Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Genotropin/Genotropin Miniquick (somatropin)

DK/W/0008/pdWS/007

Marketing Authorisation Holder: Pfizer

Rapporteur:	DK
Finalisation procedure (day 120):	07-02-2018

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Genotropin Genotropin Miniquick
INN (or common name) of the active substance(s):	Somatropin
MAH:	Pfizer
Currently approved Indication(s)	Children Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD) and growth disturbance associated with Turner syndrome or chronic renal insufficiency. Growth disturbance [current height standard deviation score (SDS) < - 2.5 and parental adjusted height SDS < - 1] in short children born small for gestational age (SGA), with a birth weight and/or length below - 2 SD, who failed to show catch-up growth [height velocity (HV) SDS < 0 during the last year] by 4 years of age or later. Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. Adults Replacement therapy in adults with pronounced growth hormone deficiency. Adult Onset: Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency. Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be reevaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a pituitary/hypothalamic disease or insult, an insulinlike growth factor-I (IGF-I) SDS < - 2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD.

	All other patients will require IGF-I assay and one growth hormone stimulation test.All other patients will require IGF-I assay and one growth hormone stimulation test.
Pharmaco-therapeutic group (ATC Code):	H01AC01
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection Genotropin: 1.3 mg, 5 mg, 5.3 mg og 12 mg. Genotropin Miniquick: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg og 2.0 mg.

I. EXECUTIVE SUMMARY

SmPC changes are proposed in section 5.1.
No PL changes are proposed.

II. RECOMMENDATION

Section 5.1 of the SmPC should be amended as set out below *(Deleted text is shown in strikethrough)*:

"In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. ~~Long-term safety data are still limited.~~"

Type IB variation to be requested from the MAH within 30 days after the finalisation of the procedure.

III. INTRODUCTION

On 11 November 2016, the MAH submitted a completed paediatric study for Genotropin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Genotropin and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Genotropin® (somatropin) is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin (somatropin). Genotropin is synthesised in a strain of *Escherichia coli* that has been modified by the addition of the gene for hGH.

Currently, Genotropin is approved in the EU for the following paediatric indications but not all of these indications are approved in all the countries, where Genotropin has received regulatory approval:

- Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency [GHD]) and growth disturbance associated with Turner syndrome or chronic renal insufficiency.
- Growth disturbance (current height standard deviation score [SDS] < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity SDS < 0 during the last year) by 4 years of age or later.
- Prader-Willi Syndrome for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

The purpose of growth hormone treatment for children with short stature due to SGA is to improve their growth and get close to the target height. For children with normal growth hormone levels with short stature due to SGA, supplementation with exogenous growth hormone has been shown to improve height corresponding to chronological age.

Assessor's comments

Genotropin has been approved for the indication Small for Gestational Age (SGA) for many years. However, it is important to document the impact on the ultimate end-point "final adult height" when clinical studies are finalised after several years.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for: Study GENASG-0021-007: Long-term study of PNU-180307 for short children born small for gestational age (SGA) without epiphyseal closure (extension of the study 307-MET-0021-002).

2. Clinical study(ies)

➢ Description

The treatment period of Study 307-MET-0021-002 (hereinafter referred to as "Study 002") previously performed was of 12 months' duration. This present study (Study GENASG-0021-007, hereinafter "Study 007") was implemented because if the GH treatment was discontinued, it would end before the short stature of the children participating in the study closed in on the target height. After that, on October 16, 2008, Genotropin® obtained additional approval for the indication of short stature due to SGA without epiphyseal closure. Most of the participating children had not yet experienced the closure of the epiphyseal plate and had not reached their final height. There were some children with a height standard deviation score (SDS) exceeding −2 SD, but if the GH treatment was discontinued, the height velocity SDS was predicted to become less than 0 and the subject's final adult height was predicted to be short stature under −2 SD.

As a result, it was decided that Study 007 would be continued as a post-marketing study (without changing the study number) after the date of marketing approval, based on the guidelines for GH treatment for short stature due to SGA announced in 2007.

Assessor's comments

It is important to report full data from post-marketing studies, and Study 007 is relevant to the indication SGA.

- **Methods**

Objective(s)

Primary objective: The primary objective was to evaluate safety of long-term administration of Genotropin® until a final height was reached in short children born SGA without epiphyseal closure.

Secondary objectives:

- To examine height velocity, height velocity Standard Deviation Score (SDS) for chronological age, height SDS for chronological age and Δ height SDS for chronological age.
- To comprehensively evaluate height velocity SDS for bone age, height SDS for bone age and Δ height SDS for bone age to examine the relationship between bone age and height increase.
- To examine changes in daily lives of children with Genotropin® treatment by means of questionnaires.

Outcomes/endpoints

Height and body weight were measured and recorded every 3 months prior to the entry into the post-marketing study, at the entry into the post-marketing study, and every 6 months during the post-marketing study calculating from the start of Study 007 as well as at the completion of the study drug (discontinuation). Subjects who had a dosage of 0.033 mg/kg/day in Study 002, but had their dosage increased to 0.067 mg/kg/day in this study (dose-increasing group), were observed at Months 13 and 14, and these measurements were recorded in the case report forms.

Bone age was evaluated based on radiographs of carpal bones in the left hand performed every 12 months, at the entry into the post-marketing study, and at the completion of the study drug (discontinuation). The original or a copy of the x-ray was submitted to the sponsor or the commissioned party for concentrated testing. When an original x-ray was submitted, the sponsor or commissioned party prepared a copy and performed the measurement using that copy.

Physical changes related to pubic hair (Tanner Stage I-V), penis/breasts (Tanner Stage I-V), presence of genital bleeding, testicular volume, and other secondary sex characteristics were observed and recorded every 3 months prior to the entry into the post-marketing study, at the entry into the post-marketing study, every 6 months from the start of Study 007 after the entry into the post-marketing study, and at the completion of the study drug (discontinuation). Subjects who had a dosage of 0.033 mg/kg/day in the Study 002, but had their dosage increased to

0.067 mg/kg/day in this study (dose-increasing group), were observed at Months 13 and 14, and these measurements were recorded in the case report forms.

Assessor's comments

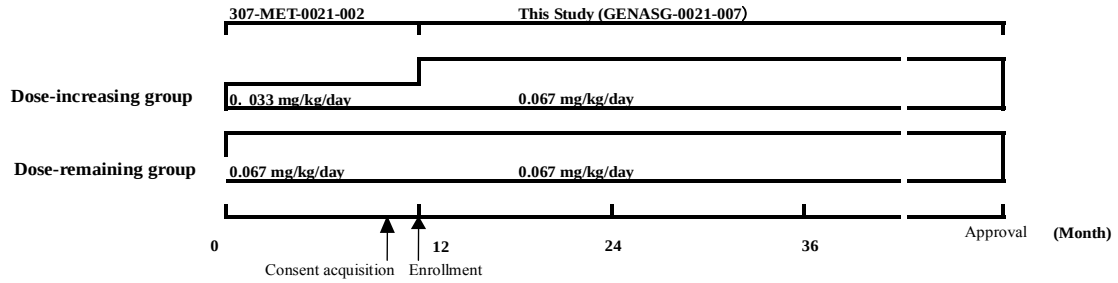
The primary endpoint is related to the safety of Genotropin® whereas the long-term efficacy is included as secondary objectives. The outcomes are appropriate and well established in the field of rhGH research; the Height SDS being the major preferred endpoint for efficacy.

Study design

Study 007 was a multi-center, long-term study carried out as an extension of Study 002. This study was continued after the approval of the indication as a post-marketing study. Subjects received a dose corresponding to their body weight (kg) once daily before bedtime.

The study design prior to the entry into the post-marketing study is shown in Figure 1. After entering this study, subjects who had been treated Genotropin® 0.033 mg/kg/day in Study 002 received a dose of 0.067 mg/kg/day as the "dose-increasing" group. However, if any adverse event had occurred in Study 002 and the dose increase was found to be difficult, 0.033 mg/kg/day could be maintained. Meanwhile, subjects in the 0.067 mg/kg/day group in Study 002 were maintained on the dose as the "dose-remaining" group.

Figure 1. Study Design (Before the Entry into Post-Marketing Survey)



Dose-increasing group: The dosage of 0.033 mg/kg/day assigned in Study 002 was increased to 0.067 mg/kg/day. However, if an adverse event occurred in Study 002 and a dosage increase was found to be difficult, a dosage of 0.033 mg/kg/day was maintained.
Dose-remaining group: The dosage of 0.067 mg/kg/day that was assigned in Study 002 was maintained.

This clinical study was performed in compliance with the general principles established in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002 Council for International Organizations of Medical Sciences [CIOMS]), GCP (1996 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], and the Declaration of Helsinki [2008 World Medical Association]) in addition to applicable laws and regulations.

Assessor's comments

It should be noted that patients in Study 002 were randomised to dosage 0.033 mg/kg/day (which is the approved dose for SGA indication) or to 0.067 mg/kg/day (which is not approved for the SGA indication). The study is not powered to document the efficacy merits of the high dose.

Study population /Sample size

Children with short stature due to SGA who received treatment for one year in Study 002, were considered eligible by the investigator/subinvestigator to continue treatment with this investigational product after approval for the relevant indication from efficacy and safety aspects, and have provided informed consent. Due to the enrollment plan (patients continued from Study002), no sample size was set.

Children who met the following criteria or were considered ineligible for the study by the investigator/subinvestigator would be excluded from the study.

- Children who had any chronic disease requiring treatment with steroid hormone that may affect growth promotion including estrogen, androgen, anabolic hormone, and corticosteroids (except those for external use), and have received the treatment.
- Children who had received radiotherapy or chemotherapy.
- Children who had serious cardiac disease, renal disease, or hepatic disease.
- Children who had diabetes mellitus with a manifestation of abnormal glucose metabolism.
- Children who had serious chronic disease.
- Children who had a malignant tumor.
- Children who were allergic to m-cresol.

Beside the above, children who met the following criteria before proceeding to the post-marketing study were also excluded from the study.

- Children who had achieved a height SDS for chronological age of 0.
- Children who had experienced puberty, and showed height velocity of <2 cm/year.
- Children who had reached bone age of 17 years for boys and 15 years for girls.

Assessor's comments

Sample size was defined by the number of patients already included in Study 002, and no calculation of statistical power was performed. In- and exclusion criteria are considered acceptable.

Treatments

In the main Study 002, patients were treated in 2 dosage groups, either 0.033 mg/kg/ day or 0.067 mg/kg/day. Based on previous information, the dosage of the subjects assigned to the 0.033 mg/kg/day group in Study 002 were increased to 0.067 mg/kg/day in this study, so that all subjects were administered 0.067 mg/kg/day. However, 0.033 mg/kg/day is recommended in the

domestic GH treatment guideline unless the subject has a poor reaction, in which case the recommendation is to increase the dosage. Given the initial recommendation of 0.033 mg/kg/day, it was determined to be permissible to reduce the dosage to 0.033 mg/kg/day after the entry into the post-marketing study if necessary based on age, puberty, growth, and safety.

Consequently, in Study 007 patients were treated with either 0.033 or 0.067 mg/kg/day. A dedicated injection device (Genotropin Pen® 5.3G or Genotropin Pen® 12G) was used to dissolve and inject the investigational product.

Assessor's comments

As noted above, patients in Study 002 were randomised to dosage 0.033 mg/kg/day (which is the approved dose for SGA indication) or to 0.067 mg/kg/day (which is not approved for the SGA indication). In Study 007, all subjects were administered 0.067 mg/kg/day but the dose could be reduced to 0.033 mg/kg/day if necessary.

Statistical Methods

Full analysis set (FAS) was used as subject population to be analyzed for efficacy. The detailed criteria for handling subjects were considered in the data review meeting.

The FAS was defined as the set of subjects who met the inclusion/exclusion criteria and were enrolled in the study except for the following subjects:

- Subjects who were never given any administration of study medication after enrollment, and
- Subjects with no study assessment data after enrollment

For height velocity SDS for chronological age, height velocity, height SDS for chronological age, height, height velocity SDS for bone age, height SDS for bone age, bone age, ratio of bone age to chronological age, PAH SDS, body weight, body weight SDS for chronological age, BMI, IGF-I, IGF-I SDS, IGFBP-3, and IGFBP-3 SDS, summary statistics were calculated by treatment group in actual values at the start of treatment in Study 002 and at the evaluation time points every 12 months of treatment, and in their changes from the start of treatment. The same analysis of height velocity SDS for chronological age and height SDS for chronological age was performed on a set that excluded subjects who continued administration of 0.033 mg/kg/day for more than one month during this study.

Assessor's comments

The statistical methods as described above appears appropriate and acceptable.

➢ Results

Recruitment/ Number analysed

Sixty-two subjects (dose-increasing group: 29 subjects, dose-remaining group: 33 subjects) were entered into this study GENASG-0021-007 (hereinafter referred to as the "Study 007") and the investigational product was administered to 61 subjects (dose-increasing group: 29 subjects, dose-remaining group: 32 subjects). Table 5 shows the subject disposition in this report.

Table 5. Subject Disposition

Number of Subjects	Dose-Increasing Group	Dose-Remaining Group
Enrolled	29	33
Treated	29	32
Completed until the date of marketing approval (not entered the post-marketing study)	5	5
Completed	2	0
Reaching a height SDS for chronological age of 0 SD during treatment	3	5
Discontinued until the date of marketing approval (not entered the post-marketing study)	8	12
Adverse events	0	1
Protocol deviation	0	1
Withdrawn consent	8	8
Others	0	2
Entered the post-marketing study	16	15
Completed	10	10
Reaching a height SDS for chronological age of 0 SD during treatment	2	0
Height velocity for chronological age <1.0 cm/year	0	1
Annual height velocity <2 cm after achieving peak velocity at puberty	0	1
Reaching a bone age of 17 years in male or 15 years in female	8	8
Discontinued	6	5
Protocol deviation	1	0
Withdrawn consent	3	2
Others	2	3

Source: Figure 14.1.1.3

Ten subjects (5 subjects in the dose-increasing group and 5 subjects in the dose-remaining group) completed the study until the date of marketing approval (not entered the post-marketing study); of these, 8 subjects (3 subjects in the dose-increasing group and 5 subjects in the dose-remaining group) reached a height SDS for chronological age of 0 SD.

Twenty subjects (8 subjects in the dose-increasing group and 12 subjects in the dose-remaining group) withdrew from the study until the date of marketing approval (not entered the post-marketing study); the most common reason for withdrawal was "Withdrawn consent" in 16 subjects (8 subjects in the dose-increasing group and 8 subjects in the dose-remaining group).

Thirty-one subjects (16 subjects in the dose-increasing group and 15 subjects in the dose-remaining group) entered the post-marketing study; of these, 20 subjects (10 subjects in the dose-increasing group and 10 subjects in the dose-remaining group) completed the study. Figure 7 shows the patient disposition with regards to analysis group.

Table 7. Analysis Sets

	Dose-increasing group	Dose-remaining group	Total
Enrolled	29	33	62
Treated	29	32	61
Efficacy analysis set: Full analysis set	29	32	61
Safety analysis set: Full analysis set	29	32	61

Source: Figure 14.1.1.3

Assessor's comments

The numbers of patients in the two groups actually completing the study are very small. This limits the possibility of assessing efficacy.

By entry to Study 007, all patients (including patients previously (in Study 002) treated with 0.033 mg/kg/day) were treated with a dose of 0.067 mg/kg/day, but according to the study protcol, the dose could be reduced to 0.033 mg/kg/day. This could be either due to age, puberty, growth, or due to safety reasons. There is no information regarding the number of patients who had the dose reduced, nor is there information regarding the reason for dose-reduction. This information should be presented by the Applicant. **(OC)** Furthermore, 16 patients withdrew consent, and the Applicant should provide information regarding the reasons for these withdrawals. **(OC)**

Baseline data

Of the 62 subjects included in this study (dose-increasing group: 29 subjects, dose-remaining group: 33 subjects), one subject not recieving the investigational product was excluded (from the dose-remaining group). The remaining 61 subjects were used for efficacy and safety evaluations as the FAS.

The male/female composition of subjects was 15 males and 14 females in the dose-increasing group and 18 males and 14 females in the dose-remaining group, and the male to female ratio was approximately the same in both groups. The mean age at the start of treatment in Study 002 was 5.20 years for the dose-increasing group and 5.40 years for the dose-remaining group. The mean height velocity SDS for chronological age at the start of treatment in Study 002 was −1.866 SD in the dose-increasing group and −1.450 SD in the dose-remaining group. The mean height SDS for chronological age was −3.014 SD in the dose-increasing group and −3.09 SD in the dose-remaining group.

Table 8 presents demographic and other baseline characteristics for the included patients.

Table 8. Demographic and Other Baseline Characteristics

Item			Dose-Increasing Group	Dose-Remaining Group
Full analysis set			29	32
Sex	Male		15 (51.7%)	18 (56.3%)
	Female		14 (48.3%)	14 (43.8%)
Height at birth (cm)		Mean ± standard deviation	40.34 ± 5.26	40.18 ± 5.34
Body weight at birth (g)		Mean ± standard deviation	1694.8 ± 556.7	1757.3 ± 612.0
Gestational age (weeks)		Mean ± standard deviation	36.4 ± 3.1	36.9 ± 3.2
002 At the start of administration of treatment				
Age (years)		Mean ± standard deviation	5.20 ± 1.64	5.40 ± 1.27
		Minimum value to maximum value	3.1 to 8.0	3.7 to 7.8
Height velocity SDS for chronological age		Mean ± standard deviation	-1.866 ± 1.221	-1.450 ± 1.600
-1.0 SD to less than 0 SD		n	10	11
Less than -1.0 SD		n	19	21
Height velocity (cm/year)		Mean ± standard deviation	5.36 ± 0.99	5.45 ± 1.21
		Median value (n)	5.20 (29)	5.70 (32)
Height SDS for chronological age		Mean ± standard deviation	-3.14 ± 0.76	-3.09 ± 0.83
-2.5 SD to less than -2.0 SD		n	7	7
-3.0 SD to less than -2.5 SD		n	4	8
Less than -3.0 SD		n	18	17
Bone age (years)		Mean ± standard deviation	4.554 ± 1.877	4.797 ± 1.618
Ratio of bone age to chronological age		Mean ± standard deviation	0.861 ± 0.247	0.867 ± 0.136
Height (cm)		Mean ± standard deviation	93.97 ± 9.88	95.42 ± 8.32
Body weight (kg)		Mean ± standard deviation	12.27 ± 2.87	12.55 ± 3.00

Source: Table 14.1.1.1, Table 14.1.1.2
SD = standard deviation, SDS = standard deviation score

Assessor's comments

The two groups were comparable with regards to demographics and baseline characteristics. The body weight at birth and the 'present' body weight was slightly higher in the dose-remaining group compared to the dose-increasing group. This difference is most likely because there was slightly more males in the dose-remaining group compared to the dose-increasing group. The difference is not considered to be clinically relevant.

Efficacy results (Secondary endpoints)

Height SDS for chronological age and the change from the start of treatment in the FAS at the start of treatment (the start of Study 002) and observed every Months 12 from the start of treatment are shown by treatment group in Table 11 and Figure 4.

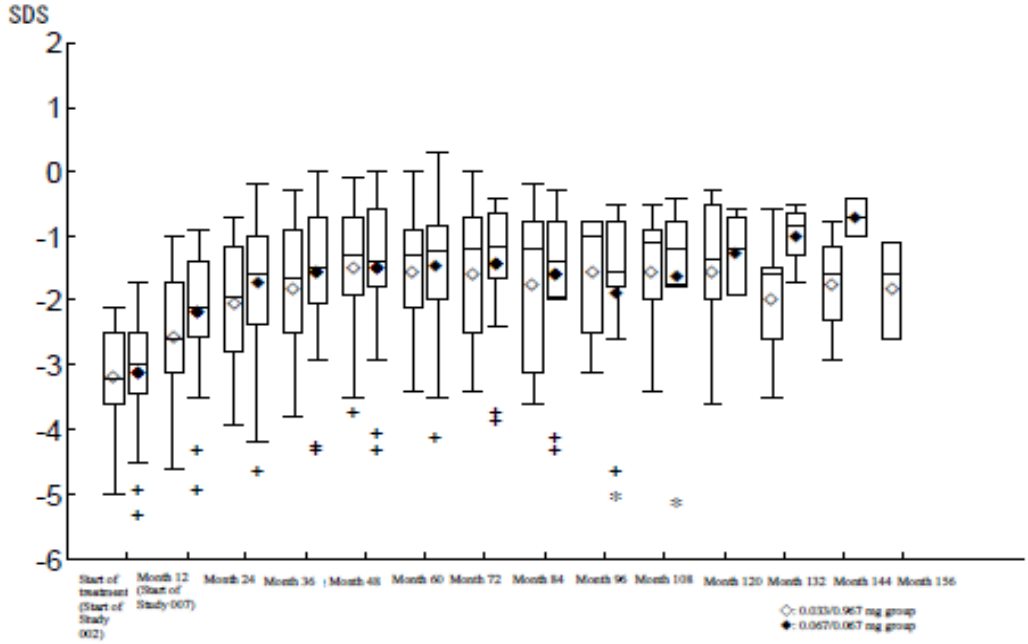
Table 11. Actual Values and Changes in Height SDS for Chronological Age

		Start of treatment (Study 002)	Month 12 (Study 002)	Month 24 (Study 007)	Month 36 (Study 007)	Month 48 (Study 007)	Month 60 (Study 007)	Month 72 (Study 007)
Dose-increasing group	Score	−3.14±0.76 (29)	−2.53±0.92 (29)	−2.02±0.97 (28)	−1.80±0.99 (26)	−1.48±1.05 (24)	−1.53±1.06 (21)	−1.56±1.11 (20)
	Change	-	0.60±0.29 (29)	1.11±0.40 (28)	1.37±0.48 (26)	1.70±0.56 (24)	1.79±0.66 (21)	1.80±0.72 (20)
Dose-remaining group	Score	−3.09±0.83 (32)	−2.17±0.96 (32)	−1.70±1.03 (32)	−1.53±1.10 (28)	−1.49±1.15 (23)	−1.44±1.10 (20)	−1.43±1.06 (16)
	Change	-	0.93±0.34 (32)	1.40±0.44 (32)	1.65±0.54 (28)	1.82±0.58 (23)	1.91±0.51 (20)	2.06±0.44 (16)

		Month 84 (Study 007)	Month 96 (Study 007)	Month 108 (Study 007)	Month 120 (Study 007)	Month 132 (Study 007)	Month 144 (Study 007)	Month 156 (Study 007)
Dose-increasing group	Score	−1.73±1.13 (15)	−1.52±0.89 (11)	−1.52±1.01 (9)	−1.52±1.20 (6)	−1.96±1.11 (5)	−1.73±0.87 (4)	−1.77±0.76 (3)
	Change	1.78±0.87 (15)	1.99±0.46 (11)	2.01±0.63 (9)	1.83±0.89 (6)	1.48±0.82 (5)	1.63±0.73 (4)	1.73±0.67 (3)
Dose-remaining group	Score	−1.58±1.17 (16)	−1.87±1.36 (14)	−1.63±1.48 (8)	−1.25±0.59 (6)	−0.98±0.51 (4)	−0.70±0.42 (2)	-
	Change	1.91±0.57 (16)	1.73±0.81 (14)	2.01±0.92 (8)	2.25±0.45 (6)	2.28±0.32 (4)	2.50±0.14 (2)	-

Source: Table 14.2.2.2 Mean ± standard deviation (n), unit: SD , -: Not applicable

Figure 4. Height SDS for Chronological Age



Source: Figure 14.2.2.8 : mean value, horizontal line in box: median value, horizontal lines at top and bottom of box: 25% point and 75% point, vertical line (whiskers): within 1.5 interquartile range from box and point most separated from the median value,+: 1.5 interquartile range - 3rd interquartile range from the box, *: values more separated from the box than the 3rd interquartile range

Assessor's comments

The results confirm the positive impact on growth on continuous therapy although a waning efficacy on prolonged treatment was observed. This is well known from other studies on rhGH in children. Due to low number after month 96 the results beyond that period is not assessable. There seems to be a numeric better response in the dose-remaining group compared to the dose-increasing group; the difference is not expected to be statistically significant, the CIs are overlapping and overall, few patients are included in each group and the study was not powered for detecting differences between treatment groups. The observed changes are considered clinically relevant for both treatment groups.

The mean height SDS for bone age was slightly higher than the mean height SDS for chronological age up to Month 60 in the dose-increasing group and up to Month 48 in the dose-remaining group. Thereafter, the mean height SDS for bone age was slightly lower than the mean height SDS for chronological age in both groups, except at Month 108 and after Month 144 in the dose-increasing group and at Month 144 in the dose-remaining group. Throughout the entire period, the mean changes from the start of treatment in height SDS for bone age at each observation time point were 0.10 SD to 1.60 SD in both groups. The results are presented in Table 13.

Table 13. Actual Values and Changes in Height SDS for Bone Age

		Start of treatment (Study 002)	Month 12 (Study 002)	Month 24 (Study 007)	Month 36 (Study 007)	Month 48 (Study 007)	Month 60 (Study 007)	Month 72 (Study 007)
Dose-increasing group	Score	−2.24±1.32 (27)	−1.19±1.20 (27)	−1.15±1.15 (26)	−1.20±1.35 (24)	−0.74±1.32 (22)	−1.16±1.21 (20)	−1.78±1.02 (16)
	Change	-	1.06±0.96 (27)	1.04±1.18 (26)	1.06±1.08 (24)	1.56±1.29 (22)	1.09±1.15 (20)	0.80±1.23 (16)
Dose-remaining group	Score	−2.10±1.20 (31)	−0.68±1.54 (31)	−0.88±1.79 (31)	−1.17±1.62 (27)	−1.46±1.01 (22)	−1.80±0.97 (19)	−1.70±0.77 (14)
	Change	-	1.42±0.77 (31)	1.19±1.18 (31)	1.09±1.09 (27)	1.00±0.88 (22)	0.66±0.99 (19)	0.71±0.90 (14)

		Month 84 (Study 007)	Month 96 (Study 007)	Month 108 (Study 007)	Month 120 (Study 007)	Month 132 (Study 007)	Month 144 (Study 007)	Month 156 (Study 007)
Dose-increasing group	Score	−1.85±1.17 (13)	−1.77±1.12 (10)	−1.41±0.97 (8)	−1.58±1.50 (5)	−2.10±1.21 (4)	−1.40±0.17 (3)	−1.55±0.92 (2)
	Change	0.21±1.59 (13)	0.55±1.51 (10)	0.71±1.51 (8)	0.46±2.12 (5)	0.35±2.25 (4)	1.60±0.46 (3)	1.25±0.49 (2)
Dose-remaining group	Score	−2.15±0.92 (13)	−2.27±1.06 (13)	−1.94±1.37 (7)	−1.38±0.98 (5)	−0.98±0.74 (4)	−0.65±0.64 (2)	-
	Change	0.38±0.92 (13)	0.15±0.79 (13)	0.10±0.74 (7)	0.26±0.66 (5)	0.38±0.53 (4)	0.25±0.92 (2)	-

Source: Table 14.2.4.2 Mean ± standard deviation (n), unit: SD, -: Not applicable

Assessor's comments

A potential concern in rhGH therapy in children can be advance in bone age compared to chronological age resulting in premature closure of epiphysis and reduced final height. Results from Study 007 reassure that bone age is not accelerated compared to growth in height on prolonged therapy.

PAH (Adjusted height for parental heights) SDS

PAH SDS and the change from the start of treatment in the FAS (start of Study 002) was reported at start of treatment and observed every Months 12 from the start of treatment. Actual values and changes in PAH SDS from the start of treatment up to Month 156 are summarised in Table 16.

Table 16. Actual Values and Changes in PAH SDS

		Start of treatment (Study 002)	**Month 12 (Study 002)**	**Month 24 (Study 007)**	**Month 36 (Study 007)**	**Month 48 (Study 007)**	**Month 60 (Study 007)**	**Month 72 (Study 007)**
Dose-increasing group	Score	-2.90 ± 1.13 (29)	-2.30 ± 1.21 (29)	-1.78 ± 1.22 (28)	-1.54 ± 1.25 (26)	-1.28 ± 1.29 (24)	-1.34 ± 1.34 (21)	-1.43 ± 1.37 (20)
	Change	-	0.60 ± 0.29 (29)	1.11 ± 0.40 (28)	1.37 ± 0.48 (26)	1.70 ± 0.56 (24)	1.79 ± 0.66 (21)	1.80 ± 0.72 (20)
Dose-increasing group	Score	-2.68 ± 1.10 (32)	-1.74 ± 1.23 (32)	-1.27 ± 1.29 (32)	-0.96 ± 1.37 (28)	-0.93 ± 1.38 (23)	-0.86 ± 1.41 (20)	-0.97 ± 1.41 (16)
	Change	-	0.93 ± 0.34 (32)	1.40 ± 0.44 (32)	1.65 ± 0.54 (28)	1.82 ± 0.58 (23)	1.91 ± 0.51 (20)	2.06 ± 0.44 (16)

		Month 84 (Study 007)	**Month 96 (Study 007)**	**Month 108 (Study 007)**	**Month 120 (Study 007)**	**Month 132 (Study 007)**	**Month 144 (Study 007)**	**Month 156 (Study 007)**
Dose-increasing group	Score	-1.46 ± 1.41 (15)	-0.98 ± 0.96 (11)	-0.94 ± 1.10 (9)	-0.65 ± 0.77 (6)	-0.96 ± 0.70 (5)	-0.78 ± 0.41 (4)	-0.63 ± 0.32 (3)
	Change	1.78 ± 0.87 (15)	1.99 ± 0.46 (11)	2.01 ± 0.63 (9)	1.83 ± 0.89 (6)	1.48 ± 0.82 (5)	1.63 ± 0.73 (4)	1.73 ± 0.67 (3)
Dose-increasing group	Score	-1.14 ± 1.40 (16)	-1.26 ± 1.56 (14)	-1.29 ± 1.44 (8)	-1.20 ± 1.18 (6)	-0.95 ± 1.12 (4)	-0.85 ± 0.07 (2)	-
	Change	1.91 ± 0.57 (16)	1.73 ± 0.81 (14)	2.01 ± 0.92 (8)	2.25 ± 0.45 (6)	2.28 ± 0.32 (4)	2.50 ± 0.14 (2)	-

Source: Table 14.2.5.1 mean ± standard deviation (n), unit: SD, -: not applicable
PAH = Adjusted height from parental heights, SDS = standard deviation score

Assessor's comments

The genetic potential from the parents has an important impact on the final adult height. Consequently, it is relevant also to report final height adjusted for parental heights. However, the conclusion on efficacy does not change from results comparing data with population references.

It should be remarked that an error exists in the table since the "remaining" group data are provided in the lower part of the table where it is written as "increasing".

In subjects who achieved Near Final Height, the mean age at Near Final Height was 16.00 years in male and 14.32 years in female. The mean Near Final Height was 159.12 cm in male and 146.94 cm in female. The mean Near Final Height SDS was −1.56 SD in male and −1.61 SD in female, and −1.59 SD in overall subjects. In subjects observable until Near Final Height, height SDS indicated a trend of being greatly improved after the start of the treatment up to onset of puberty, and thereafter remaining up to Near Final Height.

Assessor's comments

The efficacy results from study 007 supports the well-established effect of Genotropin to patients with short stature due to SGA.

Safety results (Primary endpoint)

The primary aim of the post-marketing study was to assess safety.

No subject deaths were observed during the study period.

The number of subjects who were administered the investigational product was 29 subjects in the dose-increasing group and 32 subjects in the dose-remaining group. The average treatment period (including subjects who discontinued treatment) of Genotropin®, including Study 002 period, was 2612.7 days [approximately 85.7 months] (Range: 545 to 4942 days) in the dose-increasing group and 2352.2 days [approximately 77.1 months] (Range: 658 to 4469 days) in the dose-remaining group. Table 5 shows a summary of the adverse events reported during the study.

Table 5. Summary of Adverse Events

Adverse event[a]	All-causality adverse events			Treatment-related adverse events		
	Dose-increasing group	Dose-remaining group	Total	Dose-increasing group	Dose-remaining group	Total
Full analysis set	29	32	61	29	32	61
Subjects with adverse events	27	31	58	10	12	22
Incidence (%) of adverse events	93.1	96.9	95.1	34.5	37.5	36.1
Number of adverse events	648	587	1235	27	27	54
Subjects with severe adverse events	2	0	2	0	0	0
Subjects with serious adverse events	10	5	15	1	1	2
Subjects discontinued due to adverse events	1	1	2	0	1	1

Source: Table 14.3.1.1.1, Table 14.3.1.2.1, Table 14.3.2.1

a. Includes adverse events that remained unresolved at the start of Study 007.

There were 1235 all-causality adverse events in 58 subjects (95.1%) and 54 treatment-related adverse events in 22 subjects (36.1%) of 61 subjects (Table 27). Regarding the severity of all-causality adverse events, all these events were mild or moderate other than severe adverse events in 2 subjects in the dose-increasing group (hernia inguinal and cryptorchism in 1 subject and inflicted injury in 1 subject). The treatment-related adverse events were all mild or moderate.

Table 27. Incidence of Treatment-Related Adverse Events

	Dose-increasing group	Dose-remaining group	Total
Number of subjects in full analysis set	29	32	61
WHO-ART organ classification and preferred terms[a]	Number of cases with incidences (%)		
Skin and Appendages Disorders	0	3 (9.4)	3 (4.9)
Alopecia	0	1 (3.1)	1 (1.6)
Eczema	0	1 (3.1)	1 (1.6)
Erruca	0	1 (3.1)	1 (1.6)
Musculo-skeletal System Disorders	1 (3.4)	1 (3.1)	2 (3.3)
Arthralgia	1 (3.4)	1 (3.1)	2 (3.3)
Central and Peripheral Nervous System Disorders	2 (6.9)	0	2 (3.3)
Headache	2 (6.9)	0	2 (3.3)
Gastro-intestinal System Disorders	0	1 (3.1)	1 (1.6)
Abdominal pain	0	1 (3.1)	1 (1.6)
Mouth Cyst	0	1 (3.1)	1 (1.6)
Liver and Biliary System Disorders	1 (3.4)	0	1 (1.6)
SGOT increased	1 (3.4)	0	1 (1.6)
SGPT increased	1 (3.4)	0	1 (1.6)
Metabolic and Nutritional Disorders	2 (6.9)	3 (9.4)	5 (8.2)
Glucose Tolerance Abnormal	1 (3.4)	3 (9.4)	4 (6.6)
Hyperglycaemia	1 (3.4)	0	1 (1.6)
Endocrine Disorders	1 (3.4)	3 (9.4)	4 (6.6)
Puberty Precocious	1 (3.4)	0	1 (1.6)
Endocrine Disorders NOS	0	1 (3.1)	1 (1.6)
Thyroxine decrease	0	1 (3.1)	1 (1.6)
Adenoidal hypertrophy	1 (3.4)	1 (3.1)	2 (3.3)
Respiratory System Disorders	0	1 (3.1)	1 (1.6)
Pharyngitis	0	1 (3.1)	1 (1.6)
White Cell and RES Disorders	1 (3.4)	1 (3.1)	2 (3.3)
Eosinophilia	1 (3.4)	0	1 (1.6)
Leukocytosis	1 (3.4)	1 (3.1)	2 (3.3)
Lymphocytes atypical	1 (3.4)	0	1 (1.6)
Urinary System Disorders	0	2 (6.3)	2 (3.3)
Albuminuria	0	1 (3.1)	1 (1.6)
Haematuria	0	1 (3.1)	1 (1.6)
Fetal disorder	0	1 (3.1)	1 (1.6)
Jaw malformation	0	1 (3.1)	1 (1.6)
Body as a Whole-General Disorders	2 (6.9)	2 (6.3)	4 (6.6)
Chest pain	1 (3.4)	0	1 (1.6)
Fever	2 (6.9)	0	2 (3.3)
Pain	0	2 (6.3)	2 (3.3)
Application site disorder	3 (10.3)	1 (3.1)	4 (6.6)
Injection site pain	1 (3.4)	0	1 (1.6)
Injection site reaction	0	1 (3.1)	1 (1.6)
Injection site bleeding	2 (6.9)	0	2 (3.3)
Resistance mechanism disorder	0	1 (3.1)	1 (1.6)
Abscess	0	1 (3.1)	1 (1.6)
Secondary term	0	2 (6.3)	2 (3.3)
Molluscum contagiosum	0	1 (3.1)	1 (1.6)
Scoliosis	0	1 (3.1)	1 (1.6)

Source: Table 14.3.1.2.2
WHO-ART = WHO adverse reaction reporting system terminology
a. Adverse events that had not resolved at the start of Study 007 were also included.

Assessor's comments

As can be expected for a prolonged study over years almost all patients reported adverse events. In general, the adverse events were mostly trivial minor disorders of commonly reported during

childhood. Additional, most of the most commonly reported adverse events are known adverse events already reported in the SmPC. Two (2) patients (3.3%) reported headache. This is not mentioned as a known adverse event to Genotropin® however not unlikely related. The Applicant is asked to discuss if headache should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. **(OC)** Likewise, in the present study, two (2) patients (3.3%) reported adenoidal hypertrophy; this is also likely related to the treatment with Genotropin®. The Applicant is asked to discuss if this adverse reaction should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. **(OC)**

Of note, the Guideline states *"This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports."* and further *"This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product."*

1) A Guideline On Summary Of Product Characteristics (SmPC), September 2009, page 15.

All-causality serious adverse events were observed in 15 subjects, and no deaths were reported. Of these subjects, treatment-related serious adverse events were observed in 1 subject in the dose-increasing group (adenoidal hypertrophy), and 1 subject in the dose-remaining group (tonsillar hypertrophy, adenoidal hypertrophy, and disease progression). Except for these events, the causal relationship to the study drug was ruled out for all serious AEs. Table 6 provides an overview of the serious adverse events reported during the study.

Table 30. Serious Adverse Events

Treatment group	Subject ID	Adverse event (MedDRA version 18.1 preferred term)	Causal relationship according to investigator/subinvestigator	Outcome
Dose-increasing group	S01-01	Asthma, upper respiratory tract inflammation, gastroenteritis	Not related	Recovered
	S05-01	Ovarian failure	Not related	Unresolved
	S10-03	Bronchitis	Not related	Recovered
	S13-02	Acute Tonsillitis	Not related	Recovered
	S15-02	Inguinal hernia, cryptorchism	Not related	Recovered
	S17-07	Pneumonia mycoplasmal	Not related	Recovered
	S18-03	Adenoidal hypertrophy	Treatment related	Recovered
		Otitis media	Not related	Recovered
		Sudden hearing loss	Not related	Recovered
	S19-02	Hand fracture, hepatic function abnormal	Not related	Recovered
	S19-04	Gastroenteritis	Not related	Recovered
	S20-01	Hypospadias	Not related	Recovered
Dose-remaining group	S01-02	Otitis media, chronic tonsillitis, adenoidal hypertrophy	Not related	Recovered
	S05-03	Inguinal hernia	Not related	Recovered
	S10-01	Impaired healing	Not related	Recovered
	S17-03	Retinal detachment, infectious mononucleosis	Not related	Recovered
	S18-01	Tonsillar hypertrophy, adenoidal hypertrophy, disease progression	Treatment related	Recovered

Source: Table 14.3.2.1
MedDRA: ICH Medical Dictionary for Regulatory Activities

Adverse events leading to permanent discontinuation were reported in 1 subject in the dose-increasing group (sex chromosome disorder [verbatim term: Turner syndrome]) and 1 subject in the dose-remaining group (jaw malformation [verbatim term: mandibular protrusion]). Of these events, jaw malformation was considered treatment-related; however, both events were mild in severity and reported to be stable although the outcome was classified as not resolved. For 1 subject who discontinued the study treatment due to sex chromosome disorder, the event was considered to meet the exclusion criterion specified in the protocol and the subject discontinued the study due to a protocol deviation.

Assessor's comments

Serious adverse events were few and all recovered. Only in two cases a relation to study drug was reported, and the adverse reaction consisted of a disorder already included in the tabulated list of adverse reaction in section 4.8 of the SmPC.

PPdAR REQUEST FOR SUPPLEMENTARY INFORMATION

1) By entry to Study 007, all patients (including patients previously (in Study 002) treated with 0.033 mg/kg/day) were treated with a dose of 0.067 mg/kg/day, but according to the study protcol, the dose could be reduced to 0.033 mg/kg/day. This could be either due to age, puberty, growth, or due to safety reasons. There is no information regarding the number of patients who had the dose reduced, nor is there information regarding the reason for dose-reduction. This information should be presented by the Applicant. **(OC)**
2) Furthermore, 16 patients withdrew consent, and the Applicant should provide information regarding the reasons for these withdrawals. **(OC)**
3) In the present study, 2 patients (3.3%) reported headache. This is not mentioned as a known adverse event to Genotropin® however not unlikely related to study treatment. Likewise, in the present study, 2 patients (3.3%) reported adenoidal hypertrophy; this is also likely related to the treatment with Genotropin®. The Applicant is asked to discuss if

   a) Headache should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. **(OC)**

   b) Adenoidal hypertrophy should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC **(OC)**

ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 (Rapporteur-DK):

By entry to Study 007, all patients (including patients previously (in Study 002) treated with 0.033 mg/kg/day) were treated with a dose of 0.067 mg/kg/day, but according to the study protocol, the dose could be reduced to 0.033 mg/kg/day. This could be either due to age, puberty, growth, or due to safety reasons. There is no information regarding the number of patients who had the dose reduced, nor is there information regarding the reason for dose-reduction. This information should be presented by the Applicant.

Additional comment from CMS: The Rapporteur may wish to consider the following proposal to focus the question towards potential safety concerns: There is no information regarding the number of patients who had the dose reduced, nor is there information regarding the reason for dose reduction. This information should be presented by the Applicant and discussed in context, with a focus on dose alterations/interruptions due to safety concerns.

MAH's response:

Study A6281225 (GENASG-0021-007) was a long-term study carried out as an extension of Protocol GENASG-0021-002. Study A6281225 was initiated as a clinical study and continued after the approval of the indication as a post-marketing study. The protocol for A6281225 described the intent for all patients to receive a dose of 0.067 mg/kg/day during the study though the dose could be changed for a patient to 0.033 mg/kg/day after they had entered this post-marketing study.

Two (2) patients recruited to the A6281225 study received what could be considered as a reduced dose during the study. Both of these patients had actually reduced the dose before entering this post-marketing study GENASG-0021-002.

One (1) patient in the dose-increasing group (Subject ID: S14-01) continued with the dose (0.033 mg/kg/day) they were receiving in Study GENASG-0021-002. This was at the discretion of the Principal Investigator; the investigator had made a judgement that a dose of 0.033 mg/kg/day was sufficiently efficacious. This was recorded as a protocol deviation event. For the analysis shown in the case study report (CSR) of Study GENASG-0021-002, this subject was included in the dose-increasing group.

The other patient in the dose-maintaining group (Subject ID: S08-04) had reduced the dose from 0.067 mg/kg/day to 0.033 mg/kg/day at Month 37 since the initiation of the study GENASG-0021-002. This meant that reduction in the dose took place during Study GENASG-0021-007 as Study GENASG-0021-002 lasted 2 years. This was because the subject's oral glucose tolerance test (OGTT) result was judged to be borderline.

A summary of the Genotropin® dose for subjects S14-01 and S08-04 and OGTT result for S08-04 during the Study GENASG-0021-007 is shown in Table 1 and Table 2, respectively.

Table 1. Genotropin® Dose for Subjects S14-01 and S08-04

Subject ID	Dose Group	Visit	Genotropin Dose (mg/kg/d)
S14-01	Dose-increasing	Day 0 (Study 002 initiation)	0.0325
		Month 12	0.0357
		Month 24 (Study 007 initiation)	0.0309
		Month 36	0.0323
		Month 48	0.0350
		Month 60	0.0348
		EOS	0.0316
S08-04	Dose-maintaining	Day 0 (Study 002 initiation)	0.0680
		Month 12	0.0671
		Month 24 (Study 007 initiation)	0.0698
		Month 36	0.0663
		Month 48	0.0317
		Month 60	0.0332
		Month 72	0.0332
		EOS	0.0332

Source: CSR S14-01 and S08-04 Appendix Table 16.2.4. Appendices are in Japanese and this was made known at the time of the original submission.
CSR = Case study report; EOS = end of study; ID = identification.

Table 2. OGTT Result for Subject S08-04

Subject ID	Visit	Judgement	Time Point	Blood Glucose (mg/dL)	IRI (μU/mL)
S08-04	Day 0 (Study 002 initiation)	Normal	Baseline	88	4.1
			After 30 minutes	175	25.1
			After 60 minutes	159	22.3
			After 90 minutes	118	17.9
			After 120 minutes	127	12.3
	Month 12	Normal	Baseline	86	4.3
			After 30 minutes	106	17.8
			After 60 minutes	151	37.1
			After 90 minutes	140	32.4
			After 120 minutes	125	27.1
	Month 24	Normal	Baseline	90	5.9
			After 30 minutes	161	50.3
			After 60 minutes	138	25.4
			After 90 minutes	134	37.3
			After 120 minutes	95	8.0
	Month 36	Borderline	Baseline	96	10.8
			After 30 minutes	150	81.9
			After 60 minutes	109	26.2
			After 90 minutes	116	36.6
			After 120 minutes	151	70.6
	Month 48	Normal	Baseline	79	11.2
			After 30 minutes	126	51.6
			After 60 minutes	117	43.2
			After 90 minutes	106	31.9
			After 120 minutes	103	34.5
	Month 60	Normal	Baseline	90	11.1
			After 30 minutes	166	89.8
			After 60 minutes	157	63.1
			After 90 minutes	149	97.6
			After 120 minutes	95	32.7
	Month 72	Normal	Baseline	92	15.6
			After 30 minutes	164	161.7
			After 60 minutes	121	67.2
			After 90 minutes	109	45.6
			After 120 minutes	137	97.0
	EOS		Baseline	93	10.0
			After 30 minutes	153	86.2
			After 60 minutes	122	61.6
			After 90 minutes	82	18.7
			After 120 minutes	118	57.2

Source: CSR S08-04 Appendix Table 16.2.8. Appendices are in Japanese and this was made known at the time of the original submission.

CSR = case study report; EOS = end of study; ID = identification; IRI = immunoreactive insulin; OGTT = oral glucose tolerance test.

Assessor's comments:

The protocol described the intent for all patients to receive a dose of 0.067 mg/kg/day during the study though the dose could be changed for a patient to 0.033 mg/kg/day after they had entered this post-marketing study.

Two patients received what could be considered as a reduced dose during the study. Both of these patients had actually reduced the dose before entering this post-marketing study.

One patient in the dose-increasing group (Subject ID: S14-01) continued with the dose (0.033 mg/kg/day) they were receiving before entering the Study. In their response, the MAH informs that this was at the discretion of the Principal Investigator; the investigator had made a judgement that a dose of 0.033 mg/kg/day was sufficiently efficacious. This was recorded as a protocol deviation event.

The other patient in the dose-maintaining group (Subject ID: S08-04) had reduced the dose from 0.067 mg/kg/day to 0.033 mg/kg/day at Month 37 since the initiation of the previous study. According to the MAH, this was because the subject's oral glucose tolerance test (OGTT) result was judged to be borderline and thus, one case of dose reduction may be attributable to safety concerns (glucose tolerance test (OGTT) result judged to be borderline).

Overall, the MAH has sufficiently described the number of number of patients who had the dose reduced, as well as the reasons for the patients' dose-reduction, including one case which may be associated with a safety problem as described above. The issue will not be further pursued.

Conclusion*: This issue is resolved.*

Question 2 (Rapporteur-DK):

Furthermore, 16 patients withdrew consent, and the Applicant should provide information regarding the reasons for these withdrawals.

Additional comment from CMS: It is understood that the 16 patients who withdrew consent, discontinued until the date of MA approval. The Rapporteur may wish to extend the question to provide also information on those 5 patients who withdrew consent and discontinued after having entered the post marketing study (see Table 5 in report). This will give a more detailed picture based on the cut-off of MA. In addition the reasoning behind the 'other' causes for discontinuation remains unclear. The Applicant is asked to comment on these.

MAH's response:

In Study 007, 16 subjects withdrew between the study initiation and the date of marketing approval with the reason of "Withdrawn consent".[1]

- When subjects were withdrawn or chose to withdraw from the study, investigators were instructed to record it in the Case Report Form (CRF) from 1 of the following reasons for withdrawal: AE, protocol violation, withdrawn consent, lost to follow-up or others. If the reason given was "Withdrawn consent", the CRF did not require a detailed reason to be given for this.

For the convenience of this assessment, the page from the CRF that recorded this information is provided in Appendix 1 of the response. The CRF for the study is approximately 200 pages in length and only available in Japanese. The page from the CRF included in Appendix 1 has been annotated with the English translations of the Japanese text.

The Study Protocol required the reason for withdrawal to be recorded, but a detailed reason was not expected. According to Japanese Regulation, involving the process of Clinical Trial Notification Review, the Study Protocol and CRF were submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) for review before the study could commence.

All CRFs were reviewed and verified, by the Clinical Research Associate (CRA) for the study, to ensure that the data entered into them followed completion requirements as a part of the Source Data Verification process.

As mentioned above, the detailed reason for withdrawal of consent was not required to be collected during the study. However, specific reasons for "Withdrawn consent" were provided for 5 (S07-08, S14-01, S05-02, S07-04 and S17-02) of these 16 patients. These were made available in monitoring visit reports. The available detailed reasons for the withdrawals of consent by the patients originally recruited for the study are provided in Table 3.

Table 3. Reasons for the Withdrawal of Consent by the Patients in Study GENASG-0021-007 (A6281225)

Subject ID	Dose Group	Major Reason for Withdrawal	Detailed Reason for Withdrawn Consent
S01-03	Dose-increasing	Withdrawn consent	No additional information
S07-08	Dose-increasing	Withdrawn consent	Because the subject found herself grown taller and also she was concerned about slight enlargement of breast.
S12-04	Dose-increasing	Withdrawn consent	No additional information
S13-02	Dose-increasing	Withdrawn consent	No additional information
S14-01	Dose-increasing	Withdrawn consent	Because the subject found herself grown taller enough and thus wanted to quit GH treatment by and by.
S16-01	Dose-increasing	Withdrawn consent	No additional information
S17-01	Dose-increasing	Withdrawn consent	No additional information
S17-08	Dose-increasing	Withdrawn consent	No additional information
S05-02	Dose-remaining	Withdrawn consent	Due to parent's relocation to another city
S05-04	Dose-remaining	Withdrawn consent	No additional information
S07-02	Dose-remaining	Withdrawn consent	No additional information
S07-04	Dose-remaining	Withdrawn consent	Because the subject found herself grown taller enough and regular visit to hospital was burdensome.
S11-01	Dose-remaining	Withdrawn consent	No additional information
S13-03	Dose-remaining	Withdrawn consent	No additional information
S17-02	Dose-remaining	Withdrawn consent	Because she got too busy to continue study participation due to entrance into a junior high school
S18-04	Dose-remaining	Withdrawn consent	No additional information

Assessor's comments:

The Study Protocol required the reason for withdrawal to be recorded, but a detailed reason was not expected. According to Japanese Regulation, involving the process of Clinical Trial Notification Review, the Study Protocol and CRF were submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) for review before the study could commence. All CRFs were reviewed and verified, by the Clinical Research Associate (CRA) for the study, to ensure that the data entered into them followed completion requirements as a part of the Source Data Verification process.

When subjects were withdrawn or chose to withdraw from the study, investigators were

instructed to record it in the Case Report Form (CRF) from 1 of the following reasons for withdrawal: AE, protocol violation, withdrawn consent, lost to follow-up or others. If the reason given was "Withdrawn consent", the CRF did not require a detailed reason to be given for this.

Specific reasons for "Withdrawn consent" were provided for 5 (S07-08, S14-01, S05-02, S07-04 and S17-02) of these 16 patients. These were made available in monitoring visit reports. The available detailed reasons for the withdrawals of consent by the patients originally recruited for the study are provided in Table 3 above. It appears that three patients withdrew due to an acceptable effect of the treatment. There is no information regarding how many patients may have withdrawn due to adverse reactions, which indeed could have been interesting to know. However, according to the MAH, the information is not available. Of note, from the response to Question 3 (see below) it is mentioned that the genotropin-dose was reduced in 3 patients with headache thus it is likely, that in at least 3 cases, the dose was reduced due to (possible) adverse reactions). Nevertheless, the issue will not be pursued.

Conclusion*: This issue is resolved.*

Question 3 (Rapporteur-DK):

In the present study, 2 patients (3.3%) reported headache. This is not mentioned as a known adverse event to Genotropin® however not unlikely related to study treatment. Likewise, in the present study, 2 patients (3.3%) reported adenoidal hypertrophy; this is also likely related to the treatment with Genotropin®. The Applicant is asked to discuss if

a) Headache should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC.
b) Adenoidal hypertrophy should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC.

Additional comment from CMS: The Rapporteur may wish to consider rephrasing the question asking the Applicant to include headache and adenoidal hypertrophy in section 4.8, rather than asking to discuss if it should be included. This takes into account that causality has been established (see table 27 referring to treatment related AEs), with the AEs being at least reasonably possible, as mentioned by the Rapporteur.

Additional comment from CMS: With regards to the inclusion of "headache" and "adenoidal hypertrophy" in section 4.8 this could be accepted provided that the cases are considered at least possibly related to treatment. However, the size of the study is small. Therefore, the MAH should be requested to search their clinical study safety for these two events before assigning a frequency.

MAH's response (incorporation comments from CMS):

a) Headache:

Analysis of the results of the MAH's safety database search does not provide sufficient evidence that headache is related to growth. The detailed results of MAH's safety database search are found in Appendix 2.

The literature search for headache in association with GH treatment included a search of clinical trials as well as safety surveillance database publications. The results of the analysis of the literature search found that headaches were not reported more commonly in GH-treated children than in reports of children in school health surveys (ie, non-GH-treated children). No support was

found for a direct association between headache and GH treatment. The detailed results of literature search are found in Appendix 3.

Conclusion: The review of the MAH's safety database as well as the relevant literature did not provide sufficient evidence to suggest that headache was related to GH treatment. As such, the MAH does not find sufficient justification to add 'headache' to the list of ADRs in the SmPC.

b) Tonsillar/Adenoidal Hypertrophy:

Analysis of the results of the MAH's safety database search does not provide sufficient evidence that adenoidal hypertrophy is related to GH treatment. The detailed results of MAH's safety database are found in Appendix 2.

The literature search for adenoidal hypertrophy in association with GH treatment included a search of clinical trials as well as review publications. The results of the analysis of the literature search did not find sufficient justification to add "Adenoidal hypertrophy" to the list of ADRs in the SmPC. The detailed results of literature search are found in Appendix 3.

Conclusion: The review of the MAH's safety database as well as the relevant literature does not support an association between adenoidal hypertrophy and GH treatment. As such, the MAH does not find sufficient justification to add "Adenoidal hypertrophy" to the list of ADRs of the SmPC.

Overall Conclusion: The review of the MAH's safety database as well as the relevant literature does not support a causal association between GH treatment and either "Headache" or "Adenoidal hypertrophy". As such, the MAH does not find sufficient justification to add "Headache" or "Adenoidal hypertrophy" as ADRs to Section 4.8 of the SmPC. The MAH further considers that the benefit/risk ratio for Genotropin® remains unchanged and positive.

Assessor's comments:

With regards to Question 3.a: The MAH's safety database contains cases of AEs reported spontaneously to MAH, cases reported by the HAs, cases published in the medical literature, cases from MAH-sponsored marketing programmes, non-interventional studies and cases of serious AEs reported from clinical studies regardless of causality.

A comprehensive search of the MAH's safety database identified 1352 somatropin cases reporting an event encoded to the PT Headache.

In 1159 cases, limited information was provided with regard to event outcome, concomitant/co-suspect medications, medical history, clinical details of the event, results of relevant clinical and laboratory tests (such as fundoscopy, brain imaging and blood tests), latency information and action taken with somatropin; hence precluding a meaningful medical assessment.

In 171 cases, the contributory role of somatropin to headache was plausible. However, these cases either contained various confounding factors, including patient's underlying medical history (eg, headache, tension headache, migraine, head injury, brain tumour, hydrocephalus, sickle cell anaemia, self-harming behaviour due to autistic disorder, juvenile arthritis), intercurrent illness/events (eg, infection, emotional disturbance, psychological stress, insomnia, benign intracranial hypertension (BIH), fluid retention, migraine, psychosomatic problems, allergic reaction, neck pain, pituitary enlargement, retinal detachment, recent change in prescription for corrective lenses, incorrect dose of somatropin injected), co-suspect or concomitant medications (eg, fludrocortisone, desmopressin, goserelin, bromocriptine, atomoxetine) and/or had a latency period of >1 year between start of somatropin and onset of

headache, making a definitive assessment of underlying causality difficult.

Upon review of the remaining 22 cases, no confounding factors could be identified. Patient ages among these cases ranged from 3 to 16 years, with a mean age of 9.9 years (n=20). The latency periods (for the event PT Headache) were quite scattered: <1 day (3), >1 day and <7 days (2), >7 days and <1 month (1), >1 month and <6 months (7), >6 months and <1 year (2), post-therapy (2) and unknown (5). Actions taken with somatropin were dose not changed in 8 cases, dose reduced in 3 cases, permanently withdrawn in 5 cases and temporarily withdrawn in 6 cases. Event outcomes for headache were resolved/resolving in 12 cases and not resolved in 10 cases.

In several international post-marketing surveillance databases, headache has been reported as the most common among the reported AEs. In the large databases including KIGS, OZGROW and GeNeSIS with data collected from thousands of patients, headache was reported with much lower incidence than that reported in initial pivotal clinical trials and the incidence of headache also showed some differences in different populations. The review of the KIGS database showed that the incidence of headache was significantly higher in the craniopharyngioma group (0.046%) than in the other groups. The incidence of headache in patients with CGHD (0.019%) and cranial tumours (0.022%) was significantly higher than in those with IGHD (0.010%), ISS (0.007%), TS (0.011%) and CRI (0.004%) and higher than in PWS (0.007%), suggesting that the underlying disease could be a confounding factor for the event of headache. The GH treatment duration also showed a wide range in these databases with the longest treatment duration being 4.4 years.

The MAH does not find sufficient justification to add headache to the ADR section of the SmPC since a review of the above mentioned data from the literature does not suggest that headache is more common in GH-treated children than in the general (non-GH-treated) paediatric population.

With regards to Question 3.b: A comprehensive search of the MAH's safety database identified 31 somatropin cases reporting AEs encoded to the PTs Adenoidal hypertrophy and/or Adenoidal disorder.

In 6 cases, limited information was provided with regards to 1 or more of the following factors of event outcome, concomitant medications, medical history, clinical details of the event, latency information and drug administration details for somatropin; hence precluding a meaningful medical assessment.

In 13 cases, the contributory role of somatropin to adenoidal hypertrophy/disorder was plausible. However, these cases contained various confounding factors, including the patient's underlying medical history (eg, tonsillar hypertrophy, adenoidal disorder, recurrent rhinitis/otitis, sudden hearing loss suspected to be caused by adenoid vegetation, tonsillectomy and recent history of infections) and intercurrent illness/events (eg, otitis media with hearing loss), making a definitive assessment of underlying causality difficult.

Upon review of the remaining 11 cases, no confounding factors could be identified. Patient ages among these cases ranged from 2 to 38 years, with a mean age of 8.3 years (n=11).

The latency periods (for the PTs Adenoidal hypertrophy and Adenoidal disorder) were >6 months and <1 year (6), >1 year (3) and unknown (2). Actions taken with somatropin were: dose not changed in 8 cases, permanently withdrawn in 1 case, temporarily withdrawn in 1 case and not applicable in 1 case. Event outcomes for adenoidal hypertrophy/disorder were resolved/resolving in 9 cases, not resolved in 1 case and unknown in 1 case.

Review of the MAH's safety database did not provide sufficient evidence to suggest that

Genotropin was causally-related to tonsillar hypertrophy. Therefore, the MAH does not find sufficient justification to add adenoidal hypertrophy to the ADR section of the SmPC.

Conclusion, question 3.a: *Headache is common during childhood and in clinical trials over several years, it is to be expected that some patients will report headache. Causality with drug therapy is consequently very difficult. The review of large databases as well as the literature provides no clear conclusion, and at present, it is accepted not to change the SmPC since the signal is weak and it does not support the inclusion of headache into the SmPC.*

Conclusion, question 3.b: *Registration of adenoidal hypertrophy is a rare event and the causality is unclear. At present, it is accepted that the signal is weak and it does not support the inclusion of adenoidal hypertrophy into the SmPC.*

Question 4 (CMS): SGA is an approved indication, and thus the final height SDS data from this open label study (007) should be included, as the data is considered informative for the physician. The results for final height SDS of pivotal study 002 are already reflecting in SmPC section 5.1. Further, currently section 5.1 states that long-term safety is lacking, however based on the currently submitted data this statement should be considered to be deleted.

Assessor's comments:

The MAH has neither commented on this question nor submitted a proposal for update of the SmPC. Therefore, the question remains and the MAH is asked to submit a proposal for update of the SmPC.

Conclusion*: This issue is NOT resolved.* The question remains and the MAH is asked to submit a proposal for update of the SmPC. **(OC)**

FPdAR REQUEST FOR SUPPLEMENTARY INFORMATION

SGA is an approved indication, and thus the final height SDS data from this open label study (007) should be included, as the data is considered informative for the physician. The results for final height SDS of pivotal study 002 are already reflecting in SmPC section 5.1. Further, currently section 5.1 states that long-term safety is lacking, however based on the currently submitted data this statement should be considered to be deleted. Lastly, the MAH is asked to submit a proposal for update of the SmPC.

ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 (Rapporteur-DK and CMS):
SGA is an approved indication, and thus the final height SDS data from this open label study (007) should be included, as the data is considered informative for the physician. The results for final height SDS of pivotal study 002 are already reflecting in SmPC section 5.1. Further, currently section 5.1 states that long-term safety is lacking, however based on the currently submitted data this statement should be considered to be deleted. Lastly, the MAH is asked to submit a proposal for update of the SmPC.

MAH's response:
The MAH is in agreement with the CMS on the need to amend section 5.1 of the SmPC. It is the MAH's understanding that the amendment would involve the text in section 5.1 as set out below *(Deleted text is shown in strikethrough)*:
"In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. ~~Long-term safety data are still limited.~~"

Assessor's comments

The MAH agrees to submit a variation application in order to update section 5.1 of the SmPC.

Conclusion: *This issue is resolved*

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The post-marketing Study 007 provides confirmation of a positive impact on growth in SGA children giving continuous treatment until final adult height. The study size is small and does allow analysis of subgroups or identification of predictors of response. A few other concerns were initially identified but these are all considered solved as the MAH agrees to submit a variation application in order to update section 5.1 of the SmPC. The positive benefit/risk ratio for Genotropin in SGA indication remains unchanged.

- **Recommendation**

Section 5.1 of the SmPC should be amended as set out below *(Deleted text is shown in strikethrough)*:

"In clinical trials in short children born SGA doses of 0.033 and 0.067 mg/kg body weight per day have been used for treatment until final height. In 56 patients who were continuously treated and have reached (near) final height, the mean change from height at start of treatment was +1.90 SDS (0.033 mg/kg body weight per day) and +2.19 SDS (0.067 mg/kg body weight per day). Literature data from untreated SGA children without early spontaneous catch-up suggest a late growth of 0.5 SDS. ~~Long-term safety data are still limited.~~"

Type IB variation to be requested from the MAH within 30 days after the finalisation of the procedure.