31 May 2018
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Omnitrope

somatropin

Procedure no: EMEA/H/C/000607/P46/037

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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CHMP members comments	22 May 2018
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CHMP conclusion	31 May 2018
Need for plenary discussion	No

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1. Introduction

On 18 December 2017, the MAH submitted two completed paediatric studies for Omnitrope 5 mg/ml powder and solvent for solution for injection, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These in-use-drug surveys were conducted for the purpose of investigating the safety and efficacy of Somatropin Omnitrope 1.3 mg/ml powder and solvent for solution for injection, Sandoz during real world use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Omnitrope and that no consequential regulatory action is required.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

It is assumed that the submitted studies SAN-EP00-PW and SAN-EP00-SGA are stand-alone studies.

2.2. Information on the pharmaceutical formulation used in the studies

N/A

2.3. Clinical aspects

2.3.1. Introduction

Omnitrope, a recombinant human growth hormone was developed as a biosimilar medicinal product to the reference product Genotropin and has been approved in the European Union since 2006 trough a centralized procedure (EMEA/H/C/607) for the following indications:

Infants, children and adolescents

- Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD).
- Growth disturbance associated with Turner syndrome.
- Growth disturbance associated with chronic renal insufficiency.
- Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted height SDS < -1) in short children/adolescents 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 (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 re-evaluated 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 hypothalamic-pituitary disease or insult, an insulin-like growth factor-I (IGF-I) SDS < -2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD.

Dosing

Dosing varies between indications and ranges from 0.025 to 0.050 mg/kg/day.

For PWS the dose regimen is: Generally a dose of 0.035 mg/kg body weight per day or 1.0 mg/m^2 body surface area per day is recommended. Daily doses of 2.7 mg should not be exceeded. Treatment should not be used in paediatric patients with a growth velocity less than 1 cm per year and near closure of epiphyses.

For SGA the dose regimen is: A dose of 0.035 mg/kg body weight per day (1 mg/m^2 body surface area per day) is usually recommended until final height is reached (see section 5.1). Treatment should be discontinued after the first year of treatment if the height velocity SDS is below + 1. Treatment should be discontinued if height velocity is < 2 cm/year and, if confirmation is required, bone age is > 14 years (girls) or > 16 years (boys), corresponding to closure of the epiphyseal growth plates.

This report will discuss the studies submitted by the applicant:

- A specific use-results survey of Somatropin BS S.C. Injection 5 mg, 10 mg for Prader-Willi syndrome (SAN-EP00-PW).
- A specific use-results survey of Somatropin BS S.C. Injection 5 mg, 10 mg for SGA (small for gestational age) short stature not associated with epiphyseal arrest (SAN-EP00-SGA).

2.3.2. Clinical studies

2.3.2.1. Study SAN-EP00-PW

A specific use-results survey of Somatropin BS S.C. Injection 5 mg, 10 mg for Prader-Willi syndrome.

2.3.2.1.1. Description

Rapporteur's comment: No formal study report with a clear description of the design of the survey, the results and safety observations was submitted. No formal protocol was included in the dossier. The applicant is requested to submit both the protocol and the final study report of both surveys.

Methods

Objective(s)
This specific use-results survey was conducted for the purpose of investigating the safety and efficacy of somatropin (Omnitrope 1.3 mg/ml powder and solvent for solution for injection) in current clinical practice.

Rapporteur's comment: This survey will capture real life information on treatment, efficacy and safety. As such these are the first data collected in a real-world practice setting included in this dossier.

Study design
Survey forms were collected from patients in a two-year registration period from 11 contract institutions in Japan. Patients were observed for one year and data on clinical outcome was acquired.

Rapporteur's comment: From the submitted information it is not clear how patients and centres were selected. It can thus not be assessed whether selection bias occurred. The requested protocol and the final study report should provide this information.

In this in-use drug survey no control group was included which will hamper the assessment of the efficacy results. The applicant is requested to compare the survey data with growth charts of healthy Japanese children and/or natural history data of Japanese patients with Prader-Willi syndrome.

Further a one year observational period is rather short for the assessment of efficacy (change in body composition or growth). Literature regarding this subject often described a more than 2 year study period. No information on long-term safety can be collected.

Study population /Sample size
The survey was started in September 2013 with the objective of accumulating the total number of registered subjects in the first two years or 5 subjects.

Patients with Prader-Willi syndrome were included. Diagnosis of PWS was confirmed by DNA analysis.

Rapporteur's comment: no specifications are provided about the diagnosis of Prader-Willi syndrome. It is assumed the diagnosis is confirmed with appropriate genetic testing according to the Endocrine Society international guidelines[1]. The requested protocol and the final study report should provide this information.

From the submitted summary it can be concluded that 8 out of the 9 patients were treatment naïve. Since the biggest effect (catch-up growth) of treatment is expected within the first two years, this is important information as the efficacy might be exaggerated.

No formal sample size calculation was made. The survey aims to include 5 patients. Given the rareness of the PWS this is considered acceptable.

Treatments
Somatropin (Omnitrope 1.3 mg/ml powder and solvent for solution for injection).

Rapporteur's comment: no specifications are provided about the exact dosing regimen. It is assumed that the recommendations in the SmPC are followed. The requested protocol and the final study report should provide this information.

[1] Goldstone *et al.* Recommendations for the diagnosis and management of Prader-Willi syndrome. *JCEM* (2008), 93 (11):4183-4197.

Outcomes/endpoints
The reported outcome parameters are: Change in height, height SDS value, Change in growth rate, Growth rate SDS, bone age and degree of obesity. These parameters were evaluated at the start of the administration, after 6 months and after 12 months.

Rapporteur's comment: These are the standard anthropomorphic measurements. As this is PWS it is considered a drawback that no information on body composition is measured. Furthermore, it is not to be expected that the efficacy can be reliably measured within the time frame of one year.

Statistical Methods
The 6 and 12 months measurements were compared with the measurements at the start of administration and analysed with a paired t-test.

Rapporteur's comment: as stated above, the timeframe of one year is on the short side to measure effects of Somatropin treatment. The data is analysed with a paired t-test, which is informative but due to the very low number of subjects, one should be very cautious interpreting significant results as evidence for efficacy. It is assumed that no corrections for multiple testing were applied, which would have been the correct approach. It is assumed that p-values were considered significant when $p \leq 0.05$. The requested protocol and the final study report should provide this information.

2.3.2.1.2. Results

Recruitment/ Number analysed
The final number of registered subjects was 9.

Rapporteur's comment: The aim of the survey was to include 5 patients with PWS. 9 subjects were included. From the submitted information it can be concluded that 8 out of 9 patients were treatment naïve. Given the rareness of PWS this low number of patients is to be expected. However the low number of subjects will not allow for firm conclusions.

Baseline data
7 subjects were found positive for a 15q11-13 deletion, one patient had uniparental disomy and one patient with another unspecified genetic abnormality. During the two-year registration period, the final number of registered subjects was 9. The ages of the subjects ranged from 0 years and 4 months till 11 years and 6 months old.

At the start of administration, the following baseline data (mean ± SD) was acquired:

Parameter	N	mean ± SD
Age (years)	9	3.2±3.7
Height (cm)	9	81.66 ± 24.17
Height SDS value:	9	-2.53 ± 1.23
Growth rate (cm/year)	5	9.48 ± 10.71
Growth rate SDS:	3	-8.66 ± 0.35
Bone age (years)	4	4.6 ± 4.7
Degree of obesity (kg/m^2)	4	12.44 ±16.52

Rapporteur's comment:

According to Japanese growth charts, the mean height of 81.66 cm at approximately 3 years of age matches the corresponding height SDS value of -2.53[2]. The height standard deviation score is in the range of what can be expected of PWS patients[3].

The growth rate of 9.48 cm/year seems high for normal healthy children aged 3. The reported growth rate is -8.66 SD from that of healthy children is inconsistent with the reported growth rate.

The low amount of subjects in the growth rate SDS (n=3) is unexplained. Since data on the growth rate at the start of the administration is presented from n=5 subjects, it is expected to also include these in the growth rate SDS analysis. The requested final study report should provide this information.

Growth rate SDS value is a more relevant marker for efficacy since growth rate (like height and bone age) is highly dependent on age and sex.

A growth rate of mean 9.48 cm/year is inconsistent with -8.66 SD while after 12 months of treatment they are at -1.14 SD with a growth rate of 7.52 cm/year. Clarification is needed on this point. It is also unexplained why there is only n=5 available for the 6 months observation while there is growth rate data of n=7.

The reported mean bone age of 4.6 years for this group of children with a mean chronological age of 3.2 years old seems high, especially when this is compared to the growth rate SDS of -8.66. As a lower height SDS is generally accompanied by a chronological/bone age greater than 1 indicating a delay in biological maturation these results appear inconsistent. Further clarification on the baseline data is requested.

The degree of obesity is reported as BMI (kg/m^2). The BMI of 12.44 is lower than can be expected for children with PWS[4] Further clarification on the baseline data will be requested.

Actual dosing

Patients were administered a staring dose between >0 and 1.0 mg/week after titration a maximum of 7.8 mg/week divided over 6 or 7 injections. The maintenance dose varied from 1 to 4 mg/day for most patients

Rapporteur's comment:

No information is provided on the dose administration in mg/kg. It cannot be concluded whether the dosing is according to the SmPC. The requested study protocol and final study report should provide this information. If applicable, the applicant is requested how and why and for which patients the advised dose regimen is not applied.

Efficacy results

Height

A statistically significant increase in height at 6 and 12 months ($p \leq 0.001$) compared to baseline was reported.

[2] Isojima et al, Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol. 2016 Apr; 25(2): 71–76.
[3] Nagai et al, Standard growth curves in Prader-Willi syndrome in Japan. Clin Pediatr Endocrinol. 1993 2(1).
[4] Butler et al, growth charts for non growth hormone treated Prader-Willi syndrome. Pediatrics. 2015 Jan 135 (1).

Height (cm)	N	mean ± SD
6 months	7	87.26 ± 24.17 cm
12 months	8	92.24 ± 22.21 cm

Rapporteur's comment:
As also highlighted above, height is a general anthropomorphic measurement, associated with age. Since all the included subjects are children, mostly in infancy/early childhood, an increase in height is expected. Change in height is thus not reflective of efficacy, unless it can be compared to a control arm. It would be informative to compare the growth of these patients with standard growth curves of Japanese children. Further comparison with published Japanese growth curves for PWS patients might be useful.

Height SDS
No statistically significant differences are observed in height SDS value after 6 and 12 months of treatment.

Height SDS value	N	mean ± SD
6 months	7	-2.46 ± 0.83
12 months	8	-2.22 ± 1.25

Rapporteur's comment: based on existing literature[5], the improvement in height SDS is expected to be greater in mainly treatment naïve patients than the reported values. The applicant is requested to discuss these results. It is agreed with the applicant that the absence of statistically significant outcomes might be due to the small number of subjects.

Growth rate
The applicant reports no statistically significant differences, but a tendency toward improvement, on the growth rate 6 (p=0.614) and 12 (p=0.355) months after treatment.

Growth rate (cm/year)	N	mean ± SD
6 months	7	12.38 ± 5.53
12 months	8	7.52 ± 3.90

Rapporteur's comment:
It is not agreed with the applicant that the reported growth rates, show a statistical trend towards significance (for a trend the p value should be between 0.05 and 0.1).
A growth rate of 12.38 cm/year is high, which could be indicative of a catch up growth. Interpretation of the data in light of the efficacy is not possible in the absence of a control arm.

Growth rate SDS
The applicant reports no significant differences, but a tendency toward improvement, on the growth rate 6 (p=0.198) and 12 months (p=0.052) after treatment.

Growth rate SDS value	N	mean ± SD
6 months	5	1.24 ± 4.54
12 months	8	-1.14 ± 3.01

Rapporteur's comment:
The change in growth rate SDS at 12 months of treatment approaches statistical significance despite the low subject number. As pointed out above, clarification on growth rates and the matching growth SDS values is requested.

[5] Takeda et al, Recombinant human growth hormone for the treatment of growth disorders in children; a systematic review and economic evaluation. *Health Technology Assessment* 2010; Vol. 14: No. 42

Bone age
The applicant reports no statistically significant differences, but a tendency toward improvement, on the bone age 6 (p=0.126) and 12 months (p=0.096) after treatment.

Bone age	N	mean ± SD
6 months	3	7.00 ± 5.07
12 months	4	5.60 ± 5.36

Rapporteur's comment:
As with height, bone age interpretation of the data in light of the efficacy is not possible in the absence of a control arm. In addition, the number of subjects in this analysis is extremely small. The applicant should discuss the odd results of an increase in bone age of 2.4 years after 6 months of administration compared to baseline and the subsequent drop in bone age of 1.4 years at 12 months.

Degree of obesity
The applicant reports no significant differences, but a tendency toward improvement, on the degree of obesity 6 (p=0.275) and 12 (p=0.744) months after treatment. Body fat percentage was measured in 1 subject at the start of administration and at 12months, showing improvement from 48.2% to 20.1%.

Degree of obesity (kg/m^2)	N	mean ± SD
6 months	5	-0.15 ±13.74
12 months	8	-0.08 ±13.49

Rapporteur's comment: Clarification is needed on this data. The reported values cannot be kg/m^2 as reported for baseline. It is nog agreed with the applicant that the reported p-values are indication of a tendency towards improvement.

Safety results
There were no reports of adverse reactions in all 9 subjects. The only adverse event with no causal relationship was the occurrence of dermatitis diaper in an 11 months old subject.
No other noteworthy problems were reported.
The specified priority survey items; abnormal glucose tolerance, scoliosis and respiratory disorders were not found. No requests were made for anti-GH antibody measurements and thus this data is not available.

Rapporteur's comment: the specified priority item "abnormal glucose tolerance, scoliosis and respiratory disorders" were not reported and there were no reports on adverse reactions. It is agreed that the case of dermatitis diaper is indeed unlikely to be related to the Somatropin treatment. There were no unexpected or unlisted adverse events.

2.3.2.2. Study SAN-EP00-SGA :

A specific use-results survey of Somatropin BS S.C. Injection 5 mg, 10 mg for SGA (small for gestational age) short stature not associated with epiphyseal arrest.

2.3.2.2.1. Description

Rapporteurs comment: No formal study report with a clear description of the survey, the results and safety observations was submitted. No formal protocol was included in the dossier. The applicant is requested to submit both the protocol and the final study report of both surveys.

2.3.2.2.2. Methods

Objective(s)

This specific use-results survey was conducted for the purpose of investigating the safety and efficacy of somatropin (Omnitrope 1.3 mg/ml powder and solvent for solution for injection) in current clinical practice.

Rapporteur's comment: This survey will capture real life information on treatment, efficacy and safety. As such these are the first data collected in a real-world practice setting included in this dossier.

Study design

Survey forms were collected from patients in a two-year registration period from 47 contract institutions in Japan. Patients were observed for one year and data on clinical outcome was acquired.

Rapporteur's comment: From the submitted information it is not clear how patients and centres were selected. It can thus not be assessed whether selection bias occurred.

In this in drug use survey no control group was included which will hamper the assessment of the efficacy results. At the very least it would have been better to compare the study data with natural history data of Japanese patients with SGA.

Further a one year observational period is rather short for the assessment of efficacy (change in body composition or growth). Literature regarding this subject often described a more than 2 year study period. No information on long-term safety can be collected.

Study population /Sample size

The survey was started in September 2013 with the objective of accumulating the total number of registered subjects in the first two years or 100 subjects. As the target number was not reached within 2 years, the registration period was extended with two months.

Patients with a diagnosis of small-for-gestational age short stature (SGA) were included.

Rapporteur's comment:

No specifications are provided about the diagnosis of SGA. The requested protocol and the final study report should provide this information.

From the submitted summery it is not clear if the patients were treatment naïve for Somatropin or that they were included during treatment. Since the biggest effect of treatment is expected within the first two years, this is important information. The requested final study report should provide this information.

No formal sample size calculation was made. The survey aimed to include 100 patients, given the rareness of the condition this is considered acceptable.

Treatments

Somatropin (Omnitrope 1.3 mg/ml powder and solvent for solution for injection).

Rapporteur's comment: no specifications are provided about the exact dosing regimen. The requested protocol and the final study report should provide this information.

Outcomes/endpoints

The reported outcome parameters are: Change in height, height SDS value, Change in growth rate,

Growth rate SDS, bone age. These parameters were evaluated at the start of the administration, after 6 months and after 12 months.

Rapporteur's comment: These are the standard anthropomorphic measurements from which interpretation on efficacy is difficult due to the lack of a control group. The applicant is requested to compare the results with the results of the normal, healthy Japanese population and – as far as available – with Japanese SGA growth curves. Furthermore, it is not to be expected that the efficacy can be measured within the time frame of one year.

Statistical Methods

The 6 and 12 months measurements were compared with the measurements at the start of administration and analysed with a paired t-test.

Rapporteur's comment:

As stated above, the timeframe of one year is on the short side to measure effects of Somatropin treatment. The data is analysed with a paired t-test, which is informative. It is assumed that no corrections for multiple testing were applied, which would have been the correct approach. It is assumed that p-values were considered significant when $p \leq 0.05$. The requested protocol should provide this information.

2.3.2.2.3. Results

Actual dosing

Patients were administered a starting dose varying from >0 to 5.0 mg/week after titration the maximal dose was 25 mg/week divided over 6 or 7 injections. However, divergent administration schedules of 2-5 injection per week did also occur.

Rapporteur's comment: It cannot be confirmed that the dose administration is in accordance with the SmPC. The dosing seems plausible however the recommended administration regimen is one injection per day. The occurrence of divergent schedules of 2-5 injections per week is thus not in accordance with the SmPC. The requested final study report should provide this information.

Recruitment/ Number analysed

The final number of registered subjects was 125. Three subjects were excluded from the efficacy analysis because of missing height data at the start of the administration.

Rapporteur's comment: the amount of registered subjects is 125, which exceeds the aimed 100 subjects. The number of subjects allows for statistical analysis.

Baseline data

During the registration period, 125 subjects were included in the study of which 82 were male and 43 female ranging from 3 years till 15 years and 11 months.

At the start of administration, the following baseline data (mean ± SD) was acquired:

Parameter	N	mean ± SD
Age (years)	125	7.0 ± 3.0
Height (cm)	122	103.44 ± 15.74
Height SDS value:	122	-2.8 ± 0.84

Growth rate (cm/year)	76	0.97 ± 0.87
Growth rate SDS:	76	-8.89 ± 1.20
Bone age (years)	83	5.21 ± 2.62

Rapporteur's comment: According to Japanese growth charts, the mean height of 103.44 cm at approximately 7 years of age matches the corresponding height SDS value of -2.8[6]. The height standard deviation score is in the range of what can be expected of SGA patients[7]. The growth rate of 0.97 cm/year is very low compared to growth charts of healthy children, indicative of severe growth retardation. This corresponds to the -8.89 SDS value. Growth rate SDS value is a more relevant marker for efficacy since growth rate (like height and bone age) is highly dependent on age. The reported bone age of 5.21 years for this group of children of 7 years old is also indicative of a delayed biological development.

Efficacy results

Height

The MAH reports a significant increase in height at 6 (p≤0.001) and 12 (p≤0.001) months compared to baseline.

Height (cm)	N	mean ± SD
6 months	110	107.33 ± 14.63
12 months	106	110.57 ± 14.89

Rapporteur's comment:
As also highlighted above, height is a general anthropomorphic measurement, associated with age. Since all the included subjects are children, mostly in infancy/early childhood, an increase in height is expected. Change in height is thus not reflective of efficacy, unless it can be compared to a control group. It would be informative to compare the growth of these patients with standard growth curves of Japanese children and/or those of Japanese SGA children.

Height SDS

The MAH reports a significant increase in height SDS value after 6 (p≤0.001) and 12 (p≤0.001) months of treatment.

Height SDS value	N	mean ± SD
6 months	110	-2.53 ± 0.90
12 months	106	-2.37 ± 0.94

Rapporteur's comment: It is agreed that the improvement in height SDS is significant however, it is on the lower side of what can be expected based on existing literature[7]. In addition, the reported height at 12 months seems to be more in the -1.5 SDS range when compared to Japanese growth charts. General comment with regard to the calculated SDS values; it is requested to provide the reference for the growth charts used in this study and/or those of Japanese SGA children.

Growth rate

The MAH reports a significant increase in growth rate after 6 (p≤0.001) and 12 (p≤0.001) months of treatment.

[6] Isojima et al, Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol. 2016 Apr; 25(2): 71–76.
[7] Horikawa et al, Evaluation of growth hormone treatment efficacy in short Japanese children born small for gestational age: Five-year treatment outcome and impact on puberty. Clin Pediatr Endocrinol 2017; 26(2), 63–72

Growth rate (cm/year)	N	mean ± SD
6 months	110	7.55 ± 2.69
12 months	106	7.16 ± 2.46

Rapporteur's comment: Compared to baseline, the catch up growth observed 6 and 12 months after treatment is very high. It is difficult to reconcile this with the marginal improvement in height SDS value. It is agreed that the improvement in growth rate is significant but without a control arm it is difficult to interpret in light of the efficacy. It would be informative to compare the growth of these patients with standard growth curves of Japanese children and/or those of Japanese SGA children, when available.

Growth rate SDS

The MAH reports a significant increase in growth rate SDS after 6 ($p \leq 0.001$) and 12 ($p \leq 0.001$) months of treatment.

Growth rate SDS	N	mean ± SD
6 months	110	1.82 ± 3.15
12 months	106	1.47 ± 3.25

Rapporteur's comment: It is agreed that the improvement in growth rate SDS is significant and representative of the catch up growth observed in these children.

Bone age

Bone age was also significantly increased after 6 ($p \leq 0.001$) and 12 ($p \leq 0.001$) months of treatment.

Bone age	N	mean ± SD
6 months	17	6.16 ± 2.77
12 months	51	6.48 ± 2.68

Rapporteur's comment: since all the included subjects are children, mostly in infancy/early childhood, an increase in bone age (in this case an increase of 1.27 years in one study year) is expected. The observation period of one year is too short to show complete catch up in bone age. Earlier studies in Japanese children report treatment periods of approximately 3 years to show complete alignment of bone age/chronological age in children with SGA treated with GH[7] .

Safety results

Two out of 125 subjects presented with adverse reactions; 1 subject presented with anaemia, 1 subject with increased AST and ALT. Adverse reactions were mild and administration of the drug was continued. Three adverse events with no causal relationship were reported, all minor. There were no reports of serious or fatal cases. The specified priority survey item; abnormal glucose tolerance, was not found. No requests were made for anti-GH antibody measurements and thus this data is not available.

Rapporteur's comments: the specified priority item "abnormal glucose tolerance" was not reported. The adverse reactions that were reported were mild. It is agreed that no noteworthy safety issues emerged. No unexpected or unlisted adverse events were reported. Anti GH antibodies were not measured since no unexpected absence of efficacy was observed.

2.3.3. Discussion on clinical aspects

Both studies SAN-EP00-PW and SAN-EP00-SGA are observational surveys, assessing the efficacy and safety of Omnitrope 1.3 mg/ml powder in current clinical practice in Japan. The nature of these surveys, specifically the absence of a control arm, and the lack of data on body composition measurements make the interpretation of the efficacy data difficult.
In addition, information lacks on study protocol, diagnosis of the patients, inclusion of the patients to assess whether selection bias is likely and on treatment prior to the study. Therefore, the applicant is requested to provide the protocol and the final study reports. For both studies, the observation period was 1 year which is too short to draw firm conclusions considering the safety and efficacy of GH treatment.

In study SAN-EP00-PW, 9 subjects with PWS were included in the analysis. Several uncertainties exist on the baseline data. Especially the growth rate of 9.48 cm/year and corresponding growth rate SDS of -8.66 SD seem highly improbable. In addition, the reported degree of obesity seems low for PWS patients. A significant effect of treatment was only observed on height (cm). Without a comparison to a control arm or comparison with growth data from healthy Japanese children or Japanese PWS patients no conclusions can be drawn on efficacy. No statistically significant effects were observed on height SDS, growth rate, growth rate SDS, bone age and degree of obesity. The explanation of the applicant that this is due to the very small group size is plausible. However, it could be speculated that the absence of efficacy is due to low dose administration. No important safety issues were reported. Since adequate information on posology is lacking, no assessment of the safety and efficacy data can be made at this time.

In study SAN-EP00-SGA, 125 subjects were included in the analysis. Significant effects on height, height SDS, growth rate, growth rate SDS and bone age were reported after 6 months and 1 year of treatment. Effects on height, growth rate and bone age are only informative when compared to a control arm or to growth charts of healthy peers and/or SGA patients. The effect on height SDS seems low compared to literature and also when compared to the catch up growth reflected in the increase in growth rate. No serious adverse reactions were reported. Since adequate information on posology is lacking, no assessment of the safety data can be made at this time.

3. Rapporteur's overall conclusion and recommendation

Because of the observational nature of the data, assessment on efficacy is difficult. In addition, essential information about the studies is lacking. Without adequate information on design, methodology, posology, etc. no assessment of the efficacy data is possible at this moment. As a consequence, no assessment of the benefit/risk of Omnitrope can be made. The MAH is requested to provide additional information on these studies.

☒ **Not fulfilled:**

4. Additional clarification requested

The applicant is requested to provide the **protocol** and the **final study report** for both studies submitted. The applicant should give special attention to the following questions:

1. Please provide background information on the study inclusion (especially on the selection of patients and study centres).
2. How was diagnosis of SGA and PWS confirmed and how do the included subject numbers relate to the total amount of PWS and SGA patients in Japan?
3. The applicant should confirm that the submitted studies SAN-EP00-PW and SAN-EP00-SGA are stand-alone studies.
4. Please provide dosage information in mg/kg/day for both studies.
5. The applicant is requested how, why and for which patients the advised dose regimen from the SmPC is not applied.

   Study SAN-EP00-PW

6. Please provide clarification on the inconsistencies in baseline data of study SAN-EP00-PW, specifically clarify the reported growth rates and corresponding growth rate SDS and the data on degree of obesity as well as the numbers reported. The reported values on degree of obesity after 6 and 12 months cannot be as those reported for baseline.
7. The applicant is requested to compare the growth of the PWS patients with standard Japanese growth curves and those of Japanese PWS patients.
8. Please discuss the apparent discrepancies between the improvement in height SDS value observed in this survey and the larger improvement reported in literature.
9. The applicant should discuss the odd results of an increase in bone age of 2.4 years after 6 months of administration compared to baseline and the subsequent drop in bone age of 1.4 years at 12 months.

   Study SAN-EP00-SGA

10. The applicant is requested to compare the results of study SAN-EPOO-SGA with the results of the normal, healthy Japanese population and – as far as available – with Japanese SGA growth curves.

    The timetable is <a 30 day response timetable without clock stop.>< a 30 day response timetable with clock stop.>

5. MAH responses to Request for supplementary information

With this response document the applicant would like to address the Rapporteur's comments from the preliminary Assessment Report (AR) received on 02 Mar 2018 (updated AR dated 22 Mar 2018) related to two local Japanese non-interventional post-marketing 'drug use result surveys' submitted to EMA in Dec 2017 in accordance with article 46 of the Pediatric Regulation (EC) No 1901/2006.

Background of the submitted 'drug use result surveys'

The applicant would like to emphasize that the submitted 'drug use result surveys' were performed as part of the Marketing Authorization Holder's (MAH) local post-marketing pharmacovigilance commitment as requested by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). The requested 'drug use result survey' aims to "obtain or verify information on the incidence of adverse

reactions by disease type and information on medicine quality, efficacy and safety in clinical practice, with no conditions specified for patients using the medicine in question".
Omnitrope is approved in Japan for the following indications:

- Growth hormone deficiency (GHD)
- Turner's syndrome (TS)
- Dwarfism associated with chronic renal insufficiency (CRI)
- Prader-Willi Syndrome (PWS)
- Short stature in short children born small for gestational age (SGA)
- Adults growth hormone deficiency (limited to severe cases)

Assessors comment

Following the requests, the applicant has provided the study protocols and result reports. The result reports are the same as the ones provided in the first round.
Although one of the objectives of the studies as explicitly to study the efficacy of Somatropin, and efficacy data was gathered, the applicant states the provided data makes assessment of efficacy not possible. This is agreed upon. Assessment will thus primarily focus on safety.

Request for additional clarification to be provided by The applicant

Provide the protocol and the final study report for both studies

The applicant' response:

As requested by the Rapporteur, the protocols for both submitted special drug use result surveys SAN-EP00-PWS [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 2] and SAN-EP00-SGA [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 3] are provided in English translation as part of this submission.

The applicant would like to highlight that the final survey reports for SAN-EP00-PWS [Module 5.3.5.4 SAN-EP00-PWS] and SAN-EP00-SGA [Module 5.3.5.4 SAN-EP00-SGA] submitted on 15 Dec 2017 were representative of the final clinical study reports (CSR) in a format as submitted/approved by the PMDA. Following the advice as laid out in the post-authorization procedural advice for users of the centralized procedure section 18.3 "How shall I present my article 46 pediatric study application at submission" advising to submit the final CSR, The applicant considers all requirements fulfilled.

Rapporteurs' questions concerning both studies

Question 1: Please provide background information on the study inclusion (especially on the selection of patients and study centers).

The applicant's response concerning SAN-EP00-SGA:

All details on the inclusion criteria can be found in the protocol in section 2 'Planned number of patients and its rationale' [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 3].

Selection of patients: The survey was planned to include patients who change from their previous treatment to Omnitrope. However, as the number of such patients was expected to be very small, the survey was opened to all patients receiving Omnitrope. All patients are on treatment.

Selection of study centers: Approximately 100 patients were expected to be enrolled in this survey during the enrollment period of two years with the number of participating study sites to be around 50.

The study centers have been selected based on the following criteria: Prerequisite for each hospital and clinical was the existence of a dedicated pediatric department and routine use of growth hormone treatment in short children born SGA.

The applicant' response concerning SAN-EP00-PWS:

All details on the inclusion criteria can be found in the protocol in section 2 'Planned number of patients and its rationale' [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 2].

Selection of patients: The survey was planned to include patients who change from their previous treatment to Omnitrope. However, as the number of such patients was expected to be very small, the survey was opened to all patients receiving Omnitrope. Approximately 4 patients were expected to be enrolled in the survey.

Selection of study centers: The study centers have been selected based on the following criteria: Prerequisite for each hospital and clinical was the existence of a dedicated pediatric department and experience with growth hormone treatment in children with PWS. The number of such study sites was estimated to be around 3 to 4.

Assessors comment

Study protocols were provided by the applicant for both studies **SAN-EP00-SGA and SAN-EP00-PSW.** The selection of study centers was as follows for both studies: A written request for survey will be sent to all study sites to which the product is supplied and an agreement will be entered into with those that accept the request. At participating study sites, medical representatives (MRs) will fully inform investigators and other site staff involved in the survey of the objective, methodology, items etc. of the survey.
The objective for the PWS study was to include 3 or 4 study sites with 1 or 2 patients per study site. 11 sites were finally included in the study, providing 9 patients in total.
For the SGA study the objective was to include around 100 patients from an estimated 50 study sites. 47 sites were finally included in the study, providing 125 patients in total. These numbers are in concurrence with the respective study protocols. No specific information about the included study centers was provided.
Based on the additional explanation reassurance is given that the inclusion of patients can be considered at random and that no bias is to be expected.

Issue resolved.

Question 2: How was diagnosis of SGA and PWS confirmed and how do the included subject numbers relate to the total amount of PWS and SGA patients in Japan?

The applicant's response concerning SAN-EP00-SGA:

In 2011, there were about 1,057,000 births in Japan. Of these births, approximately 5% of the children are SGA. Ninety percent of SGA neonates experience catch-up growth by the age of 2. It means that the remaining 10% are SGA children. It is estimated that every year, around 5,300 children are candidates for therapy in Japan (Karlberg and Albertsson-Wikland 1995).

For every patient enrolled in survey SAN-EP00-SGA, all data to confirm the diagnosis SGA have been collected in addition to demographic and baseline data to determine the patient's eligibility for study participation:

- Date of birth
- Age > 3 years old

- Length and weight at birth
- Gestational age at birth
- Sex
- Parental height
- Bone age
- Puberty statue (tanner stage)
- Height and weight for the past 2 years
- Past medical history
- Allergic disposition
- Growth hormone stimulation test
- Thyroid function (at the time of GH test)
- IGF-1

The applicant' response concerning SAN-EP00-PWS:

PWS is a rare disease and in Japan about 70 children are born with PWS per year (Ehara *et al* 1995). As stated in the response to 2.2.1 the survey was planned to include patients who change their previous treatment to Omnitrope. As the number of such patients is expected to be very small (Omnitrope market share is <5%), the survey was conducted on all patients receiving Omnitrope.

For every patient enrolled in survey SAN-EP00-PWS, all data to confirm the diagnosis PWS have been collected in addition to demographic and baseline data to determine the patient's eligibility for study participation:

- Date of birth
- Length and weight at birth
- Family history
- Gestational age at birth
- Parental height
- Sex
- Age (at the start of administration)
- Bone age
- Puberty statue (tanner stage)
- Height and weight for the past 2 years
- Past medical history
- Growth hormone stimulation test
- Allergic disposition
- Genetic test: DNA mutation analysis
- IGF-1

Assessors comment

The applicant provided information about which data was gathered to confirm diagnosis of PWS and SGA but not according to which guidelines the diagnosis was confirmed. From the measurements mentioned by the applicant it can be concluded that the international guidelines considering the diagnosis of PWS or SGA are applied and that for the diagnosis the criteria mentioned in the SmPC are used. Therefore it can be concluded that the patients included indeed suffered form PWS or SGA.

Issue resolved.

Question 3: The applicant should confirm that the submitted studies SAN-EP00-PWS and SAN-EP00-SGA are stand-alone studies

The applicant' response:

Herewith, The applicant confirms that the submitted drug use result surveys SAN-EP00-PWS and SAN-EP00-SGA were performed as part of the Marketing Authorization Holder's (MAH) local post-marketing pharmacovigilance commitment and are stand-alone surveys following Japanese regulations.

Assessors comment

The submitted studies SAN-EP00-PWS and SAN-EP00-SGA are stand-alone studies. Question is answered.

Issue resolved.

Question 4: Please provide dosage information in mg/kg/day for both studies.

The applicant's response concerning SAN-EP00-SGA:

Dosage and administration was according to the Japanese product information. A dose of 0.23mg/kg body weight was administered in 6 to 7 doses per week via subcutaneous route of administration. In case of insufficient treatment effect, the administered dose was increased up to 0.47mg/kg body weight per week. Dosing regimen remained the same.

Detailed information on the dosage and administration can also be found in the provided survey protocol section 4 "Dosage and Administration" [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 3].

The applicant would like to emphasize that this is in contrast to the European product information advising a dose of 0.035mg/kg body weight per day (equal to 0.245mg/kg body weight per week). A current version of the Japanese product information translated into English is attached to this response [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 4].

The applicant' response concerning SAN-EP00-PWS:

Dosage and administration was according to the Japanese product information. A dose of 0.245mg/kg body weight was administered in 6 to 7 doses per week via subcutaneous route of administration.

Detailed information on the dosage and administration can also be found in the provided survey protocol section 4 "Dosage and Administration" [Module 1.R Response to clarification request dated 02 Mar 2018 - Attachment 2].

The applicant would like to highlight this is the same dose as advised in the European product information, recommending a dose of 0.035mg/kg body weight per day (equal to 0.245mg/kg body weight per week). A current version of the Japanese product information translated into English will be attached to this response [Module 5.3.5.4 EP00-PWS].

Assessors comment

The applicant states that dosing in both studies was according to the Japanese SmPC. As outlined by the applicant, the dosing for children SGA differs between the Japanese and European SmPC (dose

increases are warranted in case of a lack of efficacy according to the Japanese SmPC). Since the minimum dose is more or less equal, the differences in dosing to not give rise to safety concerns for the European population. Although the applicant has not provided the dosages in mg/kg/day as requested, the applicant confirmed that the dosing was indeed according to the SmPC.

Issue resolved.

Question 5: The applicant is requested how, why and for which patients the advised dose regimen from the SmPC is not applied

The applicant' response:

As stated in question 4 "Please provide dosage information in mg/kg/day for both studies" dosage and administration for survey SAN-EP00-SGA was in contrast to the advised dose regimen from the European Summary of Product Characteristics (SmPC).

Table 0-1 Dosage and administration

Indication	JP product information	EU product information
	mg/kg body weight dose per day	mg/kg body weight dose per day
Short stature in short children born SGA	0.0328 (0.23 mg/week) up to 0.0671 (0.47 mg/week)	0.035 (0.245 mg/week)
Prader-Willi Syndrome	0.035 (0.245 mg/week)	0.035 (0.245 mg/week)

Assessors comment

The occurrence of deviant dosing schedules is implied by the occurrence of 2, 3 or 5 times a week injections in the SGA survey report. These deviations have not been addressed by the applicant. Although it might be of interest for patients and prescribers to know what the reasons for the deviation from the dosing schedule as mentioned in the SmPC was for the assessment of the safety profile this information is of less relevance. Therefore this issue will not further pursued.

Issue will not be further pursued.

Rapporteurs' questions concerning study SAN-EP00-PWS

Question 6: Please provide clarification on the inconsistencies in baseline data of study SAN-EP00-PWS, specifically clarify the reported growth rates and corresponding growth rate SDS and the data on degree of obesity as well as the numbers reported. The reported values on degree of obesity after 6 and 12 months cannot be as those reported for baseline

The applicant' response:

As stated in section 1.1 "Background of the submitted drug use result surveys", the limitations of the data received from survey SAN-EP00-PWS make interpretation and conclusion as requested by the Rapporteur difficult. The applicant, however, agrees with the Rapporteur that the number of available data differ from the basal to 6 month visit and to 12 month visit, but with the final data received from the survey it is not possible to draw the requested conclusions.

It is known that starting GH-treatment earlier will result in advantageous treatment outcomes. But due to the small number of patients enrolled in SAN-EP00-PWS (start of GH in 7 PWS younger than 5 years

and in 2 older than 6 years) any change will be weighting the statistical analysis and bias any conclusion drawn.

Body weight and BMI are not the ideal parameters to assess the efficacy since the positive increase of muscle mass as the on target effect of GH-treatment might increase the body weight and falsify the interpretation in this short period of report. Analysis of the lipid profile or the measurement of body impedance or composition would have been necessary to get a better understanding of the effect of GH-treatment in PWS patients (Nagai *et al* 2000).

Overall, the survey SAN-EP00-PWS was not designed to evaluate efficacy in this population but as already stated in section 1.1 'Background of the submitted drug use result surveys', safety rather than efficacy was the primary objective of the survey.

Assessors comment

The applicant has not adequately addressed the discrepancies in the data. It is agreed that the survey data can not be used for efficacy assessment however this does not justify the reporting of discrepant findings. Especially the discrepancy between growth rate and growth rate SDS is unexplained. Since growth rate SDS is derived from the growth rate, patients number are expected to match. The mismatch between growth rate and growth rate SDS might be reflective of reporting errors.

As for question 6 this question is more related to the efficacy as reported by the applicant. The efficacy information as presented in this report cannot be assessed due to inconsistencies. The safety data as presented does not give rise to any safety issue, however.

Issue will not be further pursued.

Question 7: The applicant is requested to compare the growth of the PWS patients with standard Japanese growth curves and those of Japanese PWS patients

The applicant' response:

As stated in section 1.1 'Background of the submitted use-result surveys' the limitations of the data received from survey SAN-EP00-PWS as well as safety being the primary objective make a comparison with the reference population of either healthy subjects or PWS patients difficult.

The mean height of Japanese children with PWS approximates around the −2 SD values for normal children until pubertal age. The height difference between the children with and without PWS becomes apparent during the pubertal stage. The fall-off in linear growth occurs after age 13 year in males and after 11 years in females, probably reflecting their lack of pubertal growth. All these findings indicate that the degree of short stature is more prominent in males than in females, irrespective of ethnic groups, and the growth in individuals with the syndrome is genetically determined (Nagai *et al* 2000).

Assessors comment

The applicant states that the difference in height between children with PWS and without PWS becomes apparent during the pubertal stage but is -2 SD until pubertal age. In study SAN-EP00-PWS, only prepubertal patients were included, the SDS values match that of the – 2 SD value as reported by the applicant. No comparisons have been made by the applicant to compare the growth of the PWS patients with standard Japanese growth curves however, since no assessment of efficacy can be made this is not of concern.

This issue will not be further pursued.

Question 8: Please discuss the apparent discrepancies between the improvement in height SDS value observed in this survey and the larger improvement reported in literature

The applicant' response:

Because PWS patients enrolled in the survey were of varying age and only one year of follow-up was performed, it is not advisable to compare the received data with available data from literature. However, SDS is one of the index for growth and it is thought that there is seen a trend to improvement in the height SDS value.

Assessors comment

It is agreed that one year of follow up is too short to allow for firm conclusions regarding the height improvement of PWS patients. It it not agreed that there is a trend in improvement in height SDS value however, the small patients numbers hamper the use of statistical analysis and also not allow for firm conclusions.

Issue will not be further pursued.

Question 9: The applicant should discuss the odd results of an increase in bone age of 2.4 years after 6 months of administration compared to baseline and the subsequent drop in bone age of 1.4 years at 12 months.

The applicant' response:

The odd numbers in bone age between the 6 months and 12 months' time point are a result of several factors:

- A data point for one patient with a bone age of below 1 year was missing at the 6 months' time point as compared to 12 months
- The overall small number of patients
- The heterogeneity of the group

All of the above listed factors resulted in the odd numbers observed during the survey. As a result, no meaningful statistical analysis or conclusion on the efficacy of GH-treatment can be drawn from the received data.

Assessors comment

It is agreed that no meaningful conclusions considering efficacy can be drawn from these data, the explanation that one absent data point for a patient with a low bone age skews the results is acceptable.

Issue resolved.

Rapporteurs' question concerning study SAN-EP00-SGA

Question 10: The applicant is requested to compare the results of study SAN-EP00-SGA with the results of the normal, healthy Japanese population and – as far as available – with Japanese SGA growth curves.

The applicant' response:

As stated in section 1.1 'Background of the submitted use-result surveys' the limitations of the data received from survey SAN-EP00-SGA and primary focus being safety and not efficacy make a comparison with the reference population of either healthy subjects or SGA patients difficult.

The non-interventional survey setup, the heterogeneity of children recruited and short observation period do not allow drawing any conclusions concerning efficacy of Omnitrope in this population. The main objective of this survey was to assess the safety of Omnitrope after one year of treatment and no unexpected adverse events occurred in this population during this period.

The applicant is not aware of Japanese-specific SGA growth charts that can be used for comparison of the obtained data with normal, healthy Japanese population.

Assessors comment

It is agreed with the applicant that the presented data do not allow for firm conclusions regarding the efficacy of Omnitrope in treating SGA. The data could have been compared to the growth curves of normal healthy Japanese children as requested. It is agreed that no concerns were raised concerning the safety.

Issue resolved.

6. Rapporteur's overall conclusion and recommendation

Because of the observational nature of the data, assessment on efficacy is difficult and does not allow for firm conclusions. The safety information however is assessable. No unexpected or unlisted safety issues were reported. It is agreed with the applicant that no further changes to the SmPC are necessary.