The safety study was *"poorly conducted with many errors in data".*

Overall, the deficiencies needed to be addressed with good quality final height data and safety information. Based on the information submitted, the evaluator recommended rejection.

Supplementary clinical data

The sponsor subsequently submitted supplementary data. This essentially consisted of a detailed response to the issues raised by the evaluator. These issues are discussed below:

Issue 1. The lack of a placebo arm

The sponsor responds that this is generally not feasible. Final height data in subjects with SGA are compared to historical (and untreated) controls in four published studies. Whilst these studies showed some increase in final height, the pivotal efficacy study did not show the same magnitude of increase.

Issue 2. Subjects who were GH deficient may also have been included in the studies submitted and thus, do not reflect the population who entirely satisfy the SGA indication

Study B9R-FP-0908 excluded patients with GH deficiency. However Study B9R-EW-GDGB did not use biochemical tests to exclude GH deficiency, rather this was excluded on the basis of clinical signs and symptoms. The evaluator is not able to state whether GH deficiency subjects were definitely excluded.

Issue 3. The indication requested reflects the inclusion criteria in the studies, that is, were those who had severe growth retardation and who did not achieve catch-up growth by 2 to 4 years.

Both studies recruited subjects of the ages of 6.7 to 10.8 years. However, the evaluator agrees that the enrolled subjects were those with 'severe growth failure' and who did not have catch up growth by 2-4 years as manifested by the presence of persistent growth failure.

Issue 4. The relevance of the primary efficacy outcome, HV and height SDS.

The evaluator mentions that the surrogate endpoints have not been shown to be adequate correlates to final height, in the original submission. One published paper

(Ranke *et al.,* 2010) which discusses children with Silver–Russel syndrome supports the claim that these surrogate endpoints correlate to final height.

Issue 5. Efficacy analysis in the ITT population

The analysis is submitted in the "Full analysis set". The evaluator opines that this is likely to be in line with an ITT analysis.

Issue 6. Final height data are inadequate and those presented show insufficient increase

Additional data are discussed. Several published studies and meta-analyses are discussed where somatropin reduced the final height deficit. Similarly, the Phase IV study (GeNeSIS) also discusses the final height data for patients with SGA. There was an increase in final height SDS.

Issue 7. QoL measures factored as efficacy endpoints

This was not done.

Issue 8. Minimum effective dose

There were no dose-response studies submitted. The evaluator mentions that doses chosen (0.035-0.067 mg/kg per day in Study B9R-EW-GDGB and averaged 0.07 mg/kg per day in Study B9R-FP-0908) were higher than those currently recommended in the Australian PI for use in children who are GH deficient (0.177-0.255 mg/kg per week) or have Turner syndrome (0.3 mg/kg per week). Whilst the sponsor has submitted some published studies to support the proposed dose regimen, the evaluator is of the opinion that the data are limited.

Issue 9. Long term safety data

This remains limited. The registration of Humatrope for SGA should be contingent upon *"the ongoing evaluation and reporting of outcomes in this population"*.

Issue 10. The quality of the safety data from the Phase IV post-market study

The evaluator concludes that the study findings are "limited as was less stringent than the earlier phase studies".

Issue 11. Lack of monitoring in relation to IGF-1 monitoring, precocious puberty, bone age and glucose intolerance

These were in line with the incidence reported in published papers.

Overall conclusions of the evaluator

Based on the response the evaluator recommends approval with the following caveats:

- Post market studies to investigate final height, QoL and safety at regular intervals
- Ongoing treatment with Humatrope to be subject to adequate growth acceleration for the first 2 years of treatment; such that a particular patient's height is then within the "normal" height range for their age (> -2 SD).

Postmarket safety

A French research team analysed all-cause and cause-specific mortality in a French population based register of children with isolated GH deficiency, idiopathic GH deficiency, idiopathic short stature or those born short SGA who started recombinant GH between 1985 and 1996 (n=6928) and were followed to September 2009. The outcomes of this study (SAGhE) were discussed at the TGA's Advisory Committee on the Safety of Medicines

(ACSOM) meeting in March 2012. The advice sought from this committee and its recommendations are reproduced below:

> "***There is a signal that somatropin use may be associated with osteosarcoma. Is this signal strong enough to review the association in more depth?***
>
> The committee advised that, due to the inconsistencies, methodological limitations and other quality concerns with the existing data, the signal is not strong enough to warrant further review of the existing data in relation to the association of somatropin use with osteosarcoma.
>
> However, given the biological plausibility of the association, the committee advised that the TGA put in place measures to monitor any signal of osteosarcoma associated with somatropin use.
>
> The committee would encourage the sponsor to submit additional studies which have a more robust design.
>
> ***In SAGhE, dose-dependency was seen for the outcome of all-cause mortality. Should the maximum recommended dose of somatropin be reduced to 50 μg/kg/day based on the presented data?***

Due to the concerns with the overall reliability of the data, the committee did not consider there was sufficient evidence to support reducing the maximum recommended dose of somatropin to 50 μg/kg/day.

> However, the committee advised that the TGA inform prescribers (typically paediatric endocrinologists) of the possibility of safety issues for doses of over 50 μg/kg/day. It was suggested that the Product Information documents for each product include a statement to the effect that "a study has indicated that all-cause mortality increases with dose above 50 μg/kg/day".

Delegate's comments, conclusions and proposed action

The Delegate agreed with the evaluator that the data are adequate in terms of efficacy and safety. Though the numbers of subjects with final height data are insufficient, the evidence in the supplementary data supports the claim that height SDS correlates with the final height. The Delegate agreed there need to be post market monitoring of this and safety and QoL. The recommendation of ACSOM regarding doses above 50 μg/kg/day should be included in the PI.

Proposed action

The Delegate proposed to register Humatrope for the treatment of growth failure in children born SGA who fail to demonstrate catch-up growth by age two to four years. Advice from the Advisory Committee on Prescription Medicines (ACPM) was sought.

Sponsor's response to the delegate's overview

It was noted that the Delegate's Overview refers to issues raised in the initial and supplementary clinical evaluations of the data submitted in support of this application. Eli Lilly Australia's responses to actions proposed in the Delegate's Overview were restricted to those referring to the supplementary clinical evaluation report. For responses to the initial clinical evaluation, the sponsor referred to its *Response to the Clinical Evaluation Report for Humatrope (Somatropin) Treatment of Growth Failure in Children Born Small for Gestational Age (SGA)* (see *Issues addressed*, above).

Issue 1: Lack of a placebo arm

Although desirable, the inclusion of an untreated control arm into the first Lilly study (B9R-FP-0908) was not feasible for various reasons. In particular this was a long-term study which in children is difficult to conduct, especially as the follow-up lasted several years. Had only auxological measurements been performed without provision of somatropin treatment patient enrolment would have been problematic and discontinuation rates in the untreated control group would have been high. The Study B9R-EW-GDGB was specifically designed to evaluate IAD regimens of somatropin compared to a FHD treatment. The latter was considered as the control group with a predetermined dose unchanged throughout the study. Therefore, no untreated control group data were included.

Although the two Lilly studies did not include untreated control groups, growth responses after 2 years of somatropin treatment and final height data of Study B9R-FP-0908 were in the same range as in published studies of comparable patient populations and similar treatment regimens, and gain in height was consistently higher than that reported for untreated controls in published studies.

Issue 2: Potential for inclusion of GH deficient patients

In Study B9R-FP-0908, the inclusion criteria specified that only patients who had a normal response to GH stimulation tests were included into the study and there were no protocol violations regarding this inclusion criterion.

In Study B9R-EW-GDGB, patients with known GH deficiency or any significant signs of disproportion or underlying genetically based syndromal disease (based on study investigator opinion) were excluded from the study. Based on the protocol, the investigator confirmed on the case report form that the patient was not GH deficient according to criteria of consensus guidelines of the *Growth Hormone Research Society* (2000). These guidelines state that careful consideration of auxological and clinical signs together with biochemical parameters should underlie the diagnosis of GH deficiency (*Growth Hormone Research Society,* 2000). In two patients, excluded syndromal conditions were identified after the start of treatment (1 Turner syndrome; 1 suspected mitochondrial disease) but no patient with known GH deficiency was enrolled.

A supplementary analysis of final height data from an observational study (B9R-EW-GDFC) in patients born SGA without GH deficiency (N=70) confirmed that the gain in height SDS at final height was similar to the overall group of patients born SGA (N=110), including patients with GH deficiency, and to the overall group of patients with GH deficiency (N=1873). In the subgroup of 70 non-GH deficient patients born SGA, the majority (almost 75%) reached a final height within the normal range of > –2 SDS (Quartile 1 (Q1): –1.93, Q3: –1.06).

Issue 6: Final height data

Final height in Study B9R-FP-0908 has been analysed for 20 children who started somatropin treatment at a relatively advanced age (mean +/-). Two years of Humatrope treatment at a dosage of 0.47 mg/kg per week, followed by 2 years without treatment and an additional 2 years of treatment in 4 of these 20 children, resulted in a mean increase of final height of approximately 4.2 cm. A mean final height of –2.0 ± 0.8 SDS was achieved from a baseline height SDS of –2.7 ± 0.4 in these 20 patients. The median final height was -1.9 SDS, meaning that approximately 50% of patients achieved a final height within the normal range of > –2 SDS. Therefore, the final height gain observed in Study B9R-FP-0908 was clinically relevant, although suboptimal due to the late start of treatment and the discontinuous treatment regimen.

In the Phase IV observational Study B9R-EW-GDFC among N=834 patients with short stature due to being born SGA, according to the diagnostic scheme for this study, 110

patients have reached final height. After a mean treatment duration of 4.7 ± 3.1 years and although starting at a rather advanced mean age (11.0 ± 3.2 years), more than 75% of the patients born SGA reached a final height SDS within the normal range of > –2 SDS (Q1: -1.93, Q3: –1.06) with a mean height of –1.52 ± 0.75 SDS. This group of 110 patients born SGA included patients with and without GH deficiency according to the caring physician but the results in the subgroup of 70 patients born SGA without GH deficiency were similar to the entire group. Starting from a mean height of –2.76 ± 1.15 SDS at a mean age of 11.0 ± 3.2 years and receiving a mean somatropin dose of 0.31 ± 0.09 mg/kg per week, these patients improved their height by a mean of +1.15 ± 1.14 SDS.

In addition to the available data with Humatrope, there is an increasing body of published literature reporting final height data in patients born SGA using somatropin from other manufacturers. Final height data from randomised trials are now available for several hundred children born SGA who received somatropin at similar doses as proposed for the current application of Humatrope, showing that somatropin reduced the final height deficit when compared to non-treated historical controls. These data are in line with those of smaller, non-randomised clinical trials, including Study B9R-FP-0908 and data from ongoing observational programs such as Study B9R-EW-GDFC. When treatment was started early and given continuously, 85% of treated patients achieved final height within the normal range (> –2 SDS) (van Pareren *et al.,* 2003). The data submitted for Study B9R-EW-GDFC on patients born SGA (GH deficient and non-GH deficient) who reached final height show that more than 75% of patients who received somatropin in the observational setting reached a final height within the normal range.

The Delegate has agreed that the data submitted supports an increase in final height SDS and a correlation between initial height SDS and final height and has recommended post market monitoring of final height in these children. The ongoing post authorisation Study B9R-EW-GDFC will provide an opportunity to continue the evaluation of final height in children with short stature born SGA under somatropin treatment.

Issue 7: QoL measures

It has been described that short stature may impose significant physical and psychosocial stress on affected individuals (Skuse 1987, Siegel *et al.,* 1991, Hoey 1993, Zimet *et al.* 1997, Noeker and Haverkamp 2000). However, results from clinical trials are conflicting and do not provide conclusive evidence regarding an association of quality of life and height (Sandberg 2005 and 2011). As laid out in the supplementary data submission, the related medical literature describes a variety of challenges for short children which may impair quality of life (QoL). These challenges include infantilisation, overprotection, reduced school achievement and impaired socialisation, as well as increased risk for teasing, bullying, stature-related injuries, low self-esteem, lower marriage rates, depression and anxiety, unemployment and economic dependency. Notably, short stature may be associated with significant morbidity, as evidenced by the increased rates of Caesarean section in significantly short women (Sheiner *et al.,* 2005) and the strong inverse association between height and suicide risk in a large Swedish study of over 1,000,000 men (Magnusson *et al.,* 2005). A recent study from the United Kingdom demonstrated reduced QoL in adults with short stature relative to the QoL of those of normal stature (Christensen *et al.,* 2007).

While it is acknowledged that health outcome measures including quality of life are increasingly important, QoL measurement with regard to height in particular in children is considered rather complex. In particular specific measures need to address the developmental stage of different age groups. Because adult measures may fail to address the specific aspects of QoL that are important to a child, various different tools, both generic and disease-specific, have been developed to assess QoL in children; however, their quality in terms of psychometric properties often seems questionable (Trama and Dieci 2011). QoL evaluations have therefore not been included in any of the submitted

studies on Humatrope in children born SGA. However, some data are available from published somatropin studies that did evaluate QoL and related parameters such as self-esteem, behavioural problems or wellbeing in short stature patients. Some of these studies were cross-sectional and evaluated QoL at the end of somatropin treatment, for example, when patients had achieved final or near final height, in comparison to untreated control groups, while others observed QoL for changes over time during shorter-term treatment. While the majority of QoL data comes from patients with short stature resulting from GH deficiency or ISS, few publications refer specifically to QoL in patients born SGA. A recent study describes an improvement of QoL in pre and pubertal short children born SGA during somatropin treatment (Lem *et al.,* 2011). In particular for idiopathic GH deficiency and ISS, the beneficial effect of somatropin on QoL would be related to the improvement of short stature, irrespective of the underlying condition. Therefore, the majority of studies evaluating QoL during or after somatropin treatment in short stature patients can be regarded as supportive for the proposed indication.

The majority of existing QoL data is well summarised in the supplementary data submission and concludes that there is some evidence suggesting that children with short stature born SGA who received long-term somatropin treatment experienced improvement in QoL and related psychosocial parameters either compared to baseline and/or compared to their peers. However, based on potential limitations in the existing studies methodological robust research on the association of height and psychosocial aspects would need to be addressed in well designed, rather complex controlled and large enough clinical trials. While this would not address the real world scenario or the risk/benefit analysis for an individual child, it needs to be emphasised that somatropin treatment of children born SGA is aimed primarily to achieve physical outcomes. While the reason for seeking treatment is ostensibly physical it is likely to indirectly address QoL reasons such as self esteem. The treating physician will therefore indirectly consider QoL factors along with physical symptoms when making the decision to prescribe for an individual patient. Thus, the sponsor does not agree that post market monitoring of QoL is unambiguous and supporting as an efficacy endpoint.

Issue 8: Minimum effective dose

Growth Hormone (GH) has been used to promote longitudinal growth in short children born SGA for more than 40 years (Aarskog 1963, Tanner and Ham 1969, Clayton *et al.,* 2007). The earliest description of a patient born SGA who was treated with GH dates from 1963 (Aarskog 1963). In the initial studies in short children born SGA, pituitary GH tended to be injected at high doses of up to 7–35 IU per week (variable equivalence of IU versus mg) 2-3 times per week (Tanner *et al.,* 1971, Grunt *et al.,* 1972); the later use of daily injections of lower doses of GH or recombinant somatropin elicited a better response (Foley *et al.,* 1974, Lanes *et al.,* 1979, Albertsson-Wikland *et al.,* 1989, Stanhope *et al.,* 1989, Stanhope *et al.,* 1991). In some of the early studies, a dose-response relationship following short-term treatment was described (Foley *et al.,* 1974, Lanes *et al.,* 1979).

Hence, the initial studies empirically evaluated efficacy and safety of short-term treatment; systematic dose escalation studies to identify a minimum effective dose have not been performed. As for the other approved indications of somatropin, dose finding was an empirical process. Over the years, a wide range of somatropin doses has been studied in children born SGA, revealing a pronounced variability of the individual growth responses, depending, for example, on the age at start of treatment or the severity of growth retardation. Due to this variability of responsiveness to treatment, the definition of a general minimum effective dose “per se” is problematic. More recent strategies, such as those evaluated in Study B9R-EW-GDGB, suggest individualising treatment and identifying the optimum effective dose individually for each patient. Therefore, rather than identifying a specific minimum effective dose recommendation for all patients, a dose range has been

established for the treatment of short children born SGA, based on the results of short and long term studies in various patient populations.

Based on short and long term data collected over a number of years, the effective dose range for somatropin treatment in children born SGA has been empirically defined, using the most frequently used doses of 0.23 and 0.47 mg/kg per week (corresponding to 0.033 and 0.067 mg/kg per day) as upper and lower limit. Correspondingly, the current SGA consensus guidelines recommend that the starting dose should cover the range of 0.035-0.070 mg/kg per day (Clayton *et al.,* 2007), with the higher doses to be used in patients with the most severe growth retardation.

Study B9R-EW-GDGB compared the effect of an individually adjusted dose (IAD) of Humatrope versus a fixed high dose (FHD) of Humatrope in a population of very short children born SGA. It was hypothesised that children starting treatment with a low dose of 0.035 mg/kg per day, which was then individually adjusted to a higher dose of 0.067 mg/kg per day if needed according to the results of an early growth prediction performed after the first 3 months (based on 'Cologne Growth Prediction Model'; Schönau *et al.,* 2001), would show a mean gain in height SDS at 1 year non inferior to that of children receiving a FHD regimen of 0.067 mg/kg per day from the beginning of treatment. The main finding of the study was that the IAD regimen was non inferior to the FHD regimen, based on the change in height SDS after the first year.

Analyses evaluating the treatment outcomes for patients who received the low dose and those who received the FHD of Humatrope throughout the entire study period showed the "Low Dose" group was slightly shorter than the FHD group at baseline, had a lower baseline HV SDS, and had a slightly lower height SDS gain in Year 1 (see Table 23). However, by the end of the second year, the height SDS gains for both groups were similar (+1.50 and +1.56 SDS, respectively). Changes in other efficacy variables examined (HV, height SDS minus target height SDS) were also similar for both groups. These additional data illustrate that the children for whom the somatropin dose is individualised within the proposed dose range experience a clinically similar and relevant growth response after the first and second year of treatment.

Numerous studies, including Studies B9R-EW-GDGB and B9R-FP-0908, demonstrate that children with short stature born SGA respond well to somatropin treatment at modest pharmacologic dosages. The Humatrope doses chosen for these studies were based on somatropin doses used in previous publications. Taken together, the results from published studies, the efficacy results from Studies B9R-EW-GDGB and B9R-FP-0908 and the safety data presented in this application, provide data supporting the approval of Humatrope at a dose range from 0.033 up to 0.067 mg/kg per day (corresponding to 0.23-0.47 mg/kg per week) for children with short stature born SGA.

Recent published data have demonstrated that optimal final height gains were obtained using somatropin doses of 0.47–0.49 mg/kg per week, corresponding to 0.067 mg/kg per day (de Zegher *et al.,* 2000, van Pareren *et al.,* 2003, Fjellestad-Paulsen *et al.,* 2004, Dahlgren and Wikland 2005). However, as Study B9R-EW-GDGB shows, it may be sufficient for some patients to start on a lower dose of 0.035 mg/kg per day, for example, in patients who start treatment at younger age, without a clinically relevant loss in growth response.

Table 23. Study B9R-EW-GDGB: Height SDS and other growth response parameters in "Low Dose and "High Dose" groups. Restricted full analysis set

	Low Dose Group 0.035 mg/kg/day			High Dose Group 0.067 mg/kg/day		
Efficacy Variable	n	Mean	SD	n	Mean	SD
Height SDS						
Baseline	46	-3.96	0.59	133	-3.83	0.59
Year 1	46	-3.06	0.64	133	-2.79	0.70
Change at Year 1	46	0.90	0.38	133	1.04	0.41
Baseline	32	-3.98	0.56	128	-3.83	0.59
Year 2	32	-2.47	0.64	128	-2.27	0.64
Change at Year 2	32	1.50	0.41	128	1.56	0.59
Height velocity (cm/y)						
Baseline	46	5.16	1.69	132	5.28	1.68
Year 1	46	9.34	1.55	132	9.96	1.90
Change at Year 1	46	4.18	2.73	132	4.68	2.62
Baseline	32	4.91	1.58	128	5.18	1.37
Year 2	32	7.21	1.13	128	7.85	1.52
Change at Year 2	32	2.30	1.90	128	2.67	1.84
Height velocity SDS						
Baseline	46	-2.01	2.09	132	-1.32	2.10
Year 1	46	3.59	2.07	132	4.50	2.30
Change at Year 1	46	5.60	3.44	132	5.82	3.41
Baseline	32	-2.27	1.86	128	-1.47	1.64
Year 2	32	1.30	1.33	128	2.02	1.75
Change at Year 2	32	3.57	2.39	128	3.50	2.30

Table 23 (continued). Study B9R-EW-GDGB: Height SDS and other growth response parameters in "Low Dose and "High Dose" groups. Restricted full analysis set

	Low Dose Group 0.035 mg/kg/day			High Dose Group 0.067 mg/kg/day		
Efficacy Variable	n	Mean	SD	n	Mean	SD
Height SDS minus target height SDS						
Baseline	43	-2.40	1.16	121	-2.10	1.12
Year 1	43	-1.51	1.13	121	-1.06	1.14
Change at Year 1	43	0.89	0.39	121	1.04	0.40
Baseline	29	-2.28	1.09	116	-2.09	1.13
Year 2	29	-0.75	0.99	116	-0.54	1.20
Change at Year 2	29	1.52	0.43	116	1.55	0.58
Bone age chronological age ratio						
Baseline	44	0.64	0.15	130	0.69	0.19
Year 1	44	0.75	0.15	130	0.81	0.15
Change at Year 1	44	0.11	0.12	130	0.11	0.13
Baseline	28	0.67	0.15	119	0.71	0.18
Year 2	28	0.84	0.13	119	0.88	0.12
Change at Year 2	28	0.17	0.11	119	0.17	0.15
Bone age minus chronological age						
Baseline	44	-2.08	1.08	130	-2.00	1.15
Year 1	44	-1.68	1.07	130	-1.48	1.09
Change at Year 1	44	0.40	0.78	130	0.53	0.83
Baseline	28	-1.82	0.92	119	-1.91	1.15
Year 2	28	-1.25	1.01	119	-1.04	1.00
Change at Year 2	28	0.57	0.75	119	0.88	0.92

Table 23 (concluded). Study B9R-EW-GDGB: Height SDS and other growth response parameters in "Low Dose and "High Dose" groups. Restricted full analysis set

	Low Dose Group 0.035 mg/kg/day			High Dose Group 0.067 mg/kg/day		
Efficacy Variable	n	Mean	SD	n	Mean	SD
Change in Bone age/change in chronological age						
Year 1	44	1.39	0.78	130	1.51	0.78
Year 2	28	1.28	0.37	119	1.43	0.45

Abbreviations: SD = standard deviation; n = no of patients with nonmissing values at baseline and post baseline; SDS = standard deviation score.
Low dose group = all patients in the restricted full analysis set who remained on the low dose (0.035 mg/kg/day) during the analysis period.
High dose group = all patients in the restricted full analysis set who had at least 9 (21) months of exposure to the high dose (0.067 mg/kg/day) for 1-year (2-year) analysis.

Issue 9: Long term safety

The Delegate has stated that *"The registration of Humatrope for SGA should be contingent upon 'the ongoing evaluation and reporting of outcomes in this population'."*

Analyses from the ongoing, non-interventional observational Study B9R-EW-GDFC are included in the approved risk management plan for Humatrope implemented in Europe, and are reviewed during preparation of periodic safety update reports to regulatory authorities. In addition, routine pharmacovigilance and signal monitoring are in place to ensure the benefit/risk balance continues to be favourable for all Humatrope indications. Furthermore, Study B9R-EW-GDFC has been accepted by the European Regulatory Authorities to provide safety and efficacy data on final height for patients born SGA upon regular reports. Therefore, a mechanism is in place for the ongoing evaluation requested by the Delegate.

While additional long term follow-up safety data following somatropin treatment will add to the body of available evidence, the current data available are sufficient to warrant the use of somatropin in short children born SGA.

Issue 10: Quality of safety data from the Phase IV post-market study

Study B9R-EW-GDFC, as an ongoing multinational, multicenter, open-label non-interventional observational study, is conducted based on local laws and regulations. It has been accepted as the basis for reports to authorities fulfilling regulatory commitments and 18 peer reviewed publications have been generated from this study to date.

Following the primary objective to evaluate safety and effectiveness of Humatrope treatment, the B9R-EW-GDFC interim analyses provide safety as well as effectiveness data for all patients and specific diagnostic subgroups, such as patients with short stature born SGA. The short to midterm efficacy data after 4 years of Humatrope treatment have shown that more than 75% of patients born SGA regardless of their GH-secretion status reach a height SDS within the normal range. The more recent safety analysis for the group of patients born SGA treated with Humatrope has not changed the overall safety profile of Humatrope for this subgroup of patients.

ACSOM advice

Eli Lilly agree with the committee that due to the *"inconsistencies, methodlogical limitations and other quality concerns"* associated with the French SAGhE study, further review of existing data in relation to the association of somatropin therapy with osteosarcoma is not warranted. The SAGhE study was based on a mandatory register of all patients treated with GH in France (Carel *et al.,* 2012).

In relation to the committee's recommendation to submit additional studies, Lilly have described ongoing analyses from the non-interventional observational Study B9R-EW-GDFC and routine pharmacovigilance activities to ensure a positive risk/benefit profile is maintained for Humatrope (see *Long Term Safety*).

Delegate's comments

The recommendation to include a statement in the PI on possible increase in all-cause mortality at doses above 50 μg/kg/day is based on the French SAGhE study. The ACSOM has noted inconsistencies, methodological limitations and quality concerns with the data from this French study. Based on the number and characteristics of patients enrolled, the SAGhE study was not powered to detect a relationship between dose and outcomes, and therefore does not provide sufficient evidence to warrant a label update. Given the limitations of the SAGhE study it does not seem appropriate to update the PI based on this data.

Clinical trial data from studies B9R-FP-0908 and B9R-EW-GDGB, along with a body of evidence in the literature, currently maintains a positive risk/benefit profile across the recommended dose range including the maximum recommended dose of 0.067 mg/kg per day.

Sponsor's conclusion

Eli Lilly and Company agree with the Delegate's proposal to register Humatrope for the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch up growth by age two to four years. The ongoing observational Study B9R-EW-GDFC along with routine pharmacovigilance activities will ensure that efficacy and safety of Humatrope treatment in these patients will be monitored appropriately.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the initial and supplementary evaluations and the Delegate's overview, as well as the sponsor's response to these documents, considered these products to have an overall positive benefit–risk profile for the indication:

> *For the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years.*

In making this recommendation, the ACPM noted that the efficacy data on SGA are limited and that there is no new safety data of concern, thereby supporting a positive assessment. In addition, the ACPM noted that the use will be by experienced paediatric endocrinologists.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and emphasised the need for consistency.

The ACPM agreed with the Delegate on the proposed conditions of registration, particularly in the implementation of the RMP.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products."

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of somatropin (Humatrope) for SC administration (see PI for dosage recommendations), indicated for:

> *The treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years. [See Clinical Trials].*

The full indications are now:

- *Humatrope is indicated for the long term treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone.*
- *Humatrope is also indicated for the treatment of growth disturbance associated with gonadal dysgenesis (Turner's syndrome).*
- *Humatrope is also indicated for the treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 ng/mL.*
- *Humatrope is also indicated for the treatment of growth retardation in prepubertal children with chronic renal insufficiency whose height is on or less than the twenty fifth percentile and whose growth velocity is on or less than the twenty fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 30 mL/min/1.73 m2.*

- *Humatrope is also indicated for the treatment of growth failure in children born small for gestational age (SGA) who fail to demonstrate catch-up growth by age two to four years. [See Clinical Trials].*

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
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