SCIENTIFIC DISCUSSION

1. Introduction

BioPartners GmbH applied for a marketing authorisation for Valtropin 5 mg/1.5 ml (corresponding to 3.33 mg/ml) powder for solution for injection. Valtropin contains recombinant human somatropin as active substance. The application was submitted under the legal base of Similar Biological Medicinal Product under Article 10(1)(a)(iii) of Directive 2001/83/EC, and with reference to Part II.4 of Annex I of Directive 2001/83/EC, as amended.

The reference medicinal product for this application was Humatrope powder for solution for injection, a somatropin-containing product produced by Eli Lilly originally authorised in the EU in 1990. Valtropin claims to be similar to this reference medicinal product as approved in the Community. Valtropin and Humatrope are presented in 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: long-term treatment of children with growth failure due to an inadequate secretion of normal endogenous growth hormone, treatment of short stature in children with Turner syndrome, treatment of growth retardation in pre-pubertal children with chronic renal insufficiency, and replacement therapy in adults with pronounced growth hormone deficiency of either childhood or adult-onset aetiology. These indications are the same as those approved for the reference medicinal product.

2. Quality aspects

Introduction

Valtropin contains somatropin (recombinant human growth hormone, rhGH) as active substance. It is produced in *Saccharomyces cerevisiae (S. cerevisiae)* by recombinant DNA technology and consists of a single chain, non-glycosylated polypeptide of 191 amino acids with a molecular weight of 22 kD. Two disulfide bonds between Cys53-Cys165 and Cys182-Cys189 determine a stable three-dimensional protein structure.

The drug product is presented as a sterile lyophilized powder and aqueous solvent preserved with 0.3 % m-cresol.

The powder comes in a 5cc/13mm type I glass vial, closed with a bromobutyl rubber stopper secured with an aluminium seal with a polypropylene flip-off cap. The solvent is presented in a pre-filled glass syringe containing 1.5 mL 0.3% m-cresol in water for injections.

Active substance

- Manufacture

Cell bank system
The manufacture of somatropin begins with a thoroughly characterised yeast *S. cerevisiae* master cell bank (MCB) that contains the integrated gene coding for expression of the product.

A full length hGH clone was isolated from a human cDNA library. The cDNA sequence was optimised for expression in the yeast *S. cerevisiae* by mutagenesis and synthetic oligonucleotide DNA fragments. The cDNA encodes the 192 amino acid protein under the control of yeast specific promoter and yeast transcription terminator.

The construction of the expression vector was well described. State-of-the art methods such as DNA sequencing and restriction mapping confirm the structural characteristics of the vector and also demonstrate its genetic stability during cell bank propagation. The MAH provided sufficient information on the establishment of the producer cell line.

The preparation of all cell banks was adequately described and characterisation studies were performed. The genetic stability of the end of production cells during normal production was confirmed at the end of full-scale culture. No contaminations were found and expression vector plasmid restriction patterns and DNA sequencing of the insert confirmed the authenticity of the plasmid.

Manufacturing process

The manufacturing process consists of fermentation, recovery and purification phases. The active pharmaceutical ingredient is derived from yeast *S. cerevisiae* by recombinant DNA technology. Methionyl recombinant human growth hormone (met-rhGH of 192 amino acids) is expressed from the yeast cells, folded to its native three-dimensional structure, and the N-terminal methionine residue is enzymatically cleaved to yield rhGH of 191 amino acids.

The purification involves several chromatographic and filtration steps to remove product and process related contaminants. Process validation was performed on small scale as well as the commercial production scale. All process steps were validated; the in-process controls and the critical operating parameters were based on experience gathered over several years of commercialisation of somatropin in Korea.

The validation program on commercial scale production was comprehensive and consists of the following main elements:

- Process validation for the cell growth and fermentation process and robustness of the fermentation,
- Validation studies for the harvesting and recovery process and robustness of the harvest and recovery processes
- Validation studies for the purification and downstream process and robustness of the purification and downstream process
- Evaluation of consistency in step yield during prospective process validation
- Control of product related variants arising from manufacturing processes and evaluation of the consistency in removal of these substances
- Evaluation of Process Related Substances/ Impurities and consistency in removal of these impurities
- Control of contamination by endotoxin and bioburden

Manufacturing Process Development

The manufacturing process of the drug substance is based on that initially approved by the Korean regulatory authority. The original process has been modified and changes to the production facility and procedures have been implemented since the product was first introduced.
Changes to the original process were implemented resulting in a Transitional Process 1. Further changes were implemented which resulted in a Transitional Process 2. The drug substance generated by Transitional Process 2 was used to manufacture drug product batches for pivotal clinical studies. Transitional Process 3 was the result of more changes; those changes are related to the enzyme used in the manufacture of the drug substance. The Definitive Process was set in-place in 2003 with an upgrade of quality requirements for raw materials used in the fermentation, harvest and recovery and purification processes.

Characterisation and analytical comparability

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

Structural characterisation was performed using mass spectrometry, peptide mapping, N-terminal sequencing, C-terminal sequencing and amino acid composition analysis. Physicochemical characterisation was founded on electrophoretic methods, column chromatographic techniques and on spectroscopic methods. Immunological characterisation on the basis of Western Blot analysis using specific antibodies was conducted to identify somatropin and detect impurity proteins. The biological activity was determined by the rat weight gain assay or bone growth (tibia) assay.

Impurities

Extensive scientific work on Valtropin drug substance samples was made to characterise and classify the different aberrant forms of rhGH by using a battery of selective analytical methods. The structural identity of all relevant product-related proteins of hGH has been adequately addressed.

Following analysis by optimized methods the levels of truncated/fragmented variants and oxidized forms have been effectively evaluated and were found to be very similar for batches of Valtropin and Humatrope regardless of process source or age of the drug product.

Process related impurities mainly originating from the yeast expression system were monitored during the purification process to confirm the suitability of the chromatographic steps employed. The results indicated that the initial chromatographic steps contribute significantly to the removal of the host cell proteins.

Control of Drug Substance

- Specifications

The specifications proposed for release of the DS have been selected in accordance with the appropriate guidance, taking into account the known properties and characteristics of the drug substance. The proposed test items address the physical state, identity, purity and content of the DS and the presence of potential contaminants, such as micro-organisms and bacterial endotoxins. The acceptance criteria are based on historical data from a large number of commercial scale batches. Some of these batches have been extensively characterised or tested in stability studies or in non-clinical and clinical trials. The specified limits therefore reflect the overall clinical and manufacturing experience with the batches produced to date and also the reliability and precision of the methods used for analysis. Analytical methods have been fully validated where appropriate.

Batch Analyses

The batch results were in conformance with the specification and showed consistency for the batches from the commercial process and in all relevant parameters also across the changes during process development.

- Stability

Results of the ongoing stability studies to support the claimed shelf life were provided. A shelf life of 36 months at -75±5°C and -25±5°C can be accepted. Updates of the stability data will be submitted at regular intervals.

Medicinal product

Valtropin is provided as one vial of lyophilisate and one prefilled syringe containing 1.5 ml of solvent. Each vial of powder contains 5 mg (15 IU) somatropin. Reconstituted with 1.5 ml solvent (0.3% m-cresol in WFI) corresponds to 3.33 mg/ml (10 IU/ml) of somatropin. The product does not contain an overage. Excipients used for the lyophilisate are glycine, mannitol, sodium phosphate monobasic, sodium phosphate dibasic. Sodium hydroxide and hydrochloric acid are used for pH adjustment.

- Pharmaceutical Development

During most of the clinical development program the solvent (same composition) was presented in vials.

The composition of Valtropin lyophilisate was based on the formulation of Humatrope. The compositions of Valtropin and Humatrope are qualitatively the same. The solvent is similar to that used with Humatrope consisting of water for injections containing 0.3% metacresol as an antimicrobial agent, but without glycerine. The reconstituted Valtropin is for repeat use as a multidose product.

The composition of Valtropin has not changed during clinical development with the exception of a 10 % overage used in the beginning of the development program.

Container Closure System

The drug product rhGH powder is presented in a 5 cc/13 mm vial (Type I, Ph.Eur./USP) which is closed with a bromobutyl stopper/closure with a polydimethylsiloxane coating (Ph.Eur., USP) and aluminium seal and polypropylene flip-off cap.

The diluent is presented in a 2.25 mL glass syringe (type I, Ph.Eur., USP) with Luer lock and rubber tip cap (Ph.Eur., USP). The syringe barrel is closed with a bromobutyl rubber plunger stopper (Ph.Eur., USP) with a Flurotec contact surface.

Microbiological Attributes

The lyophilisate is manufactured from aseptic somatropin drug substance that is compounded with excipients as a solution, aseptically filled into vials and vacuum lyophilised under a controlled environment and the vials stoppered under a positive pressure of sterile nitrogen. The solvent is membrane filtered and transferred into a syringe and the filled syringe is terminally sterilised using a validated cycle and procedure. Therefore, the process assurance of sterility is high through “parametric release” in process, together with the standard QC sterility testing at lot release.

Compatibility

Valtropin lyophilisate is reconstituted in water for injections containing 0.3% metacresol which is not further diluted. Doses are withdrawn over a two weeks period as directed by the labelling instructions. This aqueous solution was proven to be chemically and physically stable at 5±3°C for a minimum of 4 weeks at concentrations of 3.3 mg/mL (5 mg/1.5 mL solvent). There was further evidence of compatibility of somatropin with water in the presence of the same qualitative composition of excipients, mannitol and glycine, at dilutions of 7-15 mg/mL and 5-7 mg/mL for a minimum of 3 weeks at 5±3°C according to drug substance stability studies.

Description of Manufacturing Process and Process Controls

Lyophilisate

The manufacturing site operations and tests performed during the preparation were presented. Valtropin is manufactured by conventional formulation, aseptic filling and lyophilisation processes.

Solvent

m-cresol is dissolved in WFI and the solution is filled into 2.25 ml syringes on a filling machine. Prior to use, all parts of the filling machine coming into contact with the product are sterilised either by autoclaving or by SIP.

The manufacturing processes of both lyophilisate and solvent are adequately controlled and critical steps have been sufficiently validated to guarantee batch-to-batch consistency. The excipients employed are routinely tested according to pharmacopoeia monographs except for m-cresol. An in-house specification has been defined for this non-compendial compound and all methods employed are standard forms of physico-chemical analysis according to the respective Ph.Eur. procedures.

Control of Drug Product

- Specifications

The specifications presented are based on Ph.Eur., USP requirements and batch analysis results. Limits for some tests have been tightened compared to the monograph. The analytical methods are fully described and are properly validated, where applicable.

Batch analysis data were provided and the results met specifications.

Characterisation of impurities

The main impurity in the drug product is desamido-somatropin. The drug substance is derived from a yeast expression system and the nature and content of the product related impurities observed seemed identical to those present in *E. coli* derived preparations. In view of this it cannot be expected that a lyophilised preparation of yeast derived somatropin will show different impurities than a lyophilised preparation of an *E. coli* derived somatropin. So the batch release, which conforms to the Ph. Eur. monograph was considered adequate for Valtropin.

- Stability

A shelf life of 36 months at 2-8 °C for the lyophilisate was claimed and supported by stability studies.

The methods used to assess stability were the same as those used for routine testing. Additionally, bioidentity testing is performed.

The product complies with the shelf life specification and Ph.Eur. requirements.

At higher temperatures the formation of impurities was more pronounced but short excursions into elevated temperatures will not adversely affect the quality of the product.

In use stability

The MAH has conducted work to support a shelf life claim of 2 weeks storage under refrigeration (at 5°C), upon reconstitution of the lyophilized powder with solvent consisting of 0.3% metacresol in water for injections.

Solvent

A real-time, long-term stability study is being performed on solvent in pre-filled syringes stored at 5±3°C, the recommended storage temperature. Furthermore, accelerated studies are in progress at 25±2°C/60±5% RH and 40±2°C/75±5% RH. Real time data for 24 months have been submitted. Data for intermediate and accelerating conditions have also been presented.

Conclusions on stability:

A shelf-life of 30 months under refrigerating storage conditions (2–8 °C) will be indicated on the final packaging containing lyophilisate and solvent. An in-use stability of 21 days is supported when stored under refrigeration at 2 – 8 °C.

- Comparability exercise

Extensive characterisation studies were conducted. Humatrope, Lilly was selected as a listed reference product and included in the studies. On the basis of the characterisation data it can be concluded that Valtropin drug substance represents authentic somatropin.

Valtropin drug product was shown to be analytically comparable to the marketed European reference product Humatrope.

This conclusion was supported by comparative data on the structural integrity but also by their content of product-related proteins. No differences in higher order structure were discernable. Moreover, attention has been focused on somatropin product related impurities/substances present, such as deamidated and oxidized forms, and aggregates, to be highly similar for both products. The results show that Valtropin was analytically comparable with Humatrope with respect to protein conformation, impurity pattern and bioassay.

Adventitious Agents Safety Evaluation

No virus containing materials are used for the production of Valtropin drug substance. Therefore a viral adventitious safety evaluation was not applicable to Valtropin drug substance. The same applies to all excipients used in the manufacture of the drug product.

GMP

Satisfactory compliance with GMP has been demonstrated for all manufacturing sites.

3. Non-clinical aspects

Introduction

The pharmacological and toxicological effects of somatropins are well known, thus the focus of the non-clinical studies relied on the comparison of Valtropin with the reference product Humatrope EU. The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CPMP/42832/05) and the product specific Annex guidance on similar medicinal products containing somatropin (EMEA/CHMP/94528/2005) lays down the non-clinical and clinical requirements for somatropin-containing medicinal products claiming to be similar to another one already marketed. The non-clinical development was considered acceptable in the view of the guidelines.

During the non-clinical development programme for Valtropin, the manufacturing process has changed from transitional processes to the commercial process. Characterisation studies confirmed that Valtropin drug substance from each of the transitional processes was comparable to drug substance from the commercial process. Thus the batches from the early production processes used for

the safety pharmacological and toxicological studies were representative of the current drug product. In addition the MAH provided a 28-day toxicological study with the current formulation.

GLP

The MAH claimed that the non-clinical studies were in agreement with the GLP requirements of the country in which the studies were performed.

Pharmacology

- Primary pharmacodynamics

Data on the pharmacodynamic activity of Valtropin and EU Humatrope were compared in the rat weight gain assay. The data were derived from the quality related bioassay to determine the potency of Valtropin. In this assay two Valtropin batches were tested in comparison to EU Humatrope and the NIBSC reference standard. The rat weight gain bioassay was based on the method described in the USP monograph for somatropin at 3 dose levels (2 µg, 4 µg and 8 µg per day) per standard and each test material for parallel analysis. Sprague Dawley rats used in this test (10 animals per group; as in the prior weight gain assays only females were used) were hypophysectomised at 4 weeks of age. The body weights of the hypophysectomised rats were recorded before and after somatropin treatment. The statistical analysis was performed on the body weight gain of each rat over the 10-day treatment period.

It was found that the Valtropin batches were within the specification limit for potency recommended by Ph. Eur. However the estimated potency of the Valtropin batches tested was lower than that observed with the batch of EU Humatrope. The MAH explained this result by showing that the rat weight gain assay was inherently highly variable and that there was difference in the actual content of active substance in the batches of Valtropin and EU Humatrope tested.

It was noteworthy that in an earlier supportive experiment comparing the same batches of Valtropin with US Humatrope, the potency of the Valtropin batches was very similar to US Humatrope and to that observed with EU Humatrope in the rat weight gain assay discussed above.

It was concluded that pharmacodynamic biosimilarity was sufficiently demonstrated, albeit not with high accuracy, but it was acknowledged that for methodological reasons a higher accuracy could not be achieved.

- Secondary pharmacodynamics

No studies on secondary pharmacodynamics of somatropin containing products are required according the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CPMP/42832/05) and the product specific Annex *guidance on similar medicinal products containing somatropin* (EMEA/CHMP/94528/2005).

- Safety pharmacology programme

The safety pharmacology of Valtropin has been investigated in a range of studies in mice, guinea pigs, and rabbits (Lee et al. 1992). The studies indicated that Valtropin did not cause harmful effects on major organ systems (cardiovascular and respiration).

Safety pharmacology studies are not required for similar biological medicinal products containing somatropin as active substance (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed with Valtropin. These studies are not required according to EMEA/CPMP/3097/02, and EMEA/CHMP/94528/2005.

- Effect of somatropin on hepatic CYP450

No studies to investigate possible effects on cytochrome P450 activity are required for somatropin containing products. It is known that somatropin increases the clearance of compounds metabolised by the cytochrome P450 system. The MAH included a statement in the SPC (section 4.5) "Data from an interaction study performed in growth hormone deficient adults, suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown. Although this statement is not included in the SPC of the reference medicinal product Humatrope, the CHMP endorsed the wording, which is in line with the wording for other authorised somatropins.

Toxicology

- Single dose toxicity / Repeat dose toxicity

Two combined 28 day and 90 day repeated-dose toxicity studies were submitted; one performed in mice and one performed in rats. These studies were done in the early 1990s, with batches produced by the previous manufacturing process. In the mouse study, some effects were seen that could not be immediately related to somatropin pharmacology, namely decreased activity, impaired respiration and two deaths. There was no obvious explanation for these findings but it was thought that they may have been due to immunological effects. In the mouse, liver cell polyploidy, although present in both saline and vehicle control groups, was seen with increased incidence in treated groups. Karyomegaly, found in dose-related manner in livers of mice treated for 28 or 90 days, and correlating with increased liver weights, seems to reflect an increased protein synthesis.

In rats, glucose levels were decreased in high-dose males, other changes in biochemical parameters were minor and not considered relevant. Analysis of organ weight changes in high-dose groups showed increases in several organs: kidneys, adrenals, liver and ovaries in both species, together with increased spleen size. Histological examination of tissues in the rat did not reveal any changes attributable to Valtropin administration.

Relative brain weight was reduced in both species.

The No Observed Adverse Effect Levels (NOAELs) in these studies were 3 IU/kg/day for both mice and rats.

- Genotoxicity

The potential genotoxicity of Valtropin has been evaluated in three standard tests, gene mutation in bacteria and chromosome aberrations in Chinese Hamster Ovary (CHO) cells, both *in vitro*, and an *in vivo* micronucleus test in mice. None of these studies indicated any genotoxic potential of Valtropin.

Genotoxicity studies are not required for similar biological medicinal products containing somatropin as active substance (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).

- Carcinogenicity

No carcinogenicity studies were performed. This was acceptable according to EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005.

The potential tumour promoting effect of somatropin is reflected in the SPC.

- Reproduction Toxicity

Comprehensive summaries of reproduction toxicity studies conducted in rats and rabbits were provided. The available data do not indicate that Valtropin has a different reproductive toxicity profile compared to other marketed growth hormone preparations for which data are available from the literature (Watase et al 1993; Fukunishi et al. 1993; Hamamoto et al. 1993; Watanabe et al. 1993).

Reproduction toxicology studies are not required for similar biological medicinal products containing somatropin as active substance (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).

- Toxicokinetic data

Toxicokinetics data were obtained within the frame of the new 28-day toxicology study in rats (discussed below) to verify exposure of the animals. These data were compared to human exposure based on C_{max} and AUC, the results are summarised in the table below. As can be seen the exposures at the NOAEL were several multiples of the exposure achieved in the clinic.

Comparison of exposure to Valtropin™ in repeated-dose rat toxicity studies and in man

Species	**Dose**	**Exposure**		**Multiple of human values**	
		Cmax (ng/mL)	**AUC (ng.h/mL)**	**Cmax*****	**AUC*****
Rat	2.0 IU/kg/day	796/946*	4367/3339*	19.8	10.4
	10.0 IU/kg/day**	4355	19265	99.0	52.1
	3.0 IU/kg/day**	1306	5780	29.7	15.6
Man	0.073 mg/kg	44	370	-	-

* male/female animals, data from day 14 of 2-week toxicokinetic study

** data extrapolated from 2.0 IU/kg/day values from 2-week toxicokinetic study, taking the mean of the value in male and female animals; correction factor for GH dose: 1 mg corresponds to around 3 IU

*** as compared to the mean value in male and female animals

- Local tolerance

Preclinical local tolerance studies after subcutaneous injection (the intended route of administration in patients) were not performed. However, during the conduct of the single and repeated-dose toxicity studies no signs of local irritation were reported. Moreover, the clinical data make new preclinical studies dispensable.

Supportive Data

Pharmacodynamics

- Primary pharmacodynamics

The rat tibia length assay, carried out on samples obtained from rats dosed in the weight gain assay, yielded similar results to those observed in the weight gain assay.

Pharmacokinetics

The pharmacokinetics of Valtropin has been studied in the rabbit after intravenous and subcutaneous administration. The results obtained showed that Valtropin had similar pharmacokinetic properties to other marketed growth hormone preparations.

Pharmacokinetic parameters of Valtropin after bolus i.v. administration to rabbits:

Parameter	0.2 IU/kg	0.5 IU/kg	2.0 IU/kg	5.0 IU/kg
$t_{½}$ (min)	9.3±2.1	16.8±4.8	22.2±6.7	25.8±6.8
Vss (ml/kg)	166±32	218±27	342±73	556±46
CL_T (ml/min/kg)	14.2±5.6	10.2±0.8	13.1±2.6	14.7±3.1
CL_R (ml/min/kg)	0.0419±0.0386	0.0093±0.0483	0.0071±0.1430	0.0162±0.0455
CL_{NR} (ml/min/kg)	13.9±6.6	10.4±0.5	14.2±0.8	14.2±2.1

Vss – volume of distribution at steady-state; CL_T – total clearance;
CL_R – renal clearance; CL_{NR} – non-renal clearance.
Values are mean±SD (standard deviation).

No pharmacokinetic studies are required according to the relevant guideline (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).

Toxicology

- Repeat dose toxicity

During the procedure the MAH provided a supportive 28-day toxicology study in rats. Valtropin was compared to US Humatrope as a control. This new rat study with daily application of Valtropin in two different doses revealed the well-known pharmacodynamic effects of somatropin, e.g. dose-dependent increase in body weight. Importantly, no unexpected toxicity was observed with Valtropin.

Ecotoxicity/environmental risk assessment

Valtropin is a recombinant human growth hormone (somatropin) and 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 not cause any problems in the environment due to its peptide structure, which will be rapidly destroyed and mineralised by microbial hydrolytic processes.

Discussion on the non-clinical aspects

The pharmacodynamic profile of Valtropin was studied in comparison with the reference medicinal product Humatrope (and with the international somatropin standard). A biological assay was performed in hypophysectomised rats investigating body weight in line with standard procedures and according to the respective guideline (EMEA/CPMP/3097/02). A dose-response relationship in direct comparison of Valtropin and the original preparation Humatrope (EU source) was provided demonstrating biosimilarity with the reference medicinal product with respect to pharmacodynamics.

No pharmacokinetic studies are required according to the relevant guideline (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).

Safety pharmacology studies are not required for similar biological medicinal products containing somatropin as active substance (EMEA/CHMP/94528/2005). However, the MAH provided safety pharmacology data taken from published literature. These studies indicated that Valtropin did not cause harmful effects on major organ systems.

The MAH has not performed absorption, distribution, metabolism, excretion, or pharmacokinetic drug interaction studies with Valtropin. This was in accordance with the relevant guideline (EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005).
The toxicological studies were well designed and conducted but not comparative in nature. However the data provided show that there was no unexpected toxicity of Valtropin (i.e. toxicity not related to the known action of somatropin). Since there were robust clinical data on efficacy and safety of Valtropin, the preclinical information was considered reassuring and sufficient.

From a non-clinical point of view the comparability exercise was considered to be sufficient.

4. Clinical aspects

Introduction

The MAH submitted two comparative clinical studies with Valtropin and the reference medicinal product.

- Study *BP-EU-001*: Bioequivalence study in 24 male, healthy volunteers (BP-EU-001), using EU Humatrope as the reference product, conducted in 2002.
- Study *BP-EU-003*: Comparative, randomised, double-blind Phase III clinical study in 149 children with growth hormone deficiency (GHD), conducted during the period 2001-2003 using Humatrope as the reference product.

In *Study BP-EU-003* EU Humatrope was used as reference medicinal product, however during the conduct of the study the MAH had to switch to US Humatrope.

In addition to the comparative clinical studies, the MAH submitted the report on an open single-arm study to evaluate efficacy and safety of treatment with Valtropin in girls with short stature associated with Turner syndrome (*Study BP-EU-002).*

Two further study reports on studies conducted in Korea with an earlier formulation of Valtropin have been submitted. The data of the Korean studies are included in the safety evaluation.

GCP

A GCP inspection of *Study BP-EU-003* was performed. Although this inspection revealed findings the MAH could alleviate these concerns with the response to the CHMP list of questions. The overall validity of the study data was not compromised. The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No studies on pharmacokinetics (Adsorption / Distribution /Elimination; dose proportionality and time dependencies; special populations; pharmacokinetic interaction studies; pharmacokinetics using human biomaterials) are required according the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CPMP/42832/05) and the product specific Annex: G*uidance on similar medicinal products containing somatropin* (EMEA/CHMP/94528/2005).

- **Study BP-EU-001 (comparison of Valtopin and Humatrope EU)**

Study BP-EU-001 was a double blind, randomised, single subcutaneous (s.c.) dose, cross-over study to investigate the relative pharmacokinetic properties of Valtropin and EU Humatrope. The primary pharmacokinetic parameters determined were the area under the serum concentration time curve ($AUC_{0-\infty}$) and peak concentration (C_{max}) after baseline-correction, and time of peak concentration (t_{max}). The AUC_{0-24h}, and terminal half-life ($t_{½}$) of somatropin after baseline correction were analysed as secondary pharmacokinetic parameters.
Twenty-four (24) volunteers received two single s.c. doses of 0.073 mg/kg body weight somatropin of either Valtropin or EU Humatrope, separated by a wash-out phase of 7 days.

The pharmacokinetic parameters are shown in the table below:

	Valtropin	Humatrope	Ratio Valtropin vs Humatrope	90% CI
Parameter	**Geom. Mean (%CV)**	**Geom. Mean (%CV)**		
$AUC_{0-\infty}$ (ng·h/ml)	377.90 (24.0%)	345.30 (25.2%)	109.45%	102%-118%
AUC_{0-24} (ng·h/ml)	369.90 (26.0%)	337.50 (26.4%)	109.59%	101%-119%
C_{max} (ng/ml)	43.97 (44.9%)	38.64 (39.4%)	113.78%	97%-133%
t_{max} (h)*	4.00 (2.5-6)	5.00 (2.5-7)	-1 h#	-2 h, ±0 h
$t_{1/2}$ (h)	3.03 (41.0%)	3.12 (40.7%)	-	-

* median and range; # difference

Valtropin and Humatrope showed similar PK profiles with regard to extent of absorption and elimination rate. The calculated 90% CI for C_{max} was 0.97-1.33 and therefore lies within the pre-specified acceptance range of 0.70-1.43. The widening of the acceptance range for Cmax was justified by published data (Verhagen et al. 1995; Vahl et al. 1996; Laursen et al. 1993; Blok et al. 1991), which demonstrated that for somatropin containing medicinal products Cmax is an inherently more variable parameter than AUC.

Pharmacodynamics

- Mechanism of action

All known effects of GH result from its interactions with the GH receptor, which is a widely distributed cell-surface receptor that belongs to the cytokine receptor superfamily and contains an extracellular domain that binds GH and an intracellular domain that mediates signal transduction. Receptor activation results from the binding of a single GH molecule to two identical receptor molecules. The resulting ligand-occupied receptor dimer activates downstream signalling pathways ultimately affecting gene expression.

Although GH acts directly on adipocytes to increase lipolysis and on hepatocytes to stimulate gluconeogenesis, its anabolic and growth-promoting effects are mediated predominantly indirectly through induction of insulin-like growth factors (IGFs), predominantly IGF-1.

- Primary and Secondary pharmacology

No pharmacological studies have been submitted to confirm similarity in pharmacodynamic effects (IGF-1, lipolytic, anabolic or diabetogenic effects) of Valtropin and Humatrope. IGF-1 and IGFBP-3 levels were determined in the pivotal comparative clinical trial (*BP-EU-003*) and no marked differences in the effect of both products on these parameters were observed.

Clinical efficacy

- Dose response study(ies)

No studies were required according to EMEA/CHMP/42832/2005 and EMEA/CHMP/94528/2005.

- Main study

Double blind, multi-centre, centrally randomized, two-arm, parallel controlled Phase III study to compare efficacy and safety of a twelve months treatment with two somatropins in GHD children (*BP-EU-003*)

The study was conducted in 26 different study centres in 12 different countries.

METHODS

Study Participants

Pre-pubertal children with a confirmed diagnosis of GH deficiency (GHD) as determined by two different hGH provocation tests (defined as a peak plasma GH level of <10.0 ng/ml measured centrally via the AutoDELFIA method), standing height below -2 SDS, and height velocity (HV) below the 25th percentile as compared to a normal reference population were eligible.

Treatments

Patients were randomized 2:1 to receive Valtropin or Humatrope, respectively, at a dose of 0.1 IU/kg/day s.c., seven days a week for a total of 12 months. As 1 mg equals approximately 3.0 IU, this dose corresponds to 0.033 mg/kg/day or 0.23 mg/kg/week.

Objectives

The primary objective of the study was to demonstrate non-inferior efficacy of twelve months treatment with Valtropin compared to Humatrope. The non-inferiority margin for the primary endpoint "height velocity at 12 months" was set at -2.0 cm/year.

Outcomes/endpoints

The primary endpoint of this study was height velocity (HV) in cm/year after the first 12 months of treatment. HV was calculated for each patient from a linear regression of height against time based on the exact dates at which height was recorded. Height was measured in a standardized manner using a wall-mounted stadiometer.

Secondary endpoints were:

- Height velocity standard deviation score for chronological age (HV SDS CA)
- Height gain (HTG)
- Height standard deviation score for chronological age (HT SDS CA) at 12 months
- Height standard deviation score for bone age (HT SDS BA) at 12 months
- Predicted adult height SDS
- Bone maturation at 12 months, calculated as the ratio of change in bone age to change in chronological age (ΔBA/ΔCA)
- Weight gain
- IGF-1 and IGFBP-3 serum levels at month 12

Sample size

The sample size calculation of 111 patients was based on a 90% power to reject the null hypothesis of inferiority in favour of the alternative hypothesis of non-inferiority (with a type I error rate of $\alpha = 0.025$ (one sided)).

Randomisation

Randomisation ratio between the two treatment arms was 2:1 (Valtropin: Humatrope®).

Blinding (masking)

The study was double blind.

When Humatrope 16 IU vials were no longer available on the European market, Humatrope 15 IU vials were sourced from the US. Although every effort was made to keep the study blind, it cannot be excluded that the switch impaired effective masking

Statistical methods

The primary analysis approach was analysis of covariance (ANCOVA). The primary analysis set was the per protocol population.

RESULTS

Participant flow

149 patients were randomized and treated (99 vs. 50; Valtopin vs. Humatrope),

147 patients were evaluable for safety (98 vs. 49)

129 patients were evaluable for efficacy (full analysis set) (88 vs. 41)

102 patients were evaluable for efficacy (per protocol set) (70 vs. 32).

The full analysis set (ITT) comprised all randomized patients who had received at least one dose of active treatment and who provided valid follow-up data for the primary target variable.

The per-protocol (PP) population was small especially in the Humatrope group, since major protocol violations were observed in 29.3% vs. 36.0% in Valtropin vs. Humatrope treated patients. Criteria for major protocol violation were very stringent.

Conduct of the study

The patients received either Valtropin (15 IU) or the reference medicinal product EU Humatrope (16 IU). However during the conduct of the study the reference medicinal product became unavailable, thus the MAH switched to US Humatrope (15 IU).

Baseline data

Demographic data of the full analysis set (ITT)

Parameter	Valtropin (n=98)	Humatrope (n=49)
Male patients	69	30
Female patients	29	19
Age (years)	8.1±2.1 [8.4]	8.5±2.0 [8.3]
HT (cm)	107.2±11.8 [106.5]	110.5±11.0 [111.5]
Pre-treatment HV (cm/year)*	3.4±1.5 [3.4]	3.2±1.2 [3.3]
Weight (kg)	18.6±5.2 [18.5]	19.8±4.9 [19.3]
Body Mass Index (kg/m²)	15.9±1.7 [15.6]	16.0±2.0 [15.5]

* Pre-treatment height velocity was calculated from pre-study, visit 1 and visit 2 height measurements.

Both treatment groups were similar with regard to baseline characteristics, concomitant endocrine disorders and parental height.

GHD was idiopathic in 94 (95.9%) and 48 (98.0%) patients of the Valtropin and Humatrope group, respectively; other causes of GHD were reported in only 4 (4.1%) vs. 1 (2.0%) patients.

A history of TSH/Thyroxin deficiency was reported in 26 (26.5%) and 14 (28.6%) patients of the Valtropin and Humatrope group, respectively. All patients diagnosed with hypothyroidism were substituted before GH therapy was.

Concomitant ADH deficiency was reported in 1 (1.0%) patient in the Valtropin group and in 3 (6.1%) patients of the Humatrope group.

Outcomes and estimation

Per protocol analysis
The results of the primary efficacy variable (height velocity at 12 months) are presented in the table below.

Height velocity (HV) at 12 months – Per-protocol analysis (Visit 6, Month 12):

Height velocity [cm/year]	**Valtropin**	**Humatrope**
	Mean ± SD [Median]	**Mean ± SD [Median]**
	n = 70	**n = 32**
Pre-treatment height velocity	3.6 ± 1.5 [3.8]	3.4 ± 1.1 [3.4]
Visit 6 (month 12)	11.3 ± 3.0 [11.2]	10.5 ± 2.8 [9.6]

There was no marked difference in mean HV between the two treatment groups.

The 95% confidence limits for the mean difference of the adjusted mean HV were [-0.72, 0.90] thus demonstrating that Valtropin was not inferior to Humatrope. Considering both the upper and lower CI, the results also demonstrated therapeutic equivalence.

There was no treatment-country interaction at the 10% level (p = 0.21).

The results for the ITT population were very similar.

Secondary efficacy parameters (PP set):

Parameter	**Valtropin (n=70)**	**Humatrope (n=32)**
HT (cm)		
Visit 1 (screening)	108.4±11.9 [109.3]	111.3±9.8 [109.5]
Visit 2 (baseline)	109.0±12.0 [110.2]	112.0±9.7 [110.0]
Visit 6 (Month 12)	120.2±11.3 [120.6]	122.5±9.2 [128.5]
HTG (V2 to V6)	11.3±3.0 [11.1]	10.6±2.7 [9.6]
Weight (kg)		
Visit 1 (screening)	19.1±5.5 [18.6]	20.2±4.6 [19.4]
Visit 2 (baseline)	19.4±5.5 [18.7]	20.4±4.6 [19.4]
Visit 6 (Month 12)	23.3±6.2 [23.0]	24.6±5.5 [22.7]
Weight gain (V2 to V6)	3.9±1.7 [3.80]	4.2±1.5 [4.1]
HV SDS CA*		
Pre-treatment	-2.19±1.80 [-1.79]	-2.42±1.37 [-2.11]
Visit 6 (Month 12)	5.62±3.55 [4.86]	5.33±3.88 [3.89]
HT SDS CA		
Pre-treatment	-3.45±1.16 [-3.24]	-3.17±0.80 [-2.93]
Visit 6 (Month 12)	-2.26±0.91 [-2.15]	-2.15±0.69 [-2.00]
HT SDS BA		
Pre-treatment	-0.15±1.47 [-0.20]	-0.06±1.33 [-0.08]
Visit 6 (Month 12)	-0.09±1.61 [-0.27]	-0.00±1.40 [0.14]

* = calculated according to Prader et al. (1988)

Evaluation of 95% confidence limits for differences of mean HT, mean weight, height gain and weight gain as well as SDS for HV SDS, HT SDS CA and HT SDS BA showed no relevant differences between the treatment groups.

Finally there were no relevant differences between the treatment groups with regard to predicted adult HT, bone maturation, IGF-1 and IGFBP-3.

Ancillary analyses

In *Study BP-EU-003* European (16 IU) and US Humatrope (15 IU) were used. Commercialisation of Humatrope 16 IU multidose vials was unexpectedly discontinued in Europe. Thus in order to maintain the study blind the MAH decided to switch to the US sourced product. Of note, there was no therapy "switch" date for change from EU to US Humatrope. Change was a gradual process, which took place as supplies of EU Humatrope became depleted.

Upon CHMP request, the MAH provided a subpopulation analysis, which included only patients in the control arm that had received exclusively EU Humatrope for at least 6 months.

Mean HV and HV SDS at Visit 4 (month 6): patients who were treated with EU Humatrope only for at least 6 months

	Per-protocol analysis set		Full analysis set	
	Valtropin n = 67	EU Humatrope n = 16	Valtropin n = 88	EU Humatrope n = 20
Baseline Mean HV ± SD (cm/year)	3.60 ± 1.50	3.69 ± 1.09	3.50 ± 1.45	3.55 ± 1.06
6-month Mean HV ± SD (cm/yr)	12.68 ± 3.57	12.56 ± 3.47	12.64 ± 3.49	12.33 ± 3.12
6-month Mean Diff., 95%-CI	0.12 [-1.85;2.08]		0.31 [-1.38;1.99]	
6-month LS Mean Diff., 95%-CI (ANCOVA Model)	-1.05 [-2.48;0.37]		-0.35 [-1.64;0.95]	
Baseline Mean HV SDS ± SD	-2.20 ± 1.83	-2.02 ± 1.35	-2.34 ± 1.78	-2.09 ± 1.27
6-month Mean HV SDS ± SD	7.42 ± 4.18	7.49 ± 4.76	7.38 ± 4.17	7.25 ± 4.36
6-month Mean Diff., 95%-CI	-0.07 [-2.45;2.31]		0.13 [-1.94;2.19]	

The mean HV was almost identical in both treatment groups and similar between PP and ITT populations. The wider CIs could be primarily attributed to the smaller N. However, in the pre-specified ANCOVA analysis there were discrepancies between the results in the PP and ITT populations.

The MAH performed an additional sensitivity analysis to provide more confidence that the switch from EU to US Humatrope did not affect the overall conclusions from the trial. This analysis introduced an additional covariate, namely time spent on US Humatrope, into the pre-defined ANCOVA model. Overall, patients were exposed to EU Humatrope for approximately 90% of the total Humatrope exposure time generated in the first 6 months of the study.

Mean HV at Month 6 (Visit 4) using the modified ANCOVA model

	Per-Protocol analysis set		Full Analysis set	
	Valtropin n = 67	EU Humatrope n = 33	Valtropin n = 88	EU Humatrope n = 41
Baseline Mean HV ± SD (cm/year)	3.60 ± 1.50	3.46 ± 1.08	3.50 ± 1.45	3.39 ± 1.02
6-month LS Mean HV ± Std. Error (cm/yr)	12.28 ± 0.42	12.75 ± 0.60	12.45 ± 0.32	12.34 ± 0.49
6-month LS Mean Diff., 95%-CI (ANCOVA Model)	-0.47 [-1.74;0.81]		0.11 [-1.03;1.25]	

The results are in line with the primary analysis and suggest that the switch from EU to US Humatrope did not affect the integrity of the trial.

- Clinical studies in special populations

N / A

- Supportive study(ies)

Study BP-EU-002 in girls with Turner's syndrome

Study BP-EU-002 was an uncontrolled 12-month trial performed in 30 treatment naïve girls with short stature due to Turner syndrome (age 2-9 years). Patients were treated with daily s.c. injections of Valtropin at a weekly dose of 0.16 IU/kg/day (0.053 mg/kg/day). During the first year, HV was raised significantly from baseline 3.75 ± 1.76 cm/year to 9.73 ± 1.55 cm/year indicating that Valtropin treatment had the expected growth-promoting effect of a somatropin containing product. Since this was an uncontrolled trial and the enrolled patients differed in baseline characteristics from patients of published trials, a firm conclusion regarding efficacy was not possible.

The MAH provided study reports on the 12-month extension phases of studies BP-EU-003 and BP-EU-002. Of the 149 patients that were treated in the parent Study BP-EU-003, 135 patients (90 Former Valtropin vs. 45 Former Humatrope) were treated with Valtropin at a dose of 0.1 IU/kg body weight/day (0.23 mg/kg body weight/day) s.c. during the extension phase. All 29 patients with Turner syndrome that completed the initial 12-month treatment period of study BP-EU-002 were enrolled into the 12-month extension phase and treated with daily s.c. injections of Valtropin at a dose of 0.16 IU/kg/day (0.053 mg/kg/day).

As expected, both the Turner patients and the GHD patients experienced further catch-up growth during the extension phase of the respective studies. Patients showed the typical profile of catch-up growth with a high growth rate during the first 6 to 12 months and a subsequent decline thereafter. However, HV during the second year of treatment was still significantly greater than pre-treatment growth.

- Discussion on clinical efficacy

It was clarified that for this type of application (similar biological medicinal product) therapeutic equivalence rather than non-inferiority has to be demonstrated. The pre-specified non-inferiority margin for the primary endpoint "height velocity (HV) at 12 months" was -2 cm/year, which was considered rather wide because such a difference could matter in clinical practice. However, the limits of the calculated 95% CI for the difference of the adjusted mean HV in *study BP-EU-003* were very narrow allowing the conclusion of therapeutic equivalence of Valtropin and Humatrope. The PP and ITT yielded very similar results, which was reassuring. Nevertheless, the CHMP raised several questions regarding the validity of the study data (e.g. standardization and recording of height measurements, study blind, high rate of major protocol violations, use of US growth charts, possible

centre effects, quality of control of hypothyroidism, confounding pubertal growth spurt) and also recommended a GCP inspection.

The MAH could alleviate all these concerns with their Day 120 and Day180 response documents. Although the GCP inspection of the pivotal study *BP-EU-003* revealed findings, most of them could be alleviated retrospectively. Most importantly, the overall validity of the study data was not compromised.

During the assessment it became clear that both EU Humatrope and US Humatrope had been used in *Study BP-EU-003*. However, this was not acceptable since the current *Guideline on similar biological medicinal products* (CPMP/437/05) requires the demonstration of comparability of the product applied for to a reference product authorised in the EU. Therefore, only data obtained with EU Humatrope could be considered pivotal; the data obtained with US Humatrope were considered supportive.

Consequently, the CHMP requested that the MAH provided a subpopulation analysis comparing 6-month data (considered minimum duration for assessment of HV) from Valtropin treated patients with patients exclusively treated with EU Humatrope.

This analysis showed almost identical mean annualised HV and HV SDS. The wider 95% CIs could be primarily attributed to the smaller number of patients.

However, the pre-specified analysis strategy (ANCOVA with adjustment for chronological age, pre-treatment HV, country, and log(max GH stimulation) revealed some inconsistencies between the PP and ITT populations for the primary endpoint.

The additional *post-hoc* analysis provided by the MAH introducing an additional covariate, namely time spent on US Humatrope, into the pre-defined ANCOVA model, supported the view that the switch from EU to US Humatrope did not affect the integrity of the trial.

Nevertheless, the following criticism of the primary analysis approach existed from a regulatory point of view: (i) a rather complicated model had been fitted to the data, (ii) the use of peak serum GH values (from one stimulation test) as a covariate was questioned because of the low reproducibility of results from GH stimulation tests, and (iii) the definition of the PP-analysis population was felt to be overly restrictive (most criteria were considered to be not clinically relevant). The inconsistency between the ITT and PP populations appeared to be a consequence of fitting a too complex model to a small dataset. The MAH was therefore asked to provide simple descriptive measures (HV for 6 and 12 months) for patients randomized to the first, the second and the third segment of the trial together with a simple stratified analysis of these findings to give re-assurance that the discrepancy between the two analysis populations was due to the issues described above. The underlying idea was that results for most patients in the first segment of the trial would mainly depend on treatment with EU-Humatrope and that results in segment 2 and 3 would increasingly depend on exposure to US Humatrope.

The following table shows the stratified analysis of the 12-month height velocity data. The 6-month analyses were quantitatively similar.

Segment	N	Full Analysis set Mean ±SD	N	Per-Protocol set Mean ±SD
Segment 1				
Valtropin	27	11.05 ± 2.87	18	11.33 ± 2.98
Humatrope	15	10.37 ± 2.58	12	10.49 ± 2.80
Segment 2				
Valtropin	30	11.15 ± 3.09	27	11.28 ± 3.04
Humatrope	12	10.20 ± 2.45	9	10.09 ± 2.76
Segment 3				
Valtropin	31	11.83 ± 2.83	22	11.69 ± 2.93
Humatrope	14	11.00 ± 2.87	12	10.69 ± 2.99
Overall				
Valtropin	88	11.36 ± 2.92	67	11.43 ± 2.95
Humatrope	41	10.54 ± 2.61	33	10.45 ± 2.78

These analyses showed that the height velocity across the three segments was homogeneous and that the switch from EU Humatrope to US Humatrope had no discernable effect on the results of the study. The result of the different analyses allowed the following conclusions to be drawn: (i) there was no indication that the exchange of the study medication affected the findings from the different segments of the trial, (ii) results were consistent for the ITT and the PP populations, (iii) there were no appreciable differences between 6 months and 12-month results. The estimated HV for 12 months data was slightly smaller than results based on 6 months data, which reflects the well-known profile of catch-up growth.

Finally, it was concluded that, based on all the evidence from quality, non-clinical and clinical data and the consistency of results from different analyses of Study BP-EU-003, sufficient confidence has been provided that Valtropin and EU Humatrope have comparable efficacy.

Since comparable clinical efficacy of Valtropin and EU Humatrope has been demonstrated in the most sensitive model (GHD children), CHMP agreed to extrapolate clinical data to all indications applied for, which are identical to the indications approved for the reference medicinal product (see *Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guideline on Similar Medicinal Products containing Somatropin* (EMEA/CPMP/42832/05 and EMEA/CHMP/94528/05)

Clinical safety

- Patient exposure

A tabular overview on the overall safety database is given in the following tables.

Study ID, Reference	Clinical Phase	Design	Objective	Study Population	Total n
BP-EU-001	I	Randomised, double-blind, cross-over, comparator-controlled	Bioequivalence of Valtropin compared to Humatrope	Healthy volunteers	24
BP-EU-003	III	Multicentre, multi-national, randomised, double-blind	Efficacy and safety of Valtropin (15 IU) compared to Humatrope	Children with GHD	147 (Valtropin: 98) (Humatrope: 49)
BP-EU-002*	III	Multicentre, multi-national, single-	Efficacy and safety of Valtropin (15 IU)	Children with TS	30

Study ID, Reference	Clinical Phase	Design	Objective	Study Population	Total n
		arm, open-label			
Korean Turner Study**	III	Multicentre, randomised, open-label	Efficacy and safety of Eutropin INJ (4 IU)	Children with TS	60
HGCL-001**	III	Multicentre, randomised, double-blind, placebo-controlled	Efficacy and safety of Eutropin INJ (4 IU)	Adults with GHD	92

*supportive study
** previous formulation, safety data only

The main safety data for Valtropin were derived from a total of 128 patients, from 98 children with GHD (*Study BP-EU-003*), and from 30 children with Turner's syndrome (*Study BP-EU-002*). The patients received Valtropin for 12 months. The doses ranged between 0.033 and 0.053 mg/kg/day. Furthermore, 49 children with GHD were treated with Humatrope (0.033 mg/kg/day) for a mean duration of 12 months.

In addition, 24 healthy adult volunteers received a single dose of 0.073 mg/kg Valtropin and in a second phase the same dose of Humatrope respectively.

Dosage and duration of treatment in clinical studies performed with Valtropin or Humatrope:

	Valtropin		Humatrope	
	Dosage range	**Duration of treatment**	**Dosage range**	**Duration of treatment**
Adult healthy volunteers	0.073 mg/kg	Single dose	0.073 mg/kg	Single dose
Paediatric patients	0.033-0.055 mg/kg/day	12 months	0.033 mg/kg/day	12 months
Adult patients	0.033-0.066 mg/day 6x/week (corresponding to 0.004-0.009 mg/kg/day)	6-12 months	-	-

- Adverse events

  - *Study BP-EU-003*

In *Study BP-EU-003* in children with growth failure due to GHD, a total of 308 adverse events (AEs) were reported, comprising 206 AEs in 48 of 98 (49.0%) children with GHD in the Valtropin group, versus 102 AEs in 26 of 49 (53.1%) patients in the Humatrope group. The reported events were similar in type, frequency and severity for the two treatments (see table below). The most frequently reported AEs were headache, pyrexia, cough, vomiting, diarrhoea, pharyngitis and respiratory tract infection. The great majority of AEs were of mild to moderate intensity, whilst only 9 events (4 with Valtropin vs. 5 with Humatrope) were of severe intensity.

	Valtropin n=98	Humatrope n=49
Headache	10 (10.2%)	8 (16.3%)
Pyrexia	9 (9.2%)	8 (16.3%)
Cough	5 (5.1%)	3 (6.1%)
Vomiting	4 (4.1%)	4 (8.2%)
Diarrhoea	3 (3.1%)	4 (8.2%)
Pharyngitis	3 (3.1%)	4 (8.2%)
Respiratory tract infection NOS	5 (5.1%)	1 (2.0%)

- *Study BP-EU-001*

A total of 44 adverse events were reported: taste perversion (24) and application site reaction (8) were evenly distributed between Valtropin and the reference medicinal product. In addition, fatigue (3), paraesthesia (2), saliva increased (2), and headache, dizziness, dry mouth, oedema, and haematoma (1) were observed, most of the events being considered drug related. The intensity of one event (application site reaction following reference) was reported as moderate, all other adverse events were mild in intensity.

- *Study BP-EU-002*

In total, 17 AEs were reported in 10 of 30 (33.3%) children with Turner syndrome. The most frequently reported AEs were respiratory tract infection, ear infections and positive antibody findings. The majority of AEs were of mild intensity (11 events in 7 patients). Five events in 3 patients were of moderate intensity, while only 1event in 1 patient was of severe intensity (pain at injection site).

- *Korean study in Turner syndrome*

No AEs were reported in this study.

- *Study HGCL-001*

The most frequent AE during treatment with Eutropin INJ (4IU) was oedema (n=12). In the placebo arm oedema and urticaria (both n=4) were the most frequently reported events.

- Serious adverse event/deaths/other significant events

No deaths were reported during the course of the clinical studies.

- *Study BP-EU-003*

In *Study BP-EU-003*, 7 serious adverse events (SAEs) were reported in 5 patients in the Valtropin group (5.1%) and 2 SAEs were reported in the Humatrope group (in 2 patients: 4.1%).

Three of the 7 reported SAEs were related to treatment with Valtropin: allergic skin reaction (pruritus, urticarial rash; n=1); and in one patient elevated alkaline phosphatase (AP) and renal tubular loss of phosphates (n=2). The latter findings were considered to be signs of vitamin D deficiency unrelated to treatment.

The two SAEs described in the Humatrope group, one of which was an acute leukaemia, were considered not to be or unlikely to be drug-related.

- *Study BP-EU-002* and study *BP-EU-001*.

No SAEs were reported in *Study BP-EU-002* and *BP-EU-001*and the *Korean study in Turner syndrome*.

- *Study HGCL-001*

In *study HGCL-001*, performed in adults with GHD, 3 SAEs were reported in 2 patients during the treatment period: cerebrovascular disorder, adrenal insufficiency and hypothyroidism. During the placebo phases 1 case of acute hyperglycaemia was described in a patient with a history of diabetes. None of these events were considered to be related to the study medication.

- Laboratory findings

- *Study BP-EU-003*

Clinically significant changes (increase) in alkaline phophatase (AP) values were described in one patient in the Valtropin group and one patient in the Humatrope group.

In three patients (1 in the Valtropin group and 2 in the Humatrope group), elevated liver values were reported. However, no particular action was necessary in these patients and none of the values were considered related to the study medication. Almost one third of the clinically significant laboratory values were observed in one patient in the Humatrope group who had acute leukaemia.

- *Study BP-EU-001*

The post-study examination revealed only one laboratory parameter that was outside the normal range and considered to be of possible clinical relevance (ALT increased, but returned to clinically normal levels one week later). There were no notable individual subject changes and no individual laboratory changes that had to be considered as AEs.

- *Study BP-EU-002*

Only a few changes of laboratory parameters were observed in this study. None of the changes were considered to be clinically significant. Furthermore, there were no clinically significant findings in the urine tests.

- *Korean Turner study*

There were no clinically significant changes related to Eutropin INJ (4IU) in blood chemistry, haematology and urinalysis. Haematuria was reported in 20 patients at baseline; in 6 of these patients the condition disappeared during treatment. Microscopic haematuria was found in 15 patients during treatment; however, in 7 of these patients the condition resolved.

- *Study HGCL-001*

In *Study HGCL-001* investigating Eutropin INJ (4IU) in adults with GHD, blood count, clinical chemistry and urine parameters and HbA_{1c} were mainly within the normal range. Values outside the normal range were not considered to be of clinical significance.

- IGF-1 levels

IGF-1 levels generally remained in the normal age-adjusted range. In *Study BP-EU-003* only 2 patients in the Valtropin group and one patient in the Humatrope group had transient elevations above +2SDS.

- Thyroid parameters

Changes in thyroid parameters (fT_4, fT_3, and TSH) were described in clinical studies with Valtropin and with Humatrope in children and adults together with cases of hypothyroidism. This was in line with published data for treatment with Humatrope and other somatropin-containing medicinal products. The development of hypothyroidism is well known; a special warning is included in the SPC, as for the reference medicinal product and other somatropin containing products.

- Glucose metabolism

Somatropin may exert a diabetogenic effect; there is generally a risk of insulin resistance and hyperinsulinism, glucose intolerance and type-2 diabetes (Mehta & Hindmarsh 2002; Tanaka et al. 2002).

In studies performed with Valtropin and Humatrope, clinically significant changes in glucose metabolism (increase in fasting glucose, and HbA_{1c}) were reported. However, no clinically relevant differences between the treatment groups were observed. The rare but possible development of mild hyperglycaemia (type 2 diabetes mellitus) is well known, a special warning is included in the SPC, as for the reference medicinal product and other somatropin containing products.

- Immunogenicity

In compliance with EMEA/CHMP/94528/2005 the immunogenic potential of Valtropin and Humatrope was compared in the clinical development programme.

- *Anti GH antibodies*

In total, 135 of the 147 patients included in the *study BP-EU-003* were enrolled in the rollover treatment phase (*Study BP-EU-003-RO*). All enrolled patients were treated for an additional 12-month period with Valtropin. Forty-five patients switched from Humatrope treatment to Valtropin treatment and 90 patients continued on Valtropin treatment.

During *Study BP-EU-003*, three out of 98 patients (3.1%) in the Valtropin group and 1 out of 49 patients (2.0%) in the Humatrope group developed anti GH antibodies. During the second year of treatment, anti-hGH antibodies were reported in the same four patients (3%). These antibodies did not affect growth.

In *study BP-EU-002*, 1 out of 30 Turner patients (3.3%) developed anti-hGH antibodies. No positive sera were reported in the extension phase.

The observed frequency of anti GH antibodies in Valtropin-treated subjects was within the expected range of 2 to 5% for recombinant growth hormones. However the database is too small to draw any firm conclusions about the true frequency of antibody formation. The MAH has therefore committed to evaluate immunogenicity in a post-marketing study using a sufficiently sensitive and fully validated screening assay and to further characterise antibodies, if present, and assess their possible clinical implications. This approach is in line with EMEA/CHMP/94528/2005.

The assay used for detection of anti GH antibodies in the clinical trials was not sufficiently validated. The MAH will use a different and fully validated assay for the post-marketing period.

- Anti-host cell protein (HCP) antibodies

In *Study BP-EU-003*, two out of 98 patients (2.0%) treated with Valtropin and none of the patients treated with Humatrope developed anti yeast antibodies. The frequency of so-called “grey zone” antibodies was 8 of 98 (8.2%) in Valtropin treated and 5 of 49 (10.2%) in Humatrope treated patients, suggesting that the criteria for positivity resulted in a high degree of background noise. In the extension *study BP-EU-003-RO*, positive findings were reported in four out of 135 Valtropin treated

patients (3%) but a further 29 patients (21.5%) had so-called "grey-zone" results, which represents a doubling compared to the first year.

In *Study BP-EU-002* none of the 30 Turner patients were positive for anti-HCP antibodies. A positive finding was reported for 1 patient (3.3%) in the extension phase.

The investigation of HCP antibodies demonstrated the low antigenic potential of the preparation but the increase in "grey zone" antibodies in *Study BP-EU-003-RO* was unexplained.

Subsequently, the MAH provided a re-analysis of the anti yeast antibody results according to new criteria suggested by an expert in the field. The new criteria for positivity, which were considered acceptable because they were more in line with current scientific knowledge, resulted in a marked reduction in the number of positive sera and the elimination of the "grey zone" antibodies. There were no positive sera in *Study BP-EU-003, Study BP-EU-002* and its extension. In *Study BP-EU-003-RO* there remained 6 positive sera from 5 patients with 4 patients reporting positive results on only one occasion. Therefore, only one patient was considered to have had a biological relevant immune response.

Overall, only low anti-*S. cerevisiae* protein antibody titres were found in patients receiving Valtropin. The generation of such antibodies with low binding capacity was not considered to be of clinical relevance. Furthermore, in contrast to bacterial cell components *(i.e. E. coli)*, yeast does not appear to have adjuvant properties, which would amplify the immune response.

The assay used for detection of anti yeast antibodies was considered suitable for its intended purpose. Some additional information for full validation will be submitted with the post-marketing immunogenicity data.

- Discontinuation due to adverse events

During the clinical studies with Valtropin / Eutropin and Humatrope, 8 patients (4 children, 4 adults) withdrew from treatment. One of these withdrawals was during the placebo treatment phase in Study HGCL-001. The reason for withdrawal was considered possibly drug-related in only one case: one patient that received Valtropin in the *BP-EU-003* study experienced allergic skin reaction with systemic hypersensitivity.

No patient withdrew prematurely due to an adverse event in the extension phase of Study BP-EU-002 or the rollover Study BP-EU-003RO.

- Post marketing experience

N / A

- Discussion on clinical safety

The safety profile of the active substance somatropin is well characterised. Somatropin containing medicinal products produced by genetically engineered bacterial or mammalian cells have been on the market for more than 15 years. These products are considered safe, adverse reactions have been observed more frequently in adults than in children. The undesirable effects include injection site reactions, impaired glucose tolerance, hypothyroidism and, rarely, benign intracranial hypertension, as well as peripheral oedema, myalgia and arthralgia, particularly in adults.

At present, there is no evidence that hGH replacement therapy, in the absence of other risk factors, affects the incidence of cancer (GRS 2000, Leong & Johannsson 2003). Nevertheless, patients with pre-existing intracranial tumours have to be monitored with respect to recurrence.

The AE profile of Valtropin, obtained from studies *BP-EU-001, BP-EU-002, BP-EU-003* and the respective extension and rollover studies, is consistent with that of Humatrope and with published data for other products containing somatropin.

Regarding the immunogenicity of Valtropin evaluated during studies *BP-EU-002 and BP-EU-003*, there were no relevant differences in the development of anti-GH antibodies between Valtropin (2-3%) and the reference product Humatrope (2%). Anti-GH antibodies did not affect growth.

However, the anti GH antibody assay used in the clinical trials was not considered sufficiently validated.

The lack of validation of the anti GH antibody assay was not considered an obstacle for approval because the antibody frequency in the clinical trials was as expected for rhGH containing products (including Humatrope) and similar in both treatment arms. In addition, low titre antibodies that may have been missed are not expected to have any clinical impact.

The MAH provided an outline of the design together with some validation data for a new anti GH antibody assay to be used in the post-marketing phase, which was found acceptable. The data show that this new assay is qualified for its intended purpose. The MAH committed to provide a full validation report.

A special feature of Valtropin is the use of yeast cells (S. cerevisiae) as an expression system. The observed frequency of anti-S. *cerevisiae* antibodies (2-3%) does not raise concern, especially because such antibodies were not associated with development of anti-GH antibodies or adverse clinical outcome. In fact, in contrast to bacterial cell components (E. coli), yeast has not been described to elicit adjuvant properties amplifying the immune response to GH.

During the comparative phase of *Study BP-EU-003*, similar frequencies of "grey zone" antibodies were observed in both treatment groups (8-10%) suggesting that the criteria for positivity employed resulted in a high degree of "background noise". However, an explanation for the approximate doubling in frequency of such "grey zone" antibodies in the extension phase of *Study BP-EU-003* could not be provided but a reaction to other yeast sources was considered a reasonable possibility.

The CHMP agreed that the algorithm used for the interpretation of the anti yeast antibody results was overly-restrictive and that the new criteria recommended by an external expert and based on sound scientific knowledge should be used. The use of these new criteria for positivity resulted in a marked reduction in the number of positive sera and the elimination of the "grey zone" results. Only one patient was considered to have had a biological relevant immune response.

Therefore, Valtropin can be considered to have a very low immunogenic potential.

Although the anti-yeast antibody assay was not completely validated, it was clear that it was qualified for its intended purpose. The MAH committed to submit additional information for full validation together with the post-marketing immunogenicity data.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan:

Table: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Diabetogenic potential of rhGH	Registry (2 years treatment): patient demographics, adverse events, laboratory parameters ((fasting) insulin, HbA1c, IGF-1, IGFBP-3)	Common; mild hyperglycaemia Section 4.8 of SPC
Risk of hypothyroidism	Registry (2 years treatment): patient demographics, adverse events, laboratory parameters (TH4)	Warning risk of hypothyroidism in Section 4.4 of SPC Common: hypothyroidism Section 4.8 of SPC
Occurrence and clinical implications of anti-rhGH antibodies	Generation of further immunogenicity data	Development of antibodies included in Section 4.8 of SPC
Occurrence and clinical implications of anti-host cell antibodies	Generation of further Immunogenicity data	Development of antibodies included in Section 4.8 of SPC

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.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

An extensive characterisation study has been performed with Valtropin drug product manufactured by BioPartners from drug substance produced by the commercial process at LG Life Sciences (LGLS) against Humatrope sourced from the EU.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The MAH gave a letter of undertaking and committed to resolve these as follow up measures after the opinion, within an agreed timeframe. Moreover, during the procedure the BWP endorsed the assessment made by the Rapporteurs.

Non-clinical pharmacology and toxicology

The pharmacodynamic profile of Valtropin was studied in comparison with the reference medicinal product Humatrope (and with the international somatropin standard). A biological assay was performed in hypophysectomised rats investigating body weight in line with standard procedures and according to the respective guideline (EMEA/CPMP/3097/02). A dose-response relationship in direct comparison of Valtropin and the original preparation Humatrope (EU source) was provided demonstrating biosimilarity with the originator in respect to pharmacodynamics.

The toxicological data provided showed that there was no unexpected toxicity of Valtropin (i.e. toxicity not related to the known action of somatropin). Although this was considered to be important information it was not directly related to the biosimilarity exercise. Nevertheless, since there were robust clinical data on efficacy and safety of Valtropin, the preclinical information was considered reassuring and sufficient.

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

Efficacy

The MAH submitted a comparative single-dose pharmacokinetics study (*BP-EU-001*), a 12-month equivalence trial (*BP-EU-003*) in GHD children and a supportive uncontrolled 12-month study (*BP-EU-002*) in Turner patients. Studies *BP-EU-003* and *BP-EU-002* had a 12-month uncontrolled extension phase (*Study BP-EU-003-RO* and *BP-EU-002ext*, respectively). Studies *BP-EU-001* and *BP-EU-003* were the pivotal studies for the comparability exercise.

Study BP-EU-001 demonstrated that Valtropin and EU Humatrope have similar PK profiles with respect to the extent of absorption and elimination rate. The MAH provided convincing arguments, based on published data on other sompatropin containing medicinal products, that the widening of the acceptance range for C_{max} to 0.70-1.43 was acceptable. In conclusion, results from *Study BP-EU-001* confirmed that the PK profiles of Valtropin and EU Humatrope were similar.

Study *BP-EU-003* demonstrated therapeutic equivalence between Valtropin and EU Humatrope. The PP and ITT analyses yielded very similar results, which was reassuring.

The MAH could alleviate concerns that the validity of the study data may have been affected by various problems (e.g. standardisation and recording of height measurements, study blind, high rate of major protocol violations, use of US growth charts, possible centre effects, quality of control of hypothyroidism, confounding pubertal growth spurt).

Although the GCP inspection of the pivotal *Study BP-EU-003* revealed findings, most of them could be alleviated retrospectively. Most importantly, the overall validity of the study data was not compromised.

During the assessment it became clear that both EU Humatrope and US Humatrope had been used in study *BP-EU-003* which was not acceptable because comparable efficacy and safety has to be demonstrated to a reference product authorised in the EU.

Therefore, the CHMP requested additional analyses including a subpopulation analysis comparing 6-month data from Valtropin treated patients with patients exclusively treated with EU Humatrope and a "homogeneity" analysis.

This subpopulation analysis showed almost identical mean annualised HV and HV SDS. However, the pre-specified analysis strategy (ANCOVA with adjustment for chronological age, pre-treatment HV, country, and log(max GH stimulation) revealed some inconsistencies between the PP and ITT analyses for the primary endpoint. These were considered to be mainly due to the fitting of a complex model to a small data set.

Additional analyses, most importantly a test for "homogeneity" comparing results from three consecutive randomisation segments convincingly demonstrated that the switch from EU Humatrope to US Humatrope did not affect the study results and that the results were consistent for the ITT and the PP populations, as well as for the 6-month and 12-month results.

The CHMP concluded that, based on all the evidence from quality, non-clinical and clinical data and the consistency of results from different analyses of Study BP-EU-003,comparable clinical efficacy of Valtropin and EU Humatrope has been demonstrated with sufficient confidence.

CHMP agreed that extrapolation of the clinical data to all indications applied for, which are identical to the indications approved for the reference medicinal product, should be granted.

Safety

The AE profile of Valtropin, obtained from studies *BP-EU-001*, *BP-EU-002* and *BP-EU-003*, was consistent with that of Humatrope and with published data for other products containing somatropin.

The immunogenicity data confirmed the low immunogenic potential of Valtropin and the lack of clinical relevance of the observed low-titre antibodies.

There were no relevant differences in the development of anti-GH antibodies between Valtropin (2-3%) and the reference product Humatrope (2%).

Although the anti GH antibody assay used in the clinical trials was not sufficiently validated this was not considered an obstacle for approval. The newly developed assay intended for use in the post-marketing phase was considered suitable. The MAH committed to provide a full validation report.

The observed frequency of anti-S. *cerevisiae* antibodies was very low and did not raise concerns.

The frequency of so-called "grey zone" antibodies was similar in Valtropin and Humatrope treated patients. The rise in such borderline antibodies during the second year of treatment was unexplained but may have been due to other yeast sources. However, by introducing more appropriate evaluation criteria these "grey zone" antibodies became negative.

Although the anti-yeast antibody assay was not completely validated, it was clear that it was qualified for its intended purpose. The MAH committed to submit additional information for full validation together with the post-marketing immunogenicity data.

In conclusion, the submitted data confirmed that the safety profile of Valtropin and Humatrope was similar.

- User consultation

The MAH has provided the requested readability testing of the PL, which led to changes in layout and wording that are agreed upon from a clinical point of view because they are likely to increase comprehensibility and the ability to locate information and therefore the safe use of the product (see attached PL).

Risk-benefit 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.

Recommendation

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

Paediatric patients

- Long-term treatment of children with growth failure due to an inadequate secretion of normal endogenous growth hormone.
- Treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis.
- Treatment of growth retardation in pre-pubertal children with chronic renal insufficiency.

Adult patients

- Replacement therapy in adults with pronounced growth hormone deficiency of either childhood- or adult-onset aetiology.

Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one additional known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency. In patients with childhood-onset isolated growth hormone deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low insulin-like growth factor-I (IGF-I) concentrations (< 2 standard deviation score (SDS)), who may be considered for one test. The cut-off point of the dynamic test should be strict.

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

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