23 June 2016
EMA/479828/2016
Procedure Management and Committees Support 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/P46/036

Note

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

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Introduction

On 23 March 2016, the MAH submitted completed paediatric studies for Omnitrope, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

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

Scientific discussion

Information on the development program

The MAH stated that Exploratory Study on the Use of the AuxoLog Growth Programme in Patients with Growth Hormone Deficiency treated with a Recombinant Biosimilar Growth Hormone (SAN-2014-01) and Post Marketing Survey SAN-SPBS (EP2000-5354-975-1-0) are stand alone studies.

Information on the pharmaceutical formulation used in the study(ies)

N/A

Clinical aspects

1. Introduction

The MAH submitted final reports for:

- Exploratory Study on the Use of the AuxoLog Growth Programme in Patients with Growth Hormone Deficiency treated with a Recombinant Biosimilar Growth Hormone (SAN-2014-01)
- Post Marketing Survey SAN-SPBS (EP2000-5354-975-1-0)

The observational study SAN-ES-2014-01 includes pubescent or post-pubescent Spanish children with GHD treated with Omnitrope 5 mg/1.5 ml and 10 mg/1.5 ml solution for Injection for at least two years before the onset of puberty with data available from at least one GH production stimulation test. The objective of the study is to assess the increase in stature and growth rate in pubertal/post pubertal GHD children treated with Omnitrope and to classify them according to time of pubertal development.

Study EP2000-5354-975-1-0 included Japanese paediatric patients who were prescribed somatropin for the treatment of growth hormone deficiency (GHD), Turner's syndrome (TS) or dwarfism associated with chronic renal insufficiency (CRI). The objectives of this survey were to evaluate, in a real-world clinical practice setting, the safety and efficacy of Somatropin Injection 5 mg and 10 mg for the treatment of paediatric growth disorders. All patients were observed for a period of one year.

2. Clinical study(ies)

Exploratory Study on the Use of the AuxoLog Growth Programme in Patients with Growth Hormone Deficiency treated with a Recombinant Biosimilar Growth Hormone (SAN-2014-01)

Description

The observational study SAN-ES-2014-01 includes pubescent or post-pubescent Spanish children with GHD treated with Omnitrope 5 mg/1.5 ml and 10 mg/1.5 ml Solution for Injection for at least two years before the onset of puberty with data available from at least one GH production stimulation test. The objective of the study is to assess the increase in stature and growth rate in pubertal/post pubertal GHD children treated with Omnitrope and to classify them according to time of pubertal development.

Methods

- Objective(s)

  Primary objective:

- Evaluate the increase in height (height, height standard deviation score, growth velocity, growth velocity standard deviation score) in pubertal or post-pubertal patients with GHD treated with Omnitrope® for a minimum of two years.

  Secondary objectives:

- Identify the time of onset of the pubertal growth spurt.
- Classify patients according to the time of onset of the pubertal growth spurt.
- Evaluate the increase in height (height, height standard deviation score, growth velocity, growth velocity standard deviation score) in pubertal or post-pubertal patients with GHD treated with Omnitrope® over a complete treatment period.

- Study design

  Multi-centre, retrospective, longitudinal, observational study

- Study population /Sample size

  Patient selection criteria

  Inclusion criteria Informed Consent Form (ICF) signed by the patient and his or her legal guardian (if applicable); Patients of both sexes; Diagnosis of GHD with data of at least one GH production stimulation test: Puberty or post-puberty; Treatment with Omnitrope at least two years before the onset of puberty; Normal renal, hepatic, gastrointestinal, pulmonary, thyroid and metabolic function; No prior treatment with other GHs or anabolic agents

  Exclusion criteria: Patients who were included in the study had none of the following characteristics: GHD of known aetiology, Neonatal brain injury, Chromosomal syndromes including Turner syndrome, severe malformation syndromes and musculoskeletal diseases

  According to the sample size calculation, inclusion of approximately a total of 30 patients was

required.

- Treatments

  Omnitrope according to the SmPC

- Outcomes/endpoints

  The data to be collected in the CRF for each of the patients enrolled were:

- Date of birth
- Sex
- Birth weight and length
- Gestational age
- Height of the father and mother
- Omnitrope treatment start and end date
- During different evaluations (visits) performed at least every six months: Height, Weight, Pubertal stage (testicular volume/thelarche), Bone age, IGF-1 concentration (ng/mL), Glucose and Insulin concentration (mg/dL and µU/mL), Dose of Omnitrope (mg/kg/dL).
- Adverse events.

  All data were obtained in standard medical practice and thus CRF data were collected from the medical records of each patient after requesting their written consent.

- Statistical Methods

  Not reported.

Results

- Recruitment/ Number analysed

  A total of 23 patients were included with a mean age of 13 ± 1.33 years and uniform distribution between sexes.

- Baseline data

  Patients had been on treatment with Omnitrope® for a mean duration of 47.09 ± 8.68 months, with a steady dose of 0.03 mg/kg BW/day and occasional variations of ± 0.01 mg.

  Auxological developmental changes were determined via data entry into the AuxoLog program. Of the 23 patients recruited, 7 were excluded due to the fact that they started treatment with Omnitrope before the first two years of treatment, and another 2 because they started treatment at a height greater than -2 SDS. Thus, the calculations were made based on data from 14 patients (six girls and eight boys).

- Efficacy results

  The birth data allowed to conclude that the 14 patients enrolled were full-term and that none were categorised as small for gestational age.

  The auxological data of the patients were calculated according to the patterns corresponding of

their pubertal maturation group. At the start of GH treatment, the mean age of the patients was 9.1 ± 0.98 years and the height SDS -2.87 ± 0.4.
At the end of the first year of treatment, the height SDS was -2.08 ± 0.44 making the height SDS gain after the first year of GH treatment = 0.79 ± 0.4.
After the second year of treatment height -SDS was -1.76 ± 0.47 (height-SDS gain during the second year of GH treatment = 0.32 ± 0.4).
Compered to baseline a height-SDS gain of 1.11 ± 0.4 was observed after two years of treatment.

- Safety results

None of the patients reported any serious adverse events, pregnancy or problems with the device during the data collection period of the study.

Only six patients (26%) reported having experienced an adverse event, the total number of which was 11. These AEs were mild to moderate (63.6% and 36.4%, respectively), and unexpected in most cases (9 of 11 AEs, 81.8%). The unexpected adverse events were mesenteric adenitis, allergy to non-steroidal anti-inflammatory drugs, acute tonsillitis, arthralgia, acute headache, left foot toe fracture, gynaecomastia, right foot bone pain and recurrent parotid sialadenitis. A causal link with Omnitrope could not established for these adverse events. In two patients (18.2 %) an expected adverse event was reported (headaches and lumbago) and deemed possibly related to Omnitrope.

Post Marketing Survey SAN-SPBS (EP2000-5354-975-1-0)

Description

The post-marketing survey SAN-SPBS included Japanese paediatric patients who were prescribed somatropin for the treatment of growth hormone deficiency (GHD), Turner's syndrome (TS) or dwarfism associated with chronic renal insufficiency (CRI). The objectives of this survey were to evaluate, in a real-world clinical practice setting, the safety and efficacy of Somatropin Injection 5 mg and 10 mg for the treatment of paediatric growth disorders. All patients were observed for a period of one year.

Methods

- Objective(s)

  The objectives of this survey were to evaluate, in a real-world clinical practice setting, the safety and efficacy of Somatropin

- Study design

  Post-marketing survey

- Study population /Sample size

  The observation period for the present survey was 1 year, and the target was the total registered cases for the first 2 years or 300 cases (280 GHD cases, 18 TS cases and 3 CRI cases), whichever accumulated greater.

- Treatments

  Omnitrope according to the SmPC

- Outcomes/endpoints

  Standard auxiologic measurements (height, weight, bone age)

- Statistical Methods

  Not reported.

Results

- Recruitment/ Number analysed / Baseline data

In this post-marketing survey 298 GHD children were included, (225 male (75.50%) and 73 female (24.50%)), with a mean age of 10.5 ± 3.3 years. Further, 21 TS cases (female only) with a mean age of 12.3 ± 4.5 years were included. Amongst 5 CRI cases, there were 3 male cases (60.00%) and 2 female cases (40%), with a mean age of 6.1 ± 5.5 years.
Patients were assigned in one-year age groups, from younger than 5 years old to 16 years or older. Patient distribution is summarised below.

Age group	GHD	TS	CRI
Younger than 5 years	19 (6.38)	2 (9.52)	3 (60.00)
5 years or older and younger than 6 years	19 (6.38)	0	0
6 years or older and younger than 7 years	18 (6.04)	0	0
7 years or older and younger than 8 years	19 (38.6)	1 (4.77)	0
8 years or older and younger than 9 years	14 (4.70)	2 (9.52)	1(20.00)
9 years or older and younger than 10 years	24 (8.05)	1(4.77)	0
10 years or older and younger than 11 years	31 (10.40)	0	0
11 years or older and younger than 12 years	42 (14.09)	2 (9.52)	0
12 years or older and younger than 13 years	32 (10.74)	5 (23.81	0
13 years or older and younger than 14 years	30 (10.07)	2 (9.52)	0
14 years or older and younger than 15 years	28 (9.40)	1 (4.77)	1(20.00)
15 years or older and younger than 16 years	18 (6.04)	1 (4.77)	0
16 years or older	2 (0.67)	4 (19.04)	0

The age varied from 0.8 years (GHD) to 18.2 years (TS).

- Efficacy results

  Absolute change in body height in GHD and TS groups increased, with significant differences compared to the baseline both following 6 months and 12 months. Data were reported descriptively and testing has not been performed for CRI due to the small number of cases.
  For patients in the GHD group there was improvement with a significant difference in absolute change in body height SDS both at 6 months and 12 months. There was also clear improvement observed in growth velocity compared to the baseline at both 6 months and 12 months. Further

a statistical significant increase in absolute change in growth velocity both at 6 months and 12 months is reported.
There was no significant difference for TS.

With 120 patient (40.27%) the total cumulative dosage of 200 mg or greater and less than 300 mg was most common for GHD children, Moreover, there was a change to the dosage of the present drug in 165 GHD children (55.37%), 12 TS cases (57.14%) and 3 CRI cases (60.00%).

- Safety results

Amongst 298 GHD patients, 16 adverse events including non-serious ones were reported in 8 patients, In the TS group 0 events were reported, and 3 events were reported in 2 patients in CRI
In the GHD group the following adverse events were reported anemia(n=1), hepatic dysfunction(n=2), trauma (n=2), impaired shunt function(n=1), elevated blood creatinine phosphokinase (n=1), positive urine blood (n=1), abnormal hepatic function examination (n=1), CSF red cell positive (n=1), urine protein positive(n=1), hyperuricemia (n=1), hyperlipidemia (n=1), scoliosis (n=1), ventricular distention (n=1), and frequent urination (n=1).
In the CRI cases, anemia (n=1), hyperphosphatasemia (n=1) and urine protein (n=1) were reported.
Severe adverse events were reported in 3 GHD patients (abnormal hepatic function examination (n=1) impaired shunt function (n=2), CSF red blood cell positive (n=1), ventricular distention (n=1) and anemia(n=1) and 1 event in 1 CRI case (anemia). There were no deaths reported.

1. Discussion on clinical aspects

In study SAN-2014-01 recruitment of 30 patients was planned. Actually only 23 were enrolled after 12 months. No explanation was provided for the lack of enrolment. Because of the design (observational) of the study this issue will not be pursued.

Given the exploratory and descriptive nature of the study (SAN-2014-01) and the sample size of 23 patients treated with Omnitrope for a minimum of two years, no statistical inference was possible.

Study EP2000-5354-975-1-0 reported results after one year real-world clinical practice. The growth was within the range expected for the various patient populations included. The SAP was lacking in the submitted documentation hampering the assessment of the statistical outcome. However the descriptive statistics show results well within those reported in literature after 2 years GH treatment. Therefore this issue will not be pursued.

The unexpected adverse events reported in study SAN-2014-01 were: mesenteric adenitis, allergy to non-steroidal anti-inflammatory drugs, acute tonsillitis, arthralgia, acute headache, left foot toe fracture, gynaecomastia, right foot bone pain and recurrent parotid sialadenitis. These adverse events were considered not or unlikely drug related. Therefore these unexpected adverse events should not be included in the current SmPC

No unlisted or unexpected safety issues were reported in study EP2000-5354-975-1-0.

CHMP's overall conclusion and recommendation

These studies further confirm the know efficacy and safety of growth hormone administered to various populations indicated. No drug related unlisted or unexpected safety signals were reported.

Overall conclusion

The benefit risk of Omnitrope remains unchanged. Studies did not report findings necessitating a change in the current SmPC.

Recommendation

☒ **Fulfilled**

No regulatory action required.