SCIENTIFIC DISCUSSION

1. Introduction

Sandoz GmbH applied for a marketing authorisation for Omnitrope 1.3 mg/ml and 5.0 mg/ml powder for solution for injection. Omnitrope 1.3 mg/ml and 5.0 mg/ml contain recombinant human somatropin as active substance. The application was submitted under the legal base of Similar Biological Medicinal Product referring to Article 10.4 of Directive 2004/27/EC.

The reference medicinal product for this application is Genotropin Powder for Solution for Injection, a somatropin containing product produced by Pfizer (formerly Pharmacia) originally authorised in the EU in 1988. Omnitrope claims to be similar to this reference medicinal product as approved in the Community. Genotropin is presented in the same qualitative and quantitative composition in terms of the active substance somatropin (1.3 mg/ml and 5.0 mg/ml) and the same pharmaceutical dosage form (powder for solution for injection).

As required for a Similar Biological Medicinal Product application, the dossier contains a full quality Module 3 and reduced non-clinical and clinical Modules 4 and 5, with the required elements of the comparability exercise, respectively as required by the CHMP guidelines.

The indications applied for are as follows*:* Growth disturbance due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome or chronic renal insufficiency. Growth disturbance (current height SDS < -2.5 and parental adjusted 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 (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. Replacement therapy in adults with pronounced growth hormone deficiency.

Omnitrope will appear on the final documentation for the product, however, in certain reports, the name at the time of submission (i.e. Somatropin Sandoz) is used and also for earlier formulations during development.

2. Quality aspects

Introduction

Omnitrope (recombinant human growth hormone, rhGH) bulk solution is a clear or slightly turbid colourless solution, within the definition of the Ph. Eur. monograph 950, somatropin bulk solution. The non-glycosylated protein consists of 191 amino acid residues accounting for a total molecular weight of approximately 22,125 D, with a biological activity of 3.0 IU/mg and an isoelectric point of 5.1. The protein is produced by fermentation in an *E.Coli* host strain and subsequently isolated and purified by chromatographic means.

The active substance bulk solution is manufactured, tested and released by Sandoz GmbH, Kundl, Austria. Active substance manufactured by Covance (USA) was also used during the development programme, however, the Kundl process is that proposed for commercialisation.

Two formulations of rhGH are proposed: 1.3 mg/ml powder for solution for injection (vials) for single use, preservative free and 5.0 mg/ml powder for solution for injection (cartridges) for multiple use with benzyl alcohol as preservative. The cartridges are intended for use in CE marked pen injectors.

Drug Substance (Active Substance)

- Manufacture

One fermentation batch results from the use of one Working Cell Bank (WCB) vial. Materials comply either with Ph. Eur. or with satisfactory internal specifications.

Cell bank system
The *E. coli* host strain for the expression of recombinant rhGH was selected based on considerations of biological safety and productivity. The correct sequence of the final construct was verified by DNA sequencing. The stability of the recombinant expression system (*E.coli*) during the fermentation process was demonstrated; this maintains a high level of genetic stability throughout production.

Three vials deriving from each MCB and WCB were verified for identity, purity, and stability of the cell substrate. Appropriate acceptance criteria are set. The cell bank system was tested for yeast, fungal, and bacterial contaminants. In the course of preparation of the MCB and WCB, three vials from the MCB and both WCBs were tested for other adventitious agents, i.e. bacteriophage. Results were satisfactory. Stability on storage of both the MCB and WCBs is monitored at regular intervals for plasmid retention, cell counts and restriction analysis, which is considered acceptable for this type of cell substrate. The description of the preparation of new Working Cell Banks from the Master Cell Bank including criteria for acceptance is provided and can be accepted.

Fermentation
Fermentation starts with the preparation of the inoculum. One vial of the working cell bank is added to the medium and incubated until the required OD is reached. The inoculum may be used within one day or stored for an appropriate time until inoculation of the seed fermentor.

The seed culture is transferred to the production fermentor containing the defined culture medium. The customary process parameters are measured to control the fermentation process. The fermentation broth is harvested when the required OD and broth weight are reached.

Harvest and isolation
The active substance is expressed by the *E.coli* cells. The cells are harvested, washed with water to remove media components, and concentrated. The product is extracted and captured by column chromatography. The eluate is stored as appropriate, for long-term storage the eluate is filled into suitable bottles which are stored frozen.

Purification
A series of orthogonal chromatographic steps is used to achieve the final purity of the Omnitrope active ingredient.

Control & validation
The production process is monitored during production by operating controls, and in process controls of critical parameters. The results from the fermentation, isolation and purification validation demonstrate that all operations occur under well-controlled conditions and performed robustly within predefined parameter ranges. Satisfactory column reuse studies have been performed.

Manufacturing process development
During development several changes have been introduced, such as a transfer to a production plant in the USA (Covance Biotechnology Service Inc, CBSI), a re-transfer to Sandoz GmbH, Kundl Austria. Several improvements to the purification process were implemented at these manufacturing sites, leading to a modified downstream manufacturing process with significantly enhanced host cell protein (HCP) clearance. Following these modifications, no changes in other product characteristics were

detected. Issues with the detection of HCPs during very early development were completely resolved. The current product intended for commercialisation has never been affected by this issue.

Elucidation of structure and other characteristics
A set of state-of-the-art analytical methods was used to gain insight into the structural, physicochemical and biological characteristics of all somatropin samples integrated into the study program.

The comparability of Omnitrope active substance and Genotropin reference medicinal product was demonstrated in these characterisation studies by showing the identity of primary, secondary and tertiary structure as well as comparable impurity levels and bioactivity. Appropriate International Standards have also been included in the comparability exercise (refer also to the Section: Comparability Exercise).

Impurities
The active substance has been validated with respect to the presence of process and product related impurities. The results were consistent across a range of active substance batches, except for the higher level of host cell proteins in batches manufactured early in development.

Appropriate tests and limits have been applied to follow process related impurities.

The active substance is routinely tested for bioburden and bacterial endotoxins with appropriately defined limits set.

- Specifications

Satisfactory specifications have been defined for the active substance.
Satisfactory Validation of the analytical procedures has been performed in accordance with current ICH guidelines.

Detailed information has been provided on the reference standards and materials. All working standards have been calibrated against the International reference standard (NIBSC 88/624) or the Ph. Eur. Somatropin CRS.

- Stability

The active substance bulk solution is filled and stored in pre-sterilised non-pyrogenic PETG containers with HDPE lids.

The claimed shelf-life of active substance is supported by batch data. Sandoz GmbH commits to withdraw from the market any batch that falls outside the approved specifications or discuss the deviation with the competent authorities if Sandoz GmbH believes the deviation is not significant.

Drug Product (Medicinal Product)

Omnitrope 1.3 mg/ml (4 IU) Powder for Solution for Injection and Omnitrope 5.0 mg/ml (15 IU) Powder for Solution for Injection, represent different strengths of the same active substance, recombinant human growth hormone (rhGH).

Both medicinal products are white to off-white lyophilisates to be reconstituted with 1 ml WFI (1.3 mg/mL strength) and 1 ml of a solution of benzyl alcohol in WFI (5.0 mg/mL strength). A transfer set is needed for the reconstitution of the 5.0 mg strength. The reconstituted solution is to be injected using a pen injector. The compositions further comprise sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate heptahydrate and glycine.

The lyophilized powder is packaged in a colorless glass vial closed with a rubber stopper, which is laminated with an inert layer. The stopper is covered with an aluminum flip-off cap, which does not come in contact with the medicinal product.

The diluent for the 1.3 mL strength of the medicinal product is water for injections. It is presented in a colorless 2 mL glass vial closed with a rubber stopper and sealed with an aluminum flip-off cap.

The diluent for the 5.0 mL strength is a colorless solution of benzyl alcohol / water for injections in glass cartridge, closed on one side with a siliconized rubber plunger and on the other side with a disc and an aluminum cap which attaches the disc to the cartridge.

The composition of the product, description of the pharmaceutical form, description of the container, clinical trial formulae, manufacturing formula, manufacturing process and validation of the process, batch analysis results, specifications for excipients, specifications and routine tests for finished product, and stability results have been provided and are considered to be acceptable.

- Pharmaceutical Development

The active ingredient solution of Omnitrope complies with the Ph. Eur. Monograph Somatropin Bulk Solution and is compared with the Ph. Eur. standard (somatropin CRS). Preformulation testing of the active ingredient solution was performed in liquid and in frozen form. Further to the comparison with the Ph. Eur. Standard, the characterisation of the active substance proved the correct conformation to render it biologically active, as demonstrated by NMR in comparison with Genotropin.

- Manufacture of the Product

A suitable batch size has been given for both fill sizes. Both fill sizes formulae are given and include an appropriate overfill.

The different steps in the manufacturing process are adequately described and process controls have specified target values or ranges.

Commercial batches have been manufactured at Novartis, Stein. The manufacturing process for both fill sizes is identical, with the exception of the quantity of active ingredient and excipients per vial. During the process development, critical steps have been identified and validation experiments at the laboratory, pilot and production scale have been performed to define the optimal process conditions and the acceptable tolerances. Purity and content have been determined by chromatographic steps to assure the quality integrity of somatropin.

Excipients are in compliance with Ph. Eur./USP.- monographs

Analytical procedures, where appropriate are the ones described in the monographs. The test procedures are considered qualified as they are described in the compendial monographs.

- Product Specification

Satisfactory specifications for the lyophilised medicinal product and following reconstitution have been provided.

Appropriate tests and limits have been applied to follow product related substances and impurities in the lyophilised medicinal product.

Appropriate specifications have also been defined for the WFI and bacteriostatic diluents.

Validation of the analytical procedures has been performed in accordance with current ICH guidelines.

Batch analysis results are submitted for commercial scale production batches. In addition, results of development batches are submitted. The results are satisfactory and in support of the specifications.

A CE certified PEN device will be used for Omnitrope 5.0 mg/ml powder for solution for injection.

- Stability of the Product

Stability investigations on the finished product comprises data at long-term and accelerated test conditions conform ICH guidelines of the commercial scale batches Additionally, product in-use stability, photostability and shake stability has been demonstrated. The real time data of commercial scale batches are in support of the claimed stability in the SPC of 36 months at 5 ± 3 ^{o}C for the 5 mg/ml and 24 months at 5 ± 3 ^{o}C for the 1.3 mg/ml solution.

In-use stability has been validated for more than 21 days for the 5.0 mg/ml and for 1 day for the 1.3 mg/ml products, respectively. To conform with guidelines on this subject, it is indicated in the SPC that the 1.3 mg/ml product should be used immediately after reconstitution

The proposed in-use period of Somatropin 5.0 mg of 21 days at 5±3°C storage is acceptable.

Based on the stability data, the shelf life of 24 months of the WFI diluent in vials can be accepted. The stability data of the bacteriostatic diluent in cartridges demonstrate a shelf life of 36 months.

- Comparability Exercise

From the spectrometric and sequence data it can be concluded that Omnitrope active substance represents authentic somatropin and is thus equivalent to the pituitary-derived human growth hormone.

Omnitrope was compared to EU-Genotropin from a number of EU markets by a variety of spectrometric, sequence data, and physicochemical data. Within the limits of the analytical methods used, no significant differences were identified.

Due to the transfer and substantial changes introduced in the purification process, Omnitrope active substance manufactured at Sandoz, Kundl was compared to Omnitrope active substance manufactured at Covance. Again, within the limits of these analytical methods, the spectrometric, sequence data, physicochemical data, did not reveal significant differences. However, the Covance material contained a significantly higher amount of Host Cell Proteins (HCP) than the to-be-marketed Kundl material. The Covance material was significantly more immunogenic in patients than the Kundl material but will not be commercialised.

Omnitrope medicinal product was shown to be comparable to the reference medicinal product Genotropin, both quantitatively with regard to the overall purity, and qualitatively with regard to the impurity profile.

Reference medicinal products used for comparability exercise:
The same reference medicinal product, Genotropin from several sources in the EU was used as reference medicinal product in the comparability exercise. The company has provided all requested information regarding the reference medicinal product Genotropin. The extensive physico-chemical and biological characterisation of the reference medicinal products has sufficiently demonstrated the comparability of the Genotropin batches from the various markets in the Community. Therefore, from a chemical-pharmaceutical point of view, Genotropin authorised for the EU market can be accepted in

the nonclinical and clinical studies. Additional comparison of Genotropin sourced in the USA has confirmed that data generated with this reference medicinal product can be considered to be supportive.

Adventitious Agents Safety Evaluation
Non-viral adventitious agents (e.g. bacteria, mycoplasma, fungi) are controlled by either official Ph. Eur. methods (e.g. LAL) or by internal testing methods (e.g. bioburden).

All materials are in compliance with EMEA Guidance EMEA/410/01 on TSE.

GMP
Satisfactory compliance with GMP has been demonstrated for:
- the manufacturer of the active substance Sandoz GmbH, Kundl, Austria,
- the manufacturer of the medicinal product Novartis, Stein, Switzerland,
- the manufacturer of the WFI diluent (vial), EBEWE Pharma, Unterach, Austria,
- the manufacturer of bacteriostatic diluent (cartridges) Sandoz GmbH, Langenkampfen, Austria.

3. Non-clinical aspects

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Rat weight gain bioassays

Rat weight gain bioassays were performed to analyse the pharmacodynamics of batches of Omnitrope drug substance, Omnitrope Powder for Solution for Injection (subject of this application), Somatropin Sandoz Solution for Injection (not subject of this application) and the chosen reference medicinal product Genotropin. The international somatropin standards used were NIBSC 88/624 and/or NIBSC 98/574 (WHO standards). The test was performed over a period of 10 days in hypophysectomised rats.

The test preparations were injected s.c. at 5 or 10 µg/animal/day for 10 days in male Wistar rats. All treated animals gained weight and there was no significant difference in efficacy between the reference and the test preparations. It was concluded that in the chosen preclinical model for detection of growth hormone activity, all tested preparations had similar pharmacodynamic activity. In particular, Omnitrope Powder for Solution for Injection was as effective as Genotropin. There were no relevant signs of local intolerance at the sites of the repeated local injections. Several animals died on different days during the experiment for no apparent reason. The deaths were not considered to be related to treatment because they are scattered between the groups.

Rat tibial width assay

The purpose of the rat tibial width assay was to estimate the potency of different rhGH products, each with a high and low content of product-related impurities, by comparing their effect in increasing the width of the proximal epiphysis of the tibia in immature hypophysectomised rats with that of a WHO hGH standard (NIBSC 98/574). The low and high concentrations of related proteins were reached by storing the different growth hormone products at different temperatures, i.e. at 2-8°C for the low concentration and at 40°C for the high concentration. The effect on organ weights of the individual test products was also compared.

The determination of the potency of the tested somatropin formulations was carried out according to European Pharmacopoeia 1987-Method A. Immature hypophysectomised male rats were administered the test formulations vehicle or a standard at 0.02 or 0.16 IU/animal/day by s.c. injection for 10 days.

Measurement of the thickness of the epiphysis at ten different sites equally distributed over the full length of the epiphysis was performed. In addition, organ weight of heart, lung, kidney and testis was assessed.

The results of the rat tibial width assay show that the potency of the different rhGH products, each with a high and low content of product-related impurities, comply with the requirements of European Pharmacopeia 1987-Method A. The increase of the tibia thickness as a function of the dose administered is similar for the WHO standard and for the different rhGH. The estimated potency is not less than 80% and not more than 125 % of the stated potency. In particular, the results show that Omnitrope Powder for Solution for Injection is comparable to the chosen reference medicinal product Genotropin in terms of potency

Pharmacokinetics

No specific pharmacokinetics studies have been performed with Omnitrope. Some pharmacokinetic information is available from a toxicokinetic investigation performed in context with a 14-day toxicity study in the rat (see repeated dose toxicity).

Toxicology

- Repeat dose toxicity (with toxicokinetics)

14-Day s. c. Toxicity Test in the Rat

Sprague-Dawley rats were given Omnitrope Powder for Solution for Injection (0, 2 or 8 mg/kg/day) s.c. over 14 days. Toxicokinetic analysis was performed on days 1, 7 and 14. The chosen reference medicinal product Genotropin was not used as comparator in this study.

There were no abnormal clinical signs during the study. No relevant adverse reaction was seen at the injection sites. Treated females showed a dose-related increase in weight gain, accompanied by a high food consumption, but weight gain and food consumption of males was the same as that of the controls.

No abnormal haematological results were found. Clinical chemistry tests in males were normal. In females there were small, albeit significant decreases in ALT and AST, an increase in ALP and a decrease in serum albumin, changes that are likely to reflect pharmacodynamic effects of somatropin on metabolism. There were small increases in relative heart and kidney weight in females but no effect on organ weight in males. No histopathological abnormalities were noted.

The overall conclusion was that Omnitrope had no relevant toxic effect and that the changes in female animals probably represented its specific pharmacodynamic action.

Toxicokinetics

Serum was collected from selected animals in all groups on days 1, 7 and 14 at 0, 2, 4, 6 and 10 hours post-dosing. The hGH concentration was measured by an IRMA using an anti-human somatropin antibody.

There was slight accumulation of GH over the 14 days of treatment indicated by small increases in the pre-dosing levels on days 7 and 14 in the high-dose group. Also on day 14 in the 2 mg/kg group and on days 1, 7 and 14 in the 8 mg/kg animals the circulating level of hGH had not returned to 0 by 10 hours post-dosing. As the dose of hGH was increased there was a sub-proportional increase in C_{max} and AUC, resulting in apparently similar drug exposure in the 2 dosage groups. Release from the

injection sites appeared slower on day 14 than day 1. Total body exposure to Omitrope appeared lower on day 14 than on day 1. In fact, the relatively small numbers of animals sampled resulted in some uncertainty about the values cited. The absence of a sharp decline in C_{max} and AUC in the day 14 samples was interpreted by the non-clinical expert to provide some indication of the absence of significant antibody formation by that time.

- Local tolerance

Two formulations of Omnitrope were given daily for 7 days to male and female rabbits; dose 5 mg/animal, volume 1ml (lyophilised formulation, subject of this application)) and 1.5 ml (liquid (API Sandoz) formulation, not subject of this application). Detailed examinations of general health and of the injection sites were made every day; the animals were sacrificed on day 8 or on day 22.

There were signs of mechanical injection trauma in all groups. The liquid (API Sandoz) formulation and its vehicle were associated with slight erythema at the sites of the i.v. injections and with some local indurations. The erythema had disappeared by about day 13, i.e. 6 days after the last injection.

After administration of the lyophilisate, erythema was rare and was not noted after day 8. No particular reaction was seen at the sites of the i.m. injections other than the effects of mechanical trauma of injection. The s.c. injection sites in all groups showed small haemorrhages attributed to mechanical trauma and minimal oedema and erythema, slightly more marked after the lyophilised formulation, and some induration after the vehicle of that formulation.

Ecotoxicity/environmental risk assessment

Somatotropin Sandoz is a recombinant human growth hormone (somatropin) composed of 191 amino acids. The structural gene used is a cDNA derived from the naturally occurring hGH. The active substance of Omnitrope is chemically identical to the major component of pituitary growth hormone. The peptide is rapidly and completely degraded in the human organism. Thus the therapeutically administered compound is not released into the environment.

Inadvertent release of wasted material would also not cause any problems in the environment due to its peptide structure, which will be rapidly destroyed and mineralised by microbial hydrolytic processes.

4. Clinical aspects

Introduction

During the clinical development programme various formulations of growth hormone were used, with active pharmaceutical ingredient (API) as follows :

- Somatropin Sandoz powder for solution for injection (API Covance Biotechnology Service Inc, CBSI) abbreviated to Somatropin Sandoz powder (API Covance)
- Somatropin Sandoz powder for solution for injection (API Sandoz GmbH, Kundl, Austria) abbreviated to Somatropin Sandoz powder (API Sandoz)
- Somatropin Sandoz liquid (API Sandoz), in which the active substance is the same as Somatropin Sandoz powder (API Sandoz)

The formulation Somatropin Sandoz powder (API Sandoz) is the formulation to be marketed as Omnitrope.

In the pharmacokinetic studies (EP2K-99-PhISUSA, EP2K-99-PhIUSA, and EP2K-00-PhI^{AQ}), Somatropin Sandoz powder (API Covance) was used. The pharmacokinetic study EP2K-00-PhI^{AQ} demonstrated the equivalence between Somatropin Sandoz powder (API Covance) with Somatropin Sandoz liquid (API Sandoz).

One of the two pivotal studies (the pivotal efficacy study) was a phase III study consisting of three sub-studies. Two of these sub-studies (EP2K-99-PhIII and EP2K-99-PhIIIFo) compared the effects of the reference medicinal product Genotropin and Somatropin Sandoz powder (API Covance) in an open design over a period of 9 months (EP2K-99-PhIII covered the first 6 months and the Fo study the following 3 months) whereas the extension of EP2K-00-PhIIIFo (EP2K-00-PhIII^{AQ}) compared the effects of Omnitrope and Somatropin Sandoz liquid (API Sandoz) during the first 6 months of this study (month 9 to 15 of the complete trial) after which all patients were transferred to Somatropin Sandoz liquid (API Sandoz). All studies met the GCP guidelines. Although the GCP inspection of study EP2K-99-PhIII / EP2K-99-PhIIIFo revealed problems with drug accountability, proper transport of the study drug, and with height measurements, these findings were considered not to invalidate the overall study results. The other pivotal study (the pivotal safety study) was study EP2K-02-PhIII-Lyo, a multi-centre non-comparative study using Omnitrope**.**

In clinical studies EP2K-99-PhIII and EP2K-99-PhIIIFo with the earlier product Somatropin Sandoz powder (API Covance) up to 60% of the enrolled patients had developed anti-GH antibodies without showing any influence on growth rate. Careful investigation revealed high concentrations of host cell proteins (leading to development of anti-HCP antibodies in all patients treated with this product), which are known to enhance the antibody reaction against GH. Therefore, the manufacturing process for Omnitrope has been slightly modified by introducing additional purification steps during the development process of the product. The concentrations of host cell proteins in the subsequent formulations (API Sandoz and liquid (API Sandoz)) were within the range known from other authorised GH-containing products. Anti-GH antibody formation with Omnitrope and Somatropin Sandoz liquid (API Sandoz) was within the range known from other GH-containing products.

Pharmacokinetics

Three pharmacokinetic studies, performed in healthy volunteers, were submitted.

Study EP2K-99-PhISUSA was an exploratory pharmacokinetic study assessing the pharmacokinetic profile of Somatropin Sandoz powder (API Covance) compared to placebo. In study EP2K-99-PhIUSA the pharmacokinetic profiles of Somatropin Sandoz powder (API Covance) and Genotropin USA were compared.

In study EP2K-00-PhI^{AQ} the pharmacokinetic profile of Somatropin Sandoz (API Covance) and a Somatropin Sandoz 3.3 mg/ml solution for injection (Somatropin Sandoz Liquid (API Sandoz)) was investigated.

Furthermore, limited pharmacokinetic analysis of somatropin in Growth Hormone Deficient (GHD) children was conducted under steady-state conditions in the efficacy studies (EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIII).

$AUC_{(0-t)}$, AUC_{inf}, C_{max}, t_{max} and $t_{1/2}$ were calculated, following suppression of endogenous growth hormone secretion by a continuous administration of octreotide, a somatostatin analogue, according to standard procedures.

Statistical evaluation of the data was performed on the log-transformed AUC and C_{max} using ANOVA, with sequence, subject within sequence, period and treatment effects, and 90% confidence intervals (CI) were calculated. A priori, the acceptance range for the 90% CI was defined as 0.80-1.25 for AUC and C_{max}. The t_{max} was compared using appropriate non-parametric tests.

- **Absorption**

A phase I safety study in healthy volunteers (EP2K-99-PhISUSA) with Somatropin Sandoz powder (API Covance) to assess the safety, tolerance and pharmacokinetics of somatotropin after single subcutaneous administration was conducted.

In this double blind, randomised, placebo-controlled, two-way crossover study, a total of 12 healthy volunteers (six male/six female, 18-45 years) received either 5 mg Somatropin Sandoz powder (API Covance) or placebo (water for injection) administered subcutaneously (s.c.). The washout period between treatments was one week. To accurately assess the pharmacokinetics of somatropin, endogenous growth hormone (GH) was suppressed by a continuous infusion of octreotide over 25 hours (from 1 hour before until 24 hours after the injection of somatropin or placebo). The efficacy of this latter treatment was assessed in the placebo group. The pharmacokinetic variables of somatropin after injection of Somatropin Sandoz powder (API Covance). AUC_{inf}, C_{max}, $t_{1/2}$. CL/F, T_{lag} are shown in the table as mean ± SD, t_{max} as median (range).

n=12	somatropin (Somatropin Sandoz 5 mg s.c.)
AUC_{inf} (µg.h/l)	291 ± 42
C_{max} (µg/l)	37 ± 9
t_{max} (h)	3.5 (2.9-4.5)
$t_{1/2}$ (h)	2.4 ± 0.4
CL/F (l/h)	18 ± 3
t_{lag} (h)	0.7 ± 0.5

The study demonstrated that continuous iv infusion of octreotide is effective in suppressing endogenous GH secretion in healthy human volunteers. Isolated GH serum values were above 0.1 µg/l. The highest value was 0.7 µg/l and contributed to a GH AUC of 2 µg·h/l. This C_{max} and AUC are considered negligible as compared with a mean C_{max} of 37 ± 9 µg/l and AUC of 291 ± 42 µg·h/l after administration of 5 mg of Somatropin Sandoz powder (API Covance).

- **Study EP2K-99-PhIUSA**

In a double blind, randomised, two-way crossover, comparative study (EP2K-99-PhIUSA), a total of 25 healthy volunteers (twelve male/thirteen female, 18-45 years) received either 5 mg Somatropin Sandoz powder (API Covance) or Genotropin s.c. The washout period between treatments was one week. One female volunteer withdrew after treatment period 1, leaving data from 24 volunteers for analysis. To accurately assess the pharmacokinetics of somatropin, endogenous GH was suppressed by a continuous infusion of octreotide, from one hour before until 24 hours after administration of Somatropin Sandoz powder (API Covance) or Genotropin USA . The pharmacokinetic variables of somatropin after injection of Somatropin Sandoz powder (API Covance) or Genotropin, AUC_{0-t}, AUC_{inf}, C_{max}, $t_{1/2}$, V_z, CL/F, MRT_{last}, and MRT_{inf} are shown in the table as mean ± SD, t_{max} as median (range).

n=24	Somatropin Sandoz 5 mg s.c.	Genotropin 5 mg s.c.
AUC_{0-t} (µg.h/l)	413 ± 111	396 ± 106
AUC_{inf} (µg.h/l)	416 ± 110	400 ± 105
C_{max} (µg/l)	52 ± 21	48 ± 20
t_{max} (h)	4.1 (2.1-8.1)	4.1 (2.0-10.1)
$t_{1/2}$ (h)	2.7 ± 0.6	2.9 ± 0.6
V_z (l)	52 ± 24	57 ± 27
CL/F (l/h)	13 ± 3	13 ± 4
MRT_{0-t} (h)	7.0 ± 1.3	7.0 ± 1.2
MRT_{inf} (h)	7.1 ± 1.5	7.2 ± 1.3

The AUC_{inf} and C_{max} of Somatropin Sandoz powder (API Covance) and Genotropin USA were tested for criteria for equivalence using the program BIOSTAT 4.0 (ANOVA). The 90% confidence intervals of the AUC_{inf} and C_{max} are within the acceptance range of 0.80-1.25. The pharmacokinetics of Somatropin Sandoz (API Covance) and Genotropin USA can therefore be considered as comparable with respect to the rate and extent of absorption after a single dose.

With regard to $t_{1/2}$, mean and median values, which were found to be slightly lower for Somatropin Sandoz powder (API Covance), the Applicant performed an additional statistical analysis of intra-individual differences in $t_{1/2}$ using the Wilcoxon signed-rank test (significance level a = 0.05, SAS version 8.2). No statistically significant difference was found for $t_{1/2}$ (p = 0.081). For the parameter CL/F, exactly the same means and medians were observed under the two treatments (i.e., 13 l/h). Analysis of intra-individual differences, again using Wilcoxon signed-rank test (significance level a = 0.05), revealed no statistically significant difference in CL/F (p = 0.069). These additionally derived results indicate that Somatropin Sandoz powder (Covance) and Genotropin do not differ with respect to the elimination rate.

Study EP2K-99-PhIUSA demonstrates comparable pharmacokinetic profiles of Somatropin Sandoz and Genotropin USA. These data further support the demonstration of therapeutic omparability between Omnitrope and Genotropin EU as demonstrated in the clinical efficacy study.

- **Study EP2K-00-PhI^{AQ} (comparison of Somatropin Sandoz powder (API Covance) and Somatropin Sandoz Liquid (API Sandoz)**

In this double blind, randomised, two-way crossover study (EP2K-00-PhI^{AQ}), a total of 24 healthy volunteers (twelve male/twelve female, 23-48 years) received either 5 mg Somatropin Sandoz powder (API Covance) or Somatropin Sandoz Liquid (API Sandoz) s.c. The washout period between treatments was at least one week. To accurately assess the pharmacokinetics of somatropin, endogenous GH production was suppressed by a continuous infusion of octreotide, from one hour before until 24 hours after administration of the test and reference Somatropin Sandoz formulations.

Pharmacokinetic variables of somatropin after injection of Somatropin Sandoz. AUC_{0-t}, AUC_{inf}, and C_{max} are shown as geometrical mean ± SD, $t_{1/2}$ as mean ± SD, and t_{max} as median (range)

n=24	Somatropin Sandoz Liquid (API Sandoz) 5 mg s.c.	Somatropin Sandoz 5 mg s.c.
AUC_{0-t} (µg.h/l)	422 ± 45	453 ± 43
AUC_{inf} (µg.h/l)	426 ± 45	456 ± 44
C_{max} (µg/l)	51.7 ± 9.9	54.6 ± 12.9
t_{max} (h)	3.0 (2.0-8.0)	3.0 (2.0-10)
$t_{1/2}$ (h)	2.4 ± 0.7	2.4 ± 0.6

The 90% confidence intervals of the AUC_{inf} and C_{max} are within the acceptance range of 0.80-1.25. Therefore, the Somatropin Sandoz Liquid (API Sandoz) and Somatropin Sandoz powder (API Covance) formulation is considered comparable with respect to the rate and extent of absorption.

Special populations

- **Gender and weight**

Both for Somatropin Sandoz and Genotropin, statistically significantly different AUC, V_z and CL/F values were observed between males and females. C_{max} and t_{max} values were not statistically different in males and females. The gender differences observed could at least partially be explained by weight

differences between males and females. Therefore, a weight-based dosing would have been preferable. As the dosing advice is based on administration per kg body weight, the observed difference is expected not to be of clinical significance.

Correlations were observed between volunteer weight and somatropin C_{max} (r = -0.6), and between volunteer weight and somatropin AUC_{inf} (r = -0.8).

- **Pharmacokinetics in target population**

Steady-state pharmacokinetics

From study EP2K-99-PhISUSA it appeared that the somatropin serum level after administration of Somatropin Sandoz powder (API Covance) would always return to baseline before the next daily administration, making it unlikely that accumulation could occur during repeated daily administration. This result is in accordance with the body of knowledge currently available on somatropin. Consequently, the MAH did not perform a steady-state pharmacokinetic/pharmacodynamic study during the development of Omnitrope.

However, the MAH carried out an analysis in 86 GHD children treated in the EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIII^{AQ} studies after 0, 9, 18 and 24 month of treatment with either Omnitrope or Genotropin. Somatropin plasma levels measured in children 10 to 16 hours after somatropin administration were compared with those obtained after single dose administration in healthy volunteers. The data suggest that Omnitrope does not accumulate under steady state conditions in GHD children.

Pharmacodynamics

The company submitted three pharmacodynamic studies. All pharmacodynamic assessments were part of the studies EP2k-99-PhIUSA, EP2K-99-PhIUSA and EP2K-00-PhI^{AQ} described above and included measurements of IGF-1, IGFBP-3 and NEFA at pre-defined time points until 96 hours post dose.

Somatropin Sandoz had the expected effects on IGF-1, IGFBP-3 and NEFA. Moreover, plasma levels of these parameters were similar for Somatropin Sandoz (API Covance and Genotropin USA and for the two Somatropin Sandoz formulations Somatropin Sandoz powder (API Covance) and Somatropin Sandoz Liquid (API Sandoz).

Conclusions regarding pharmacodynamic equivalence are not possible because endogenous GH was suppressed only part of the study duration, the variance of the measured parameters was high, and pre-defined or generally accepted equivalence margin are missing. Further the results of the study should be interpreted with caution for pharmacodynamic endpoints were only secondary and the great variance will decrease the power of the study. Results of the study did not show any difference between Somatropin Sandoz and Genotropin USA, but in the light of the decreased power of the study this is not unexpected. Since neither IGF-1 nor IGFBP-3 nor NEFA are accepted surrogate markers for efficacy of a somatropin, the described short-comings of the pharmacodynamic assessments are not considered relevant for the decision on whether Omnitrope is similar to Genotropin.

The safety assessment is hampered by the use of octreotide and therefore only of limited value. No death or serious adverse events were encountered during the study.

Clinical efficacy

One phase III study consisting of three sub-studies was submitted. The two sub-studies EP2K-99-PhIII and EP2K-99-PhIIIFo (pivotal efficacy studies) compared the effects of Somatropin Sandoz powder

(API Covance) and the EU reference medicinal product Genotropin in an open design over a period of 9 months (EP2K-99-PhIII covered the first 6 months and the Fo study the following 3 months) whereas the extension of EP2K-00-PhIIIFo (EP2K-00-PhIII^{AQ}) compared the effects of Omnitrope and Somatropin Sandoz liquid (API Sandoz) during the first 6 months of this study (month 9 to 15 of the complete trial) after which all patients were transferred to Somatropin Sandoz liquid (API Sandoz).

Besides this study the Applicant submitted study EP2K-02-PhIII-Lyo (pivotal safety study), an open, multicentre, non-comparative study using Omnitrope.

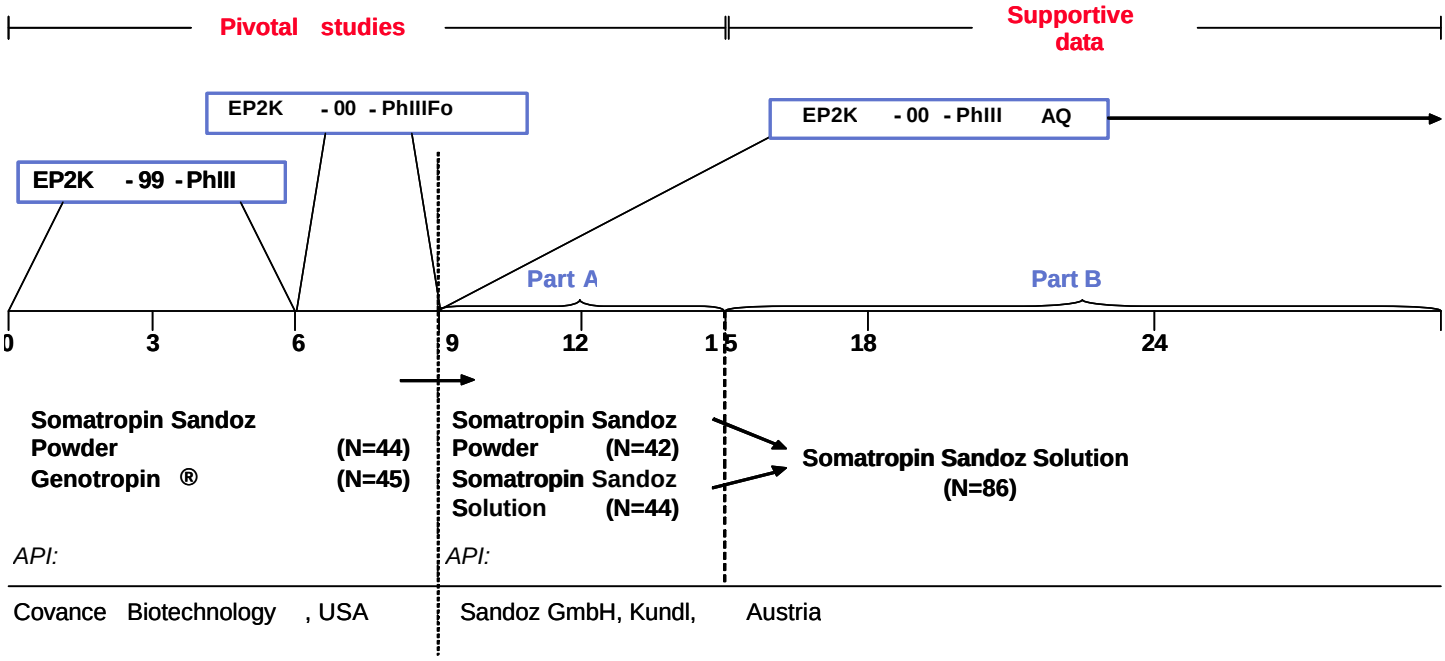
- **Study EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIIIAQ**

Study **EP2K-99-PhIII/EP2K-00-PhIIIFo** compared the effects of Somatropin Sandoz powder (API Covance) and the reference medicinal product Genotropin on the growth in children with GH deficiency.

The same patients were included in **EP2K-00-PhIIIAQ,** an open, multicentre, comparative, follow-up trial evaluating the efficacy and safety of two formulations of Somatropin Sandoz, i.e. Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation.

Methods

The design of Study EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIIIAQ is detailed in the following Figure.



Study Participants

Eighty-nine prepubertal, GH-deficient patients were enrolled in study **EP2K-99-PhIII / EP2K-00-PhIIIFo**.

Patients with a stature of <-2 SDS for chronological age, and a spontaneous growth rate of <-1 SDS over an interval of at least six months prior to enrolment were eligible. Patients with chronic systemic diseases or evidence of tumour growth, with skeletal or chromosomal abnormalities as well as patients on medication known to affect growth were excluded from the study. Although transfer patients were allowed according to the protocol, in fact only treatment-naïve patients were recruited.

The same patients were included in the follow-up trial **EP2K-00-PhIIIAQ**

Treatments

In study **EP2K-99-PhIII / EP2K-00-PhIIIFo** patients were randomised to receive either 0.03-mg/kg-body weight/day (0.1 IU/kg/day) Somatropin Sandoz powder (API Covance) or Genotropin once daily given s.c.

In study **EP2K-00-PhIIIAQ** patients were treated with the same dose they were using in the previous studies. Patients previously treated with Somatropin Sandoz powder (API Covance) were switched to Omnitrope, patients previously treated with Genotropin were switched to Somatropin Sandoz liquid (API Sandoz).

Outcomes/endpoints

In study **EP2K-99-PhIII/EP2K-00-PhIIIFo** primary endpoints were the height and the height standardised for age and sex (Height Standard Deviation Score, HSDS) at month 9, the height velocity as well as the height velocity standard deviation score (HVSDS) between month 0 and 9.

Secondary efficacy endpoints included IGF-1 and IGFBP-3 serum levels at months 1, 3 6, and 9. Besides physical examinations, safety assessment consisted of adverse event recording, standard and specific laboratory tests, e.g. on anti-hGH-antibody formation, glucose metabolism and thyroid function.

In study **EP2K-00-PhIIIAQ** primary endpoints were height, HSDS), height velocity HVSDS; secondary endpoints were IGF-1and, IGFPB-3; further a standard safety analysis was performed

Statistical methods

Initially, the study was designed as a superiority study and was later re-designed to show similarity between Somatropin Sandoz powder (API Covance) and Genotropin. Therefore, sample size calculation was based on a superiority hypothesis. Comparison of efficacy was done by analysis of variance (ANOVA). For transfer patients, the length of time of previous GH treatment was to be used as a covariate.

RESULTS

Baseline data

The patients included were all treatment-naïve. Treatment groups were comparable with respect to the main baseline characteristics.

Efficacy data

- Height

During the EP2K-99-PhIII / EP2K-00-PhIIIFo phase (first 9 months) of the trial, height increased from 113.3cm to 121.9cm in the Somatropin Sandoz powder (API Covance) treated group, and from 109.3cm to 117.7cm in the Genotropin group. The 95% CI for the estimate of the difference in height between treatment groups after 9 months of treatment (-0.59, 1.06) indicates that both treatments resulted in comparable increases in height.

During the controlled phase of study EP2K-00-PhIII^{AQ} (first 6 months) mean height increased by 4.2 and 5.7 cm in the Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation, respectively.

- HSDS

During the EP2K-99-PhIII / EP2K-00-PhIIIFo phase of the trial, mean HSDS increased from –3.0 and –3.1 at baseline to –2.7 and –2.9 after 3 months, to –2.4 and -2.6 after 6 months, and to –2.3 and –2.5 after 9 months of therapy with Somatropin Sandoz powder (API Covance) and Genotropin respectively. The 95% CI for the estimate of the difference in height SDS between treatment groups after 9 months of treatment (-0.05, 0.30) indicates that both treatments resulted in comparable increases in height SDS.

During the controlled phase of study EP2K-00-PhIII^{AQ} (first 6 months) HSDS increased from –2.3 and –2.5 to –2.0 and –2.2 after 6 months with the Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation, respectively, in the uncontrolled phase of this study the HSDS further increased to -1.7 in the overall group.

- Height velocity

During the EP2K-99-PhIII/ EP2K-00-PhIIIFo phase of the trial, mean annualised height velocity increased from 3.8 and 4.0 cm/year at baseline to 12.0 and 12.0 cm/year after 3 months to 11.7 and 11.6 cm/year after 6 months, and to 10.7 and 10.7 cm/year after 9 months of therapy with Somatropin Sandoz powder (API Covance) and Genotropin, respectively. The 95% CI for the estimate of the difference in height velocity between treatment groups after 9 months of treatment (-1.35, 0.92)indicates that treatment with Somatropin Sandoz powder (API Covance) and treatment with Genotropin resulted in comparable increases in height velocity.

During the controlled phase of study EP2K-00-PhIII^{AQ} (first 6 months), height velocity was 8.5 and 8.6 cm/year at 6 months in the Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation, respectively; in the uncontrolled phase of this study the height velocity decreased to 7.4 cm/year in the overall group.

- HV-SDS

During the EP2K-99-PhIII/ EP2K-00-PhIIIFo phase of the trial, mean HV-SDS increased from –2.4 and –2.3 at baseline to 7.5 and 6.8 after 3 months and 7.3 and 6.3 after 6 months, and 6.1 and 5.4 after 9 months of therapy with Somatropin Sandoz powder (API Covance) and Genotropin, respectively. The 95% CI for the estimate of the difference in HV-SDS between treatment groups after 9 months of treatment (-0.81, 2.13) indicates that both treatments resulted in comparable increases in height velocity SDS.

During the controlled phase of study EP2K-00-PhIII^{AQ} (first 6 months), HV-SDS was +3.4 and +3.2 at 6 months in the Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation, respectively. In the uncontrolled phase of this study the height velocity SDS decreased to 2.5.

Treatment response in children with and without anti-GH antibodies

The antibodies detected during the clinical trial EP2K-99-PhIII / EP2K-00-PhIIIFo were non-neutralising and therefore not expected to modulate the efficacy of the formulation. This assumption is confirmed by the data of study EP2K-99-PhIII showing comparable clinical efficacy results for Somatropin Sandoz powder (API Covance) and the reference medicinal product Genotropin. Children with or without antibodies had the same growth rates (see table below).

To evaluate a possible interference of the increased occurrence of antibody formation with growth, an analysis of the primary efficacy endpoints for patients with anti-GH antibodies was performed. Overall, 30 patients (26 in the 'Somatropin Sandoz powder (API Covance)' group and 4 in the 'Genotropin' group) had anti-GH antibodies at least once during the three Phase III studies. A non-parametric Mann-Whitney statistical comparison was performed between patients with and without anti-GH antibodies for all primary efficacy endpoints (height, HSDS, height velocity and HVSDS) at Months 0, 3, 6, 9, 12, 15, 18 24; the results of the p-values are shown in the table below.

Table: HSDS and HVSDS from Month 0 to Month 24 for patients with and without antibodies

	HSDS (Mean ± SD)			**HVSDS (Mean ± SD)**		
	Patients with anti-GH antibodies *	Patients without anti-GH antibodies	Mann Whitney test (p value)	Patients with anti-GH antibodies *	Patients without anti-GH antibodies	Mann Whitney test (p value)
Month 0	-3.1 ± 0.7	-3.1 ± 0.9	0.75	-2.5 ± 1.2	-2.3 ± 1.2	0.64
Month 3	-2.7 ± 0.6	-2.9 ± 0.9	0.84	7.5 ± 4.1	7.0 ± 5.4	0.34
Month 6	- 2.4 ± 0.5	-2.6 ± 0.8	0.50	6.8 ± 3.3	6.8 ± 4.1	0.56
Month 9	-2.3 ± 0.5	-2.4 ± 0.8	0.35	5.6 ± 3.2	5.8 ± 3.6	0.98
Month 12	-2.1 ± 0.6	-2.3 ± 0.8	0.14	4.5 ± 3.8	2.9 ± 2.8	0.06
Month 15	-2.0 ± 0.6	-2.2 ± 0.8	0.20	3.6 ± 2.6	3.1 ± 2.8	0.49
Month 18	-1.9 ± 0.7	-2.0 ± 0.8	0.21	2.1 ± 3.2	2.7 ± 4.3	0.51
Month 24	-1.7 ± 0.7	-1.9 ± 0.8	0.23	3.5 ± 8.1	1.9 ± 2.0	0.94

* Patients were considered anti-GH antibodies positive if they had one or more positive results for GH antibody from month 0 to month 24.

Considering antibody data from the first 30 months of hGH-treatment, the presence of anti-GH antibodies apparently had no effect on growth. No statistically significant differences at any time-point between patients with and without anti-GH antibodies regarding height, HSDS, height velocity and HVSDS could be detected. These results indicate that the presence of anti-GH antibodies had no effect on any of the growth efficacy parameters.

- IGF-I serum level

During the EP2K-99-PhIII/ EP2K-00-PhIIIFo phase of the trial mean serum IGF-I levels increased from 159 and 158 ng/ml at baseline to 200 and 193 ng/ml after 3 months, to 257 and 248 ng/ml after 6 months, and to 291 and 302 ng/ml after 9 months of therapy with Somatropin Sandoz powder (API Covance) and Genotropin, respectively.

- IGFBP-3 serum level

During the EP2K-99-PhIII/ EP2K-00-PhIIIFo phase of the trial, mean IGFBP-3 serum levels increased from 3.5 and 3.5µg/ml at baseline to 3.8 and 3.7 µg/ml after 6 months and 4.6 and 4.0 µg/ml after 9 months of therapy with Somatropin Sandoz powder (API Covance) and Genotropin, respectively.

- Projection of final height

During the EP2K-99-PhIII/ EP2K-00-PhIIIFo phase of the trial the "projected final height", calculated based on the assumption that for an individual child the HSDS at final height is equal to the HSDS at a given prior time point, demonstrated a positive effect of GH therapy. For patients in the 'Somatropin Sandoz Powder (API Covance)' group, mean projected height increased from 154.5 ± 7.02 cm at baseline to 159.0 ± 7.08 cm at Month 9; for patients in the 'Genotropin ' group, mean projected height increased from 151.3 ± 7.87 cm at baseline to 155.1 ± 7.33 cm at Month 9. Projected height increased significantly between Months 0 and 9, irrespective of gender and treatment.

During the 6 month controlled phase of study EP2K-00-PhIII^{AQ}, mean projected height increased from 159.0 ± 7.08 cm to 160.7 ± 7.06 cm for the 'Somatropin Sandoz Powder (API Covance)' group, and from 155.1 ± 7.33 cm to 156.9 ± 7.54 cm for the 'Somatropin Sandoz Liquid (API Sandoz) group (ex-'Genotropin ' group). During the uncontrolled phase of this study, projected height increased from 158.8 ± 7.51 cm to 161.4 ± 8.17 cm in the overall group.

- **Study EP2K-02-PhIII-Lyo.**

Study EP2K-02-PhIII-Lyo is an ongoing open, multicentre, non-comparative, non-controlled study, 12-month data were evaluated. The study duration is planned for 24 months after which the MAH committed to continue the observation of the patients.

Study participants

Fifty-one treatment naïve children with GH deficiency were enrolled.

Patients with a height of <-2 SDS and a spontaneous growth rate of <-1 SDS over an interval of at least six months prior to enrolment were eligible. Patients with chronic systemic diseases or evidence of tumour growth, with skeletal or chromosomal abnormalities as well as patients receiving medication known to affect growth were excluded from the study.

Treatment

The patients received 0.03mg/kg/day, Omnitrope (s.c injection at bedtime).

Outcomes/endpoints

Primary efficacy endpoints were height, H-SDS, height velocity (HV), and HV-SDS. Secondary endpoints were IGF-I and IGFBP-3. Standard safety analysis was performed including serum levels and frequency of the development of anti-hGH antibodies and anti-Host Cell Proteins (HCP) antibodies. Further, the final height was calculated based on bone age (predicted FH = FHpre) and on the projection method (FHpro).

Statistical methods

In the 12-month interim report, demographic and background characteristics were analyzed descriptively. Statistical investigation of primary and secondary efficacy endpoints was done by analyzing intra-individual changes between the baseline visit 01 (start of rhGH treatment) and visits 02, 03, 04, and 05 (12 months of rhGH treatment), respectively. For each efficacy endpoint, statistical analysis was performed by calculating 95% confidence intervals (CIs) for the mean difference between visit 01 and each of the later visits.

Safety data were evaluated descriptively using summary tables and shift tables. Summary statistics were reported as mean, SD, minimum, maximum, or proportions, where appropriate. Analyses for efficacy parameters were performed on the ITT and PP populations. Safety analyses were performed on the safety population.

RESULTS

Fifty one patients (30 boys and 21 girls, mean age 8.04 ± 2.64 years, range 2.5 to 14.2 years) were enrolled. All of them were pre-pubertal and of Caucasian origin. Forty-seven patients (92.2%) had isolated GH deficiency and 4 patients (7.8%) had multiple hormone deficiency. Mean standing height at the start of rhGH treatment was 111.9 ± 15.5 cm. After 6 and 12 months of treatment, height had increased significantly by an average of 5.95 cm and 10.37 cm to a mean height of 117.9 ± 14.7 cm and 122.3 ± 14.3 cm, respectively.

All patients experienced an evident increase in HV during rhGH treatment. Average annualized HV increased from 3.72 ± 1.40 cm/year at baseline to 11.97 ± 3.24 cm/year during the first 6 months of treatment and to 10.39 ± 2.50 cm/year during the first 12 months. The mean difference in HV between baseline and month 6 was 8.25 cm/year, 95% CI [7.13; 9.37]. The mean difference in HV between baseline and month 12 was 6.66 cm/year, 95% CI [5.76; 7.57].

The mean HSDS of –3.19 ± 1.02 in the ITT group at the start of rhGH treatment demonstrated a major height deficit relative to normally growing children. Mean HSDS improved to –2.51 ± 0.86 and –2.15 ± 0.79 after 6 and 12 months of rhGH treatment, respectively. The mean difference in HSDS between baseline and month 6 was 0.68 , 95% CI [0.58; 0.78]. The mean difference in HSDS between baseline and month 12 was 1.05, 95% CI [0.89; 1.21].

The mean HVSDSPC (pc = peak-centered reported by Prader) at baseline was –2.72, clearly below that of normally growing children. The sharp increase in HV during the first 3 months of rhGH treatment is also reflected in the time course of mean HVSDSPC. Over the first 3 months, the mean HVSDSPC increased to +9.23. The observed difference to baseline of 11.95 in HVSDSPC was highly significant, as indicated by the 95% CI [9.97; 13.93]. Mean HVSDSPC was +6.18 during the first 12 months reflecting a mean increase of 8.89 compared to baseline, with a corresponding 95% CI of [7.64; 10.15]. Calculated CIs indicate a statistically significant increase in all defined primary efficacy endpoints during treatment.

The 51 patients started rhGH treatment at an average IGF-1 serum level of 78.8 ± 46.9 ng/ml. At 6 months, IGF-1 levels had increased to a mean of 182.5 ± 92.8 ng/ml. The 95% CI for the increase from baseline was [86.0; 121.4]. At 12 months, mean IGF-1 serum levels were 208.4 ± 105.9 ng/ml. The 95% CI for the increase from baseline was [110.2; 148.9], again indicating a significant change between the considered time points.

Serum levels of IGFBP-3 increased from 2.7 ± 1.0 mg/l at baseline to 3.8 ± 1.0 mg/l at 6 months and to 3.7 ± 0.8 mg/l at 12 months. The corresponding 95% CIs for the changes over time were [0.82; 1.35] (visit 03 vs baseline) and [0.73; 1.10] (visit 05 vs baseline), respectively.

At baseline, average bone age was 6.2 ± 2.82 years, which corresponds to a mean delay of 1.7 years compared to chronological age. After 12 months of treatment, mean bone age had increased by 1.54 years to 7.8 ± 2.95 years. Average height age was 5.5 ± 2.08 years at baseline. At 12 months, the delay in height age compared to chronological age had decreased from 2.4 years to 2.1 years. For both sexes, marked increases were observed for predicted final height (FHpre) and projected final height (FHpro) during the first year of treatment. In boys, mean FHpre increased from 161.7 ± 6.7 cm to 166.9 ± 5.5 cm, and mean FHpro increased from 155.9 ± 6.6 cm to 162.7 ± 4.9 cm. In girls, mean FHpre increased from 154.9 ± 3.5 cm to 158.4 ± 4.3 cm, and mean FHpro increased from 145.5 ± 6.1 cm to 151.9 ± 5.1 cm.

The applicant commited to submit a report based on the first 24 months of treatment as well as the final data from EP2K-02-PhIII-Lyo. The report will be available in April 2006. In addition, the study will be extended beyond the originally planned 24-month treatment phase.

Clinical safety

- **Studies EP2K-99-PhIII/ EP2K-00-PhIIIFo**

Overall 36 (82%) of the patients in the Somatropin Sandoz powder (API Covance) group reported 172 adverse events; in the Genotropin treated patients 43 (96%) of the patients reported 201 adverse events.

All adverse events in studies EP2K-99-PhIII/ EP2K-00-PhIIIFo

	Somatropin Sandoz	Genotropin
Allergic reactions	3 (7%)	--
Increased hematocrit	4 (9%)	5 (11%)
Fever	1 (2%)	4 (8%)
Influenza-like	2 (5%)	2 (4%)
Cephalgia	3 (7%)	3 (6%)
Headache	2 (5%)	2 (4%)
Hypothyroidism	4 (9%)	1 (2%)
Thyroid activity decreased	4 (9%)	3 (7%)
Abdominal pain	4 (9%)	--
Diarrhoea	--	3 (7%)
Vomiting	5 (11%)	2 (4%)
SGOT increased	1 (2%)	3 (7%)
Elevated serum cholesterol	5 (11%)	2 (4%)
Hypertriglyceridaemia	2 (5%)	2 (4%)
Haemoglobin increased	4 (9%)	3 (7%)
Haematoma	4 (9%)	6 (13%)
Viral infection	1 (2%)	4 (9%)
Bronchitis	2 (5%)	5 (11%)
Coughing	4 (10%)	2 (4%)
Pharyngitis	5 (12%)	11 (24%)
Rhinitis	5 (11%)	6 (13%)
Tonsillitis	4 (9%)	6 (11%)
Upper respiratory tract infection	7 (16%)	11 (24%)
Varicella	3 (7%)	2 (4%)
Urinary tract infection	--	4 (9%)
Eosinophilia	7 (18%)	4 (9%)

There were no notable trends in clinically significant laboratory data abnormalities, vital signs, fundoscopy or physical findings.

- Serious adverse event/deaths/other significant events

No deaths were encountered during the time of the studies.

EP2K-99-PhIII/ EP2K-00-PhIIIFo

Five serious adverse events were reported (hospitalisation for various reasons) none of them related to the study drug according to the physician.

Study EP2K-00-PhIIIAQ

Four serious adverse events were reported (hospitalisation for acute gastritis, tonsillitis or adenoidectomy) none of them related to the study drug according to the physician. Adverse events profile fit the profile seen in the previous studies

Study EP2K-02-PhIIILyo

The overall extent of drug exposure to Omnitrope during the 12 months of rhGH treatment covered in this report is 52.13 patient-years. During the first 12 months of treatment, 459 AEs were reported in 47 patients, 42 of which were assessed as at least remotely drug-related. The majority of AEs was considered mild in intensity. Five serious adverse events (SAEs) were reported, none of which were considered drug-related. Based on the extensive experience with rhGH treatment, none of the observed AEs was unexpected. There were no deaths during the study period and no withdrawals due to AEs.

- Laboratory findings

Seven of the 51 patients in study EP2K-02-PhIIILyo had clinically significant changes in laboratory values, all of which were related to an AE (i.e., blood sugar increase, hypothyroidism, eosinophilia (which was the most common drug-related laboratory adverse event), cystitis-related abnormal blood values, alkaline phosphatase increase.

- Immunological events

In clinical studies EP2K-99-PhIII and EP2K-99-PhIIIFo with the earlier formulation Somatropin Sandoz powder (API Covance) up to 60% of the enrolled patients developed non-neutralising anti-GH antibodies and all patients developed anti-HCP antibodies. However, these antibodies did not affect efficacy of the product. Only one batch manufactured by Covance, USA, was used in studies EP2K-99-PhIII and EP2K-00-PhIIIFo, and was found to have a high content of host cell proteins (HCP). These HCP are known to be able to enhance the antibody reaction against GH. Therefore, a slightly modified downstream manufacturing process was used which significantly improved the HCP clearance but did not change any other product characteristics. Consequently, the concentrations of *E. coli* proteins in the subsequent formulations (Omnitrope and Somatropin Sandoz liquid (API Sandoz)) were within the range known from other authorised GH-containing products. Anti-GH antibody formation with Omnitrope and Somatropin Sandoz liquid (API Sandoz) was within the range known from other GH-containing products.

With regard to the adequacy of safety data collection for Omnitrope Somatropin Sandoz, complete 12-month immunogenicity results, i.e., anti-hGH and anti-HCP antibody data, and safety data from the study EP2K-02-PhIII-Lyo are available. Therefore, the overall exposure to Omnitrope is 72 patient-years in all studies.

None of the 51 patients in study EP2K-02-PhIII-Lyo developed anti-hGH and one patient developed anti-HCP antibodies during the study period so far. The applicant commits to submit the final study report of this still ongoing study to obtain additional safety and efficacy data. The study will be extended beyond the originally planned 24-month treatment phase.

Indirect comparison of anti-hGH antibody development between Omnitrope assessed in study EP2K-02-PhIII-Lyo and Genotropin assessed in study EP2K-99-PhIII / EP2K-99-PhIIIFo is presented in the table 3. This comparison is possible because all antibody measurements were performed in the same laboratory using the same assay. The numbers of patients who developed anti-hGH antibodies after 9 and 12 months of treatment with Omnitrope (EP2K-02-PhIII-Lyo) and after 9 months of treatment with Genotropin (EP2K-99-PhIII/EP2K-00-PhIII-Fo) are given in Table 3. Twelve-month data for Genotropin are added from the literature. Estimated incidences of anti-hGH antibody development for Omnitrope were found to be 0% (95% CI [0.0, 7.0]). Therefore, there is no evidence to assume a clinically relevant difference in anti-hGH antibody development between Omnitrope and Genotropin.

Comparison of anti-hGH antibody development between Omnitrope (EP2K-00-PhIII-Lyo) and Genotropin (EP2K-99-PhIII/EP2K-00- PhIIIFo) during the first year of treatment

Product	Study	**Number of patients tested for antibodies**	**Number of patients with positive test result**	**Estimated incidence [95% CI]**
Omnitrope	EP2K-02-PhIII-Lyo 12 months	**51**	**0**	0% [0; 6.98]
Genotropin	EP2K-99-PhIII/ EP2K-00-PhIIIFo 9 months	**44**	**1**	2.27% [0.06; 12.02]
	Literature* 12 months	**229**	**4**	1.75% [0.48; 4.41]

*One year results published in: Lundin K, Berger L, Blomberg F, et al. Development of anti-hGH antibodies during therapy with authentic human growth hormone. Acta Paediatr Scand (Suppl) 1991;372:167-8.

One Omnitrope-treated patient (study EP2K-02-PhIII-Lyo) and no Genotropin-treated patient (study EP2K-99-PhIII/EP2K-00-PhIII-Fo) developed anti-HCP antibodies. Again, there is no evidence for a clinically relevant difference in immunogenicity between Omnitrope and Genotropin.

In addition, the frequency of anti-hGH antibodies among the patients of studies EP2K-99-PhIII/EP2K-00-PhIII-Fo who had been treated with Somatropin Sandoz (API Covance) and were switched to Omnitrope diminished from 57% (24/42 patients) at month 9 to 36% (15/42 patients) at month 15. Anti-GH antibody frequency continued to decrease after these patients were switched to somatropin Sandoz Liquid (API Sandoz), declining to 20% (8/40 patients) at month 24 and 14% (5/35 patients) at month 48.

For immunogenicity assessments, the same antibody assays and the same central laboratories were used throughout all clinical trials with Somatropin Sandoz, including trials EP2K-99- PhIII, EP2K-00-PhIII-Fo, EP2K-00-PhIIIAQ and EP2K-02-PhIII-Lyo. Anti-hGH antibodies were determinedusing a radiolabeled immunoassay (RIA). Anti-HCP antibodies were determined using an immunoblot assay (Western blot).

Readability testing
The applicant performed readability testing ("user consultation") and a satisfactory report has been provided.

Pharmacovigilance

Description of pharmacovigilance system
A detailed description of the pharmacovigilance system has been provided. The CHMP considered that the description has deficiencies that should be addressed as part of the follow up measures. The applicant has made the commitment to update the description of the pharmacovigilance system where applicable, prior to placing the product on the market:

Risk Management Plan
The MAA has submitted a risk management plan, summarised as follows:

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Diabetogenic potential of rhGH therapy in short children born SGA	Phase IV prospective, single arm clinical trial in short children born SGA (part of registry reviewing patients demographics, long term safety and immunogenicity).	Warning regarding diabetic potential in Section 4.4 of SPC. Rare cases of type II diabetes mellitus in Section 4.8 of SPC.
Occurrence and clinical implications of anti-rhGH antibodies	Phase IV prospective, single arm clinical trial in short children born SGA measuring immunogenicity. Prolongation of ongoing Phase III study EP2K-02-PhIIIlyo to provide long-term immunogenicity data Immunogenicity testing for children enrolled in registry as appropriate (e.g. loss of efficacy).	Development of antibodies included in Section 4.8 of SPC.
Occurrence of malignancies in rhGH treated patients	Registry of patients reviewing patients demographics, long term safety including malignancy and other safety issues.	Warning in Section 4.4 regarding reoccurrence of malignancy. Leukaemia mentioned as a very rare adverse effect in Section 4.8.
Risks of rhGH treatment in PWS patients	Registry expected to include patients with PWS and will record demographics, long term safety as well as other safety issues in this group.	Warnings on use of rhGH in PWS in Section 4.4. • Respiratory impairment and infection • Sleep apnoea • Severe obesity • scoliosis

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

With regard to the quality part of the dossier, a positive CHMP opinion may be granted, since:

- The company has resolved all outstanding quality issues.
- The Summary of Product Characteristics and Package Leaflet have been adapted as requested.
- The extensive physico-chemical and biological characterisation of the reference medicinal products has sufficiently demonstrated the comparability of the Genotropin batches from the various markets in Europe in the Community and these can be accepted for use in the non-clinical and clinical studies.
- The remaining Follow Up Measures (FUMs) and time-frames can be accepted.

Non-clinical pharmacology and toxicology

The pharmacodynamic activity of Omnitrope has been confirmed by biological tests in the rat (rat weight gain bioassays and rat tibial width assay) in which a similar quantitative activity as an International Standard to the reference medicinal product Genotropin was demonstrated. The studies have confirmed the comparability with international reference standards of human somatropin, of the marketed reference medicinal product Genotropin and of several lots of Omnitrope, manufactured at both pilot and commercial scales, with respect to pharmacodynamic effects characteristic of somatropin (body weight gain and increase in tibial width in hypophysectomised rats). Both bulk substances and the finished product Omnitrope Powder for Solution for Injection have been tested.

The pharmaco-toxicological action of growth hormone is well known, thus secondary pharmacodynamic studies as well as safety pharmacology studies were not considered necessary.

The applicant did not provide information on potential drug interactions in the non-clinical part of the dossier but this information could be retrieved from the clinical overview. In this respect the text on product interactions in section 4.5 is agreed.

The applicant has not performed absorption, distribution, metabolism, excretion, or pharmacokinetic drug interaction studies with Omnitrope. These is in accordance with the "Annex: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues: Guidance on medicinal products containing Somatropin".

The extent of scientific knowledge of somatropin, and the nature of this product as a recombinant protein, has made it unnecessary to do genotoxicity or reproduction toxicity testing. Similarly carcinogenicity studies have not been undertaken because they were considered unnecessary in the light of the experience with other somatropins.

The local tolerance study in rabbits demonstrates that there are no marked differences between the reactions at the administration site induced by the drug product and its respective vehicle.

From a non-clinical point of view the comparability exercise is considered to be sufficient and the benefit/risk balance is considered positive.

Efficacy

Study EP2K-99-PhIII/ EP2K-00-PhIIIFo compared the effects of both Somatropin Sandoz powder (API Covance) and Genotropin in 89 treatment naïve patients.

The 95% CI for the estimate of the difference in height velocity between treatment groups after 9 months of treatment (-1.35, 0.92) indicates that treatment with Somatropin Sandoz powder (API Covance) and treatment with Genotropin resulted in comparable increases in height velocity. The 95% CI for the estimate of the difference in HV-SDS between treatment groups after 9 months of treatment (-0.81, 2.13) indicates that both treatments resulted in comparable increases in HV-SDS. Therefore,

comparable efficacy of Somatropin Sandoz Powder (API Covance) and Genotropin has been demonstrated. The development of anti-GH antibodies in almost 60% of the patients treated with Somatropin Sandoz Powder (API Covance) did not affect the efficacy of the product.

HSDS increased significantly during the study, indicating that the treatment naive patients reduced their growth deficit ("catch-up growth") compared to normal age and gender-matched children. The establishment and maintenance of a positive HVSDS indicates that the patients continued to grow more rapidly than normal children of the same gender and age.

The pivotal clinical efficacy study has been adequately performed in prepubertal, treatment naïve children with GH deficiency , which are considered as the most sensitive model for the assessment of the efficacy of somatropin. Study groups were well balanced with regard to baseline characteristics which is important for the sensitivity of the trial and the accuracy of the endpoints.

In conclusion, Study EP2K-99-PhIII/ EP2K-00-PhIIIFo demonstrated comparable efficacy between Somatropin Sandoz powder (API Covance) and Genotropin.

Somatropin Sandoz powder (API Covance) and Omnitrope are similar, except for two additional purification steps for Omnitrope which are not expected to affect bioavailability or efficacy, the results from study EP2K-99-PhIII / EP2K-00-PhIIIFo showing comparable efficacy of these products are transferable to Omnitrope, the product to be marketed. The almost superimposable growth response curves during treatment with Omnitrope (in study EP2K-02-PhIII-Lyo) or Somatropin Sandoz powder (API Covance) (in study EP2K-99-PhIII/ EP2K-00-PhIIIFo) further support this conclusion.

Supportive data

Comparable pharmacokinetic profiles for Somatropin Sandoz powder (API Covance) and Genotropin USA were demonstrated in the supportive pharmacokinetic study EP2K-99-PhIUSA, and between Somatropin Sandoz powder (API Covance) and Somatropin Sandoz Liquid (API Sandoz) in study EP2K-00-PhI^{AQ}. Somatropin Sandoz powder (API Covance) and Omnitrope are similar, except for two additional purification steps for Omnitrope. These additional steps are not expected to affect bioavailability of somatropin, and therefore the results obtained from study EP2K-99-PhIUSA are also considered to be valid for Omnitrope.

The applicant has provided data suggesting the absence of accumulation of somatropin under steady-state conditions in GH deficient children. Accumulation is also not expected from the known single-dose pharmacokinetic profile of somatropin. In fact, multidose studies are not required.

All pharmacokinetic data have been obtained using the 5 mg / ml formulation. Considering the linear somatropin pharmacokinetics, results obtained for this strength are also valid for Omnitrope 1.3 mg/ml.

In conclusion, comparable therapeutic efficacy between Somatopin Sandoz powder (both API Covance and API Sandoz) and the reference medicinal product Genotropin has been demonstrated.

Safety

The most important difference between Somatropin Sandoz powder (API Covance) and Genotropin in study EP2K-99-PhIII/ EP2K-00-PhIIIFo was the formation of antibodies in 57% and 2 % of the patients, respectively. However, no statistically significant or clinically relevant differences at any time-point between patients with and without anti-GH antibodies regarding height, HSDS, HV and HVSDS could be detected. This result indicates that the presence of anti-GH antibodies had no effect on efficacy. The formation of anti-GH antibodies was most likely related to the presence of an increased level of HCP proteins. Somatropin Sandoz powder (API Covance) and Omnitrope (API

Sandoz) are similar, except for two additional purification steps for Omnitrope to reduce the amount of *E. coli* proteins. The submitted data from study EP2K-02-PhIII-Lyo confirm that the issue of antibody induction is now solved. The clinical comparability in terms of safety and immunogenicity between Omnitrope and Genotropin has been demonstrated.

Benefit/risk assessment
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- no additional risk minimisation activities were required beyond those included in the product information

Based on the submitted data it is concluded that Omnitrope 1.3mg/ml and 5.0mg/ml and the reference medicinal product Genotropin are similar with regard to clinical efficacy and safety. The benefit/risk assessment for Omnitrope 1.3mg/ml and 5.0mg/ml is therefore positive.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Omnitrope in the treatment of:

Children
Growth disturbance due to insufficient secretion of growth hormone (GH) and growth disturbance associated with Turner syndrome or chronic renal insufficiency.
Growth disturbance in short children born small for gestational age (SGA), who failed to show catch-up growth by 4 years of age or later.
Prader-Willi syndrome (PWS), for improvement of growth and body composition, the diagnosis of which should be confirmed by appropriate genetic testing.
Adults

Replacement therapy in adults with pronounced growth hormone deficiency.

was favourable and therefore recommended the granting of the marketing authorisation.