EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2013
EMA/CHMP/229458/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Somatropin Biopartners

International non-proprietary name: somatropin

Procedure No. EMEA/H/C/002196/0000

Note

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

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

AB	antibodies
ACTH	Adrenocorticotropic Hormone
AE	Adverse event
AEX	Anion exchange
ALS	Acid-Labile Subunit
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
Anti-hGH	Anti-Human Growth Hormone (Antibodies)
AO	Adulthood Onset
AP	Aminopeptidase
AST	Aspartate aminotransferase
AUC	Area under the Curve
AUCinf	Area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUCinfcorr	Corrected AUCinf
AUClast	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration
AUClastcorr	Corrected AUClast
BA	Bone Age
BHT	Butylhydroxytoluene
BMD	Bone Mineral Density
BMI	Body mass index
BRP	Biological reference preparation
BW	Body Weight
CA	Chronological Age
CD	Circular Dichroism
cDNA	Complementary DNA
CE	Capillary electrophoresis
CFU	Colony forming unit
CI	Confidence interval
Clast	Time of the last quantifiable concentration
Cmax	Maximum Serum/Plasma Concentration
Cmaxcorr	Corrected Cmax
CO	Childhood Onset
CPA	cell proliferation assay
CPF	cut point factor
CRF	Case Report Form
CRP	C-Reactive Protein
CV	Coefficient of variation
d	Day
Da	Dalton
DEAE	Diethylaminoethylcellulose
DEXA	Dual Energy X-ray Absorptiometry
DP	Drug product
DS	Drug substance
E. coli	Escherichia coli
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
FA	Full Analysis
FAS	Full Analysis Set: All ramdomized patients who received at lest one dose of study medication and had a baseline value for the primary efficacy variable
FM	Fat Mass
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GH	Growth Hormone
GHD	Growth hormone deficiency
GHRH	Growth Hormone releasing Hormone
h	Hour(s)
HA	Sodium hyaluronate
hCG	Human chorionic gonadotropin

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HDL	High-Density Lipoprotein
hGH	Human growth hormone
HI	Hydrophobic interaction
HMW	Higher molecular weight
HPC	high dose positive control
HPLC	High Performance Liquid Chromatography
HR	Hours
HRP	Horseradish peroxidase
HTG	Height gain
HTSDS	Height Standard Deviation Score (Height expressed as number of standard deviations difference from the mean population height for appropriate gender and CA)
HV	Height Velocity
HV SDS	Height Velocity Standard Deviation Score
HVSDSB	Height Velocity Standard Deviation Score for Gender and Bone Score
IDSMB	Independent Drug Safety and Efficacy Monitoring Board
IEF	Isoelectric focusing
IgE	Immunglobulin E
IGF	Insulin-like Growth Factor
IGFBP	Insulin-like Growth Factor Binding Protein
IGFBP 3	IGF binding protein-3
IGF-I	Insulin-like growth factor 1
IgG	Immunglobulin G
IGHD	Isolated Growth Hormone Deficiency
IgM	Immunglobulin M
IPC	immunglobulin positive control
IPC	In process control
IPT	In-Process tests
ITT	Insulin Tolerance Test
IU	International Units
kD	Kilodalton
kDa	Kilodalton
kg	Kilogramme
KIGS	Kabi Pharmacia International Growth Study
L	Litre
LB03002	Biopartners human growth hormone sustained release formulation
LBM	Lean Body Mass
LC	Liquid Chromatography
LDL	Low-Density Lipoprotein
LLOQ	Lower limit of quantification
LPC	low dose positive control
LS	Least Square
MAA	Marketing Authorization Application
mAb	Monoclonal antibody
MCT	Medium Chain Triglycerides
MedDRA	Medical dictionary for regulatory activities
met-rhGH	Methylated rhGH
mg	Milligramme
mL	Millilitre
mo	month
MPC	mid dose positive control
MPHD	Multiple Pituitary Hormone Deficiencies
MS	Mass spectrometry
Mw	Molecular weight
NA	Not Applicable
NC	negative control
NCO	negatice cut off
ng	Nanogramme
NIBSC	National Institute for Biological Standards and Control
OD	Optical density
PAH	Predicted adult height
PC	positive control
PD	Pharmacodynamic(s)
PEG	Polyethylenglykol
Ph. Eur.	European Pharmacopoeia

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PK	Pharmacokinetics
PP set	all randomized patients that either completed the study without any major protocol violation or who terminated the study prematurely due to lack of efficacy
QC	Quality control
qd	once a day dosing
QoL	Quality of Life
rhGH	Recombinant Human Growth Hormone
RIP	Radio immunoprecipitation
RPA	Radio Precipitation Assay
RP-HPLC	Reverse Phase HPLC
s.c.	Subcutaneous(ly)
SAE	Serious Adverse Event(s)
SC	Subcutaneous
SD	Standard deviation
SDS	Standard Deviation Score
SEC	Size Exclusion chromatography
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SR-hGH	Sustained-Release Human Growth Hormone
t½	Terminal Half Life
T3	Triiodothyronine
T4	Thyroxin
TEAE	Treatment Emergent Adverse Event
tmax	Time of Occurrence for Cmax
TSH	Thyroid Stimulating Hormone
UF	Ultrafiltration
USP	United States Pharmacopoeia
UV	Ultraviolet
vs	Versus
wk	Week
WCB	Working cell bank
WE	Western Europe
YCP	Yeast cell protein

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioPartners GmbH submitted on 30 January 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Somatropin Biopartners, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Paediatric patients

Somatropin Biopartners is indicated for long-term treatment of growth failure in children (2 to 11 years old) and adolescents (12 to 18 years old) with an inadequate endogenous secretion of growth hormone.

Adult patients

Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency.

Adult-onset: Patients with 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.

Childhood-onset: In patients with childhood-onset isolated growth hormone deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be performed after completion of growth, except for those having low insulin-like growth factor-1 (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.

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC, as amended - complete and independent application. The applicant indicated that somatropin was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable.

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Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Somatropin Biopartners has been given a Marketing Authorisation in South Korea on 25 August 2006 (adult use) and on 31 January 2008 (paediatric use).

A new application was filed in the following countries: USA.

1.2. Manufacturers

Manufacturer of the biological active substance

LG Life Sciences, Ltd.
Iksan Plant,
601 Yongje-dong,
Iksan-si,
Jeonbuk-do 570-350
South Korea

An inspection of this manufacturing site was carried out by the Competent Authority of Germany. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

Manufacturer responsible for import and batch release in the European Economic Area

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Martina Weise** Co-Rapporteur: **Barbara van Zwieten-Boot**

- The application was received by the EMA on 30 January 2012.

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- The procedure started on 22 February 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2012.
- During the meeting on 21 June 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 June 2012.
- The summary report of the GCP inspection carried out at the following sites; Ukraine, Belarus and Egypt on 26-28 June 2012, 3-4 September 2012 and 6-7 September 2012, respectively, was issued on 8 September 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 November 2012.
- The summary report of the inspection carried out at the following site: LG Life Sciences Ltd, Iksan Plant, between 19-22 November 2012, was issued in December 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 January 2013.
- During the CHMP meeting on 17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 April 2013.
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 3 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 13 May 2013.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Somatropin Biopartners.

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2. Scientific discussion

2.1. Introduction

Somatropin Biopartners contains the active substance somatropin (recombinant human growth hormone, rhGH), which is produced in S. cerevisiae yeast cells by recombinant DNA technology. It consists of a single chain, non-glycosylated polypeptide of 191 amino acids with a molecular weight of 22 kD. Two disulfide bonds are formed between Cys53-Cys165 and Cys182-Cys189 and determine a stable three-dimensional protein structure. Its primary structure is identical to that of the major protein of natural, pituitary-derived human growth hormone (pit-hGH) and to the one of Valtropin, authorised in the EU in 2006 (EMA/H/C/000602) and subsequently withdrawn in 2012 for commercial reasons.

Somatropin Biopartners (also referred to as LB03002), is a new prolonged-release formulation of an established recombinant human growth hormone (somatropin, rhGH) drug substance (INN – somatropin; ATC code H01AC01). Somatropin is formulated in the drug product with the excipients sodium hyaluronate, lecithin, and sodium phosphate buffer in microparticles. The product is supplied as a spray-dried powder in a glass vial, co-packaged together with the solvent injection vehicle, medium chain triglycerides, which is provided in a separate glass vial. The spray-dried powder is intended for reconstitution in the solvent to form a homogeneous milky suspension for subcutaneous injection. Following absorption of water after subcutaneous administration, the microparticles swell and enable the release of solubilised somatropin by diffusion.

Five different strengths are proposed: Somatropin Biopartners 2 mg, 4 mg and 7 mg for a final concentration of 10 mg/ml for use in adults and Somatropin Biopartners 10 mg and 20 mg for a final concentration of 20 mg/ml for use in children. The recommended dose in children is 0.5 mg/kg/w s.c. The recommended starting dose in adults is 2-3 mg/w s.c. with subsequent dosage adjustment based on clinical response and serum IGF-I concentrations.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) may present as isolated hormone deficiency or together with other pituitary hormone deficiencies (Multiple Pituitary Hormone Deficiencies (MPHD)). Deficiency in GH may already develop early in (prenatal) life and, if severe, present clinically with micropenis in males, exaggerated jaundice and/or hypoglycaemia but may also develop and / or manifest later during development or in adult life. The indications for, and the aims of therapeutic intervention are different in the paediatric and the adult population.

The typical symptom of GHD in children is growth failure, and consequently, the aim of treatment is the normalization of the growth rate during childhood and attainment of normal adult height. Therefore, the effects of hGH replacement in children can be evaluated by assessing the increase in height velocity and related auxological parameters as well as bone maturation.

Adult GHD presents with a more subtle and complex syndrome. The clinical features associated with this syndrome are abdominal obesity, decreased lean body mass (LBM), reduced muscle strength and exercise capacity, abnormalities in lipid status, reduced bone mineral density (BMD), dry skin, fatigue and impaired psychological well-being resulting in impaired quality of life (QoL). The increased cardiovascular mortality observed in adult patients with hypopituitarism has been attributed to these metabolic abnormalities. Thus, the aim of treatment of GHD in adults is to reverse the abnormalities in

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body composition (increased body fat, decreased lean body mass and bone mass), improve lipid status (decrease in serum cholesterol, increase in HDL-cholesterol), exercise capacity and QoL.

With current treatment algorithms paediatric rhGH doses are based on the body weight of the growing child which corrects for the higher physiological need for GH during growth compared to adults. IGF-I plasma concentrations should be maintained in the normal age and sex-adjusted range for safety reasons. GH doses for adults are much lower and are given on a mg/d basis; the individual optimal dose is achieved by titration according to clinical efficacy and IGF-I levels. Excessive rhGH doses can induce significant fluid retention and other side effects particularly in the elderly. Thus, monitoring of IGF-I and titration of the dosage to keep the serum IGF-I between the mean and +2 SD for age and gender has become a typical management strategy for adult GHD. A periodic check of IGF-I levels is required because they may increase over time, even if the rhGH dosage does not change.

The efficacy and safety of rhGH is generally recognised. The biological effects of rhGH are equivalent to those of human growth hormone of pituitary origin. The most prominent effect of somatropin is the stimulation of the growth plates of long bones. Additionally, it promotes cellular protein synthesis and nitrogen retention.

2.2. Quality aspects

2.2.1. Introduction

Somatropin Biopartners (also referred to as LB03002), is a prolonged-release formulation of an established recombinant human growth hormone (somatropin, rhGH) drug substance, that allows reducing dosing to once a week. Somatropin is formulated in the drug product with the excipients sodium hyaluronate, lecithin, and sodium phosphate buffer in microparticles. The product is supplied as a spray-dried powder in a glass vial, co-packaged together with the solvent injection vehicle, medium chain triglycerides, which is provided in a separate glass vial. The spray-dried powder is intended for reconstitution in the solvent to form a homogeneous milky suspension for subcutaneous injection. Following absorption of water after subcutaneous administration, the microparticles swell and enable the release of solubilised somatropin by diffusion. The product is presented in five strengths differing in fill weights per vial but with identical compositions. These strengths allow administration of doses from 2 mg to 20 mg rhGH per vial.

2.2.2. Active substance

Somatropin is a recombinant human growth hormone (rhGH) having the same structure of growth hormone produced by the human pituitary. It consists of a single chain, non-glycosylated polypeptide of 191 amino acids with a molecular weight of 22 kD. Two disulfide bonds are formed between Cys53-Cys165 and Cys182-Cys189 and determine a stable three-dimensional protein structure.

The drug substance (LB03002) is derived from yeast *Saccharomyces cerevisiae* by recombinant DNA technology. Methionyl recombinant human growth hormone (met-rhGH) is expressed from the yeast cells, and the N-terminal methionine residue is enzymatically cleaved to yield rhGH of 191 amino acids.

The biological activity of DS has been determined by the rat weight gain assay and a cell proliferation assay. The results of testing using both methods show that the DS meets the requirements of the Ph.Eur. monograph 950 which states the product should have a biological activity of at least 2.5 IU/mg.

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Manufacture

Origin of the Cells and Cell Banking System

The drug substance is produced in *S. cerevisiae*. The development genetics including construction of the expression vector and establishment of the production strain have been adequately described.

The cell banking system was established as a three-tiered cell bank with a Master Cell Bank used to generate an intermediate Master Cell Bank from which the Working Cell Bank (WCB) is prepared. Appropriate characterisation has been performed to verify the sequence and also to demonstrate the genetic stability during cell bank propagation and at the end of production cells. Preparation of the cell banks has been described satisfactorily.

Manufacture

The manufacturing process of Somatropin drug substance comprises three stages: growth / fermentation, harvest / recovery and purification / modification and results in somatropin bulk drug substance, which is stored at -70°C.

The cell growth and fermentation process comprises three sequential culture steps, seed culture I, seed culture II and main fermentation. Following fermentation, the cells are harvested by centrifugation and disrupted to release met-rhGH. This is followed by a chromatography step and precipitation. Further purification is achieved by sequential column chromatography steps and a treatment step to process met-rhGH to met-free rhGH. Another chromatography step removes variants of rhGH while a final chromatography step is used for final polishing of drug substance. Subsequently, the purified rhGH solution is formulated and stored at -70°C.

The approach to development and control of the manufacturing process is a traditional one. The manufacturing steps are monitored by process controls. A classification of in-process control parameters in critical quality attributes, important quality or yield parameters and indirect parameters have been provided. The manufacturing process was validated using small scale and commercial scale batches. The small scale studies demonstrated that the critical operating parameters are suitable to ensure consistent production of drug substance. A prospective validation in a commercial scale has been conducted on 6 consecutive batches of drug substance and focused on consistency of the manufacturing process in its entirety. Both validation campaigns were successfully completed.

Manufacturing process development

Process development included five distinct stages of the somatropin manufacturing process ranging from the "original process" via Transitional processes 1, 2 and 3 to the "definitive process". Since 2004, all of the DS lots used to prepare DP for the phase III clinical trials were manufactured using the definitive process. This definitive process has been validated and is the process which was approved for Valtropin in EU. The development of the commercial ("definitive") process starting from the "original" process is described with sufficient detail. Comparability studies were performed and support the comparability of drug substances produced from the different processes.

Characterisation and Impurities

Characterisation of drug substance has been performed by analytical evaluation of representative drug substance lots and compared to reference standards (Ph. Eur. BRP, NIBSC). The studies were performed using an appropriate panel of orthogonal analytical methods and comprise analysis of the primary structure, modifications in the primary sequence (disulfide bonds, deamidation, oxidation, acid isoforms) as well as studies on the presence of high and low molecular weight forms. In addition, the secondary structure as well as the biological activity has been investigated. Characterisation studies were performed using appropriate state of the art methods such as MS, tryptic peptide mapping and

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LC/MS analysis, IEF, SEC, RP-HPLC, DEAE-HPLC, HI-HPLC and CD. Forced degradation studies have been performed to investigate potential degradation pathways and to conclude on appropriate analytical methods.

Potential impurities include product- and process-related impurities derived from the manufacturing process or degradation of the drug substance during storage. Effective removal of all impurities through the DS purification process has been demonstrated by using a battery of selective analytical methods.

Specification

For the drug substance a specification has been provided which comprises testing of appearance and pH, identity by CE, HPLC (RP, SEC), peptide map and N-terminal sequencing, content assay by SEC, purity by determination of high molecular mass proteins (SEC), related substances including met-rhGH (RP-HPLC), charged variants (CE), host cell proteins and DNA as well as sterility and endotoxin content. This specification is in compliance with the EP monograph.

Most of the analytical procedures mentioned in the specification are compliant to the methods indicated in the EP monograph for Somatropin (950). CE is newly introduced in the commercial process and replaces IEF. The proposed acceptance criteria are referenced from Ph. Eur. The applicant has committed to gather data for subsequent batches and to subsequently revise the limits based on batch analysis. Determination of biological activity has formerly been performed with the rat weight gain assay which has been replaced by a cell proliferation assay (CPA) but is not performed as a routine release assay.

The validation of non-compendial analytical methods is considered acceptable. The methods are validated according to ICH Q2A and all respective method validation reports have been provided. All validation requirements for the respective methods have been met.

The drug substance has a long history, the specification and analytical methods are the same as those approved for drug substance used to make Valtropin (with the exception of the capillary electrophoresis). The acceptance criteria are based on historical data from numerous commercial scale batches and correspond (where appropriate) to the mean ± 2 SD of the results obtained. The acceptance criteria for related proteins and dimer and HMW substances have been tightened compared to the monograph requirements.

Four primary, compendial reference standards (NIBSC, Ph. Eur. CRS) have been used to establish and calibrate in-house reference materials for use in release and stability testing of DS and DP as well as in comparative characterisation studies. Four in-house reference materials have been established to date. A protocol for establishment of a new in-house reference standard has been provided.

Stability

Stability data has been presented for a sufficient number of batches. All results for batches stored at -75 ± 5ºC and -25 ± 5ºC for 36 months comply with the defined specification limits. Accelerated studies determined stability at 5 ± 3ºC and 4 weeks; acceptance parameters were met for 2 weeks. Stability of the drug substance is considered confirmed when stored at -75±5ºC or -25±5ºC up to 36 months in polycarbonate bottles protected from light.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union.

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Comparability exercise for active substance

Not applicable.

2.2.3. Finished medicinal product

The finished product is a prolonged-release formulation somatropin (compound code: LB03002). It is supplied as a spray-dried, sterile powder in a glass 3 mL vial with rubber closure, co-packaged together with the LB03002 drug product solvent, Medium Chain Triglycerides (MCT) Injection Vehicle, which is supplied in a separate 2 mL glass vial. The powder contains the active ingredient (somatropin) which is formulated with the excipients sodium hyaluronate (HA) and lecithin in phosphate buffer (pH 7.5±0.5).

The compositions of the applied LB03002 drug product strengths are presented in Tables 1 and 2 below.

Table 1: *Composition of LB03002 Drug Product*

Component	Function
Somatropin (rhGH)	Active ingredient
Sodium Hyaluronate	Release modulator
Lecithin	Emulsifying agent
Sodium phosphate monobasic monohydrate	Buffering agent
Sodium phosphate dibasic hepta-hydrate	Buffering agent

Table 2: *Reconstitution of LB03002 Drug Product*

Component	Function
Somatropin [b] (rhGH)	Active ingredient
MCT Injection Vehicle [c]	Diluent
Dose concentration	-

Pharmaceutical development

In order to verify that somatropin of the sustained-release formulation has comparable physicochemical and biological properties as rhGH formulated for immediate release, extensive characterisation studies were performed by comparing rhGH extracted from LB03002 with in-house standards, international reference standards and a marketed product. Adequate orthogonal methods were applied for evaluating differences in structure, impurity profile and biological activity. The results confirm identical structure and comparable biological activity.

The choice of the excipients sodium hyaluronate (HA) and lecithin has been justified.

The LB03002 production process consists of preparation of a sterile formulation, production of the powder by spray drying, powder screening, drying and filling. Special emphasis was laid on the development of a suitable spray drying process with the aim to obtain spheric microparticles with a specified size distribution.The impact of high temperature needed for spray drying of LB03002 on rhGH stability and the quality of sodium hyaluronate and lecithin was adequately investigated.

All drug product batches used in phase II clinical study SHCL002 and in the phase III clinical studies were manufactured at commercial scale and at the manufacturing site proposed for commercial

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production. The applicant has provided a clear overview of all changes introduced in the manufacturing process of the drug product during and after the phase III clinical studies. These changes did not adversely affect the quality of the drug product.

The microbiological attributes of the starting materials of LB03002 drug product are specified. Sodium hyaluronate is supplied as a sterile powder and is aseptically processed. Somatropin meets compendial specification for sterility although it is not declared as a sterile drug substance.

Excipients

Sodium hyaluronate (HA) is a glycosaminoglycan consisting of D-glucuronic acid and N-acetyl-D-glucosamine disaccharide units. Evidence has been provided that HA manufacturing process is adequate to assure sterility of the substance prior to introducing the excipient into the aseptic production process for LB03002 product.

The production strain, its development, cell bank system, the raw materials involved in production as well as TSE risk assessment have been addressed.

The proposed release tests provide assurance that the sodium hyaluronate has a pharmaceutical quality in terms of physical properties and purity. Furthermore, it should be noted that LG Life Sciences, Ltd.(LGLS) holds an EU Certificate of Suitability (CoS) for sodium hyaluronate. The CoS confirms that HA as manufactured by LGLS is suitably controlled by Ph. Eur monograph 1472 for Sodium Hyaluronate when supplemented with tests for residual EDTA, residual ethanol and metal ions.

Lecithin is sourced from eggs and the major components are phosphatidylcholine and phosphatidylethanolamine. The quality of the substance is specified according to the respective US-NF monograph. In addition, the specification was supplemented by 18 additional test parameters which are routinely analysed by the supplier. Maximum amounts of the unwanted degradation products lysophosphatidylcholine and lysophosphatidylethanolamine are specified at acceptable levels. All analytical methods are validated.

Adventitious agents

No animal derived materials are used in the manufacture of rhGH drug substance.

The applicant has provided sufficient data regarding TSE and viral safety of the animal-derived substance lecithin, which is used as excipient in LB03002 drug product. TSE safety was also confirmed for the media used for cultivation of the Master Cell Bank in the manufacturing process of the excipient sodium hyaluronate.

Manufacture of the product

LB03002 drug product is manufactured at LG Life Sciences, Ltd., South Korea. A description of the process including the in-process controls has been presented. The entire process from compounding up to capping of the filled vials is conducted under aseptic conditions. Sufficient evidence is provided that the process is capable to assure sterility of the final product.

The final formulated rhGH solution is obtained by adding the rhGH solution to the HA and lecithin mixture.

In-process controls (IPC) have been established and are classified with respect to their criticality on drug product quality. The acceptance ranges of the implemented process parameters are based on the results of process development and are considered justified.

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The manufacturing process was validated by producing three full scale batches. Appropriate activities were conducted for process validation of the formulation and the spray drying steps. Besides measuring all IPCs further parameters were monitored to investigate the impact of the process on hGH purity, on bioburden, on endotoxin contamination and further product properties..

Filters intended for sterile filtration were validated in the presence of lecithin and rhGH solution with respect to retention capacity, flow rate, weight change, bubble point and extractables. Microbiological validation was conducted by media fill runs.

Container closure system

The LB03002 drug product is provided in a Ph.Eur. Type I glass vial. It is closed with a non-laminated chlorobutyl rubber stopper. The two components comply with the respective Ph.Eur. monographs. Appropriate compatibility studies with the selected container closure system including the lubricant silicon oil were performed to demonstrate compatibility with LB03002 drug product.

Product specification

Routine testing of LB03002 drug product at release and end of shelf life will be performed according to the specifications provided. The tests proposed for release of the drug product powder have been selected in accordance with the European Pharmacopoeia monograph for Somatropin for injection. In addition, tests are included for appearance and suspension time, particle size distribution of the suspended powder, in vitro release of rhGH from the suspension, content uniformity, HA content and lecithin content. To better control batch consistency and drug product quality the acceptance ranges for protein related proteins determined by SEC and RP-HPLC and for the assay were revised during the procedure.

The impurity profile of rhGH in LB03002 drug product was studied by applying different orthogonal analytical methods. It can be concluded that a higher amount of dimers, oxidised and deamidated variants is present in LB03002 when compared with reference material. Aggregates were not detectable in a higher amount.

Batch results were provided for all batches produced so far. Approximately 100 commercial batches of different fill weights of LB03002 drug product have been produced at the commercial plant. Whilst predominantly 12 mg rhGH/vial was manufactured batch results are also available for 2 mg rhGH/vial, 9 mg rhGH/vial, 4 mg rhGH/vial and 24 mg rhGH/vial. The results of all test parameters fulfilled the acceptance criteria.

Stability of the product

The proposed shelf-life for the drug product is 36 months at 2-8°C. Several stability studies have been initiated with commercial batches covering the range of fill weight from minimum up to maximum in a bracketing model. The storage conditions comply with ICH requirements. The container closure system used for the stability studies is identical to that of commercial LB03002. Long term stability was tested at 5±3°C, stability under accelerated conditions at 25±2°C / 60%RH.

The batch data provided demonstrate stability of LB03002 drug product when stored at 5 ± 3°C with regard to all parameters tested. The results support the shelf-life and storage conditions as included in the SmPC.

The SmPC requires immediate use after reconstitution.

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In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Medium Chain Triglyceride injection vehicle

The drug product solvent is a mixture of triglycerides of saturated fatty acids, mainly of caprylic (octanoic) and capric (decanoic) acid. The solvent is called Medium Chain Triglyceride (MCT) Injection Vehicle.

The manufacturing process consists of compounding of the calculated amount of Miglyol 812, in-line filtration through 0.22 µm membrane, filling into the vials and stoppering. In order to satisfy the requirements for an aseptic process an adequate limit for bioburden control prior to sterile filtration was established. This limit is in conformance to the generally accepted value. As a result, it can be concluded that sterile filtration and the aseptic production process assure the sterility of MCT injection vehicle.

Process validation demonstrated that the manufacturing process of MCT injection vehicle is adequate to consistently produce LB03002 solvent of the intended quality. The filter device and the filter membrane utilised for sterile filtration were evaluated for compatibility and bacterial retention capacity in the presence of the triglyceride solution.

The testing program and the acceptance criteria for MCT injection vehicle at release conform to the Ph. Eur. monograph. Sterility, endotoxin amount and extractable volume are added to the compendial testing program.

The container closure system of MCT solvent consists of 2 mL colourless Type I glass vials and a chlorobutyl rubber stopper. Both components are claimed to be in compliance with the respective Ph.Eur. monographs although it should be considered that the monograph on rubber stopper is not applicable for oily liquids. Compatibility studies revealed that butylhydroxytoluene (BHT) is leached from the selected rubber stopper and migrates into MCT solution. The amount of BHT in MCT is less than when BHT is used as an antioxidant and does not present a safety concern from a toxicological point of view. Nevertheless, the search of a new and more suitable rubber stopper for MCT diluent is considered crucial. The applicant has agreed to comprehensively study the compatibility of the current and a new rubber material with the container content including potential leaching of BHT and other organic compounds as well as on possible swelling of the rubber material by absorption of the oily liquid.

Stability of 1.5 mL MCT injection vehicle was demonstrated for up to 4 years when stored at 25 ± 2°C. This result supports the claimed shelf life of 48 months for the diluent. After having selected a more suitable rubber stopper, the MCT diluent stability will have to be confirmed by new stability studies.

Stability was further studied at 5°C with two batches of MCT vials filled with 1.0 mL solvent to support a shelf life of 36 months of the final pack (i.e. drug product co-packaged with diluent) at 2-8°C.

Comparability exercise for finished medicinal drug product

Not applicable.

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[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union.

GMP

GMP inspection at the contract manufacturer LG Life Sciences Ltd., Korea conducted by the supervisory authorities on request of CHMP confirmed the suitability of LB03002 manufacturing process as no critical findings were identified which would challenge GMP compliance. The aseptic part of the manufacture of sodium hyaluronate was also inspected and found suitable.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The drug substance LB03002 (somatropin, rhGH) is identical to the one of Valtropin, authorized in the EU in 2006 (EMA/H/C/000602) and subsequently withdrawn in 2012 for commercial reasons. The applicant has provided adequate information on the drug substance production process applied by the manufacturer LG Life Sciences Ltd. (LGLS), Korea. The drug substance part is based on extensive manufacturing experience and is considered to be of good quality.

Consistent performance of the manufacturing process has been demonstrated by process validation studies in small scale and at commercial scale. Extensive characterization studies of the drug substance have been performed and verified the comparability with the reference standards regarding structure, impurity profile and biological activity. Since rhGH production at LGLS has a long history, the specification and analytical methods are nearly all the same as those approved for drug substance used to make Valtropin with the exception of the newly introduced capillary electrophoresis (CE) and are considered appropriate to control LB03002 drug substance quality. Regarding the detection of impurities by CE it is recommended to tighten the drug substance release and shelf life limits for these impurities when more batch analysis data are available.

Five major objections were identified during the assessment procedure concerning the drug product part. These major objections related to the following deficiencies:

- The operational parameters of the spray drying process.

- The sterility of both the drug product powder and the diluent.

- The reconstitution of the drug product.

- The storage following reconstitution and stability data presented.

Following the assessment of the applicant's responses during the procedure, it is concluded that all issues have been adequately and sufficiently resolved.

The development of Somatropin Biopartners spray-dried powder is described in a satisfactory manner. The selected dosage form, the drug product composition in terms of the chosen excipients and the conditions applied during the manufacturing process are sufficiently justified by the findings of appropriate studies during pharmaceutical development. Potential impact of the manufacturing process on the critical quality attributes has been adequately studied. The aseptic manufacturing process was demonstrated to be sufficient under control to consistently produce drug product of the defined quality. Critical process parameters (CPP) have been evaluated during pharmaceutical development and adequate acceptance ranges have been established to keep the process in the intended operating space. The overall control strategy is considered adequate.

The excipient sodium hyaluronate, crucial for obtaining the desired sustained rhGH release, is

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produced by fermentation at LGLS in Korea, the identical manufacturing site as for rhGH and the final product. The purification process was demonstrated to ensure sterile product of sufficient quality to be introduced into the aseptic Somatropin Biopartners production process.

Drug product release and shelf life specification include all relevant quality attributes. Due to the harsher process conditions during spray drying process of rhGH solution, a slightly different impurity profile was found in the spray-dried powder when compared with a liquid rhGH formulation. To ensure an adequate control of the impurity profile, separate specification limits for the individual product-related proteins/impurities are established. Re-evaluation of the currently implemented specification limits is intended when more batch data are available.

Data of stability studies presented in the dossier support the claimed shelf life of 36 months when stored at 2-8°C.

Prior to application the powder has to be suspended by use of Medium Chain Triglyceride (MCT) diluent which is presented in a separate glass container and co-packed with Somatropin Biopartners powder. Based on the data submitted the aseptic manufacturing process and control of the diluent are assessed to be suitable to ensure a product quality adequate for the intended use. However, the selected chlorobutyl rubber closure of the vial was not considered appropriate from a quality point of view as leaching of the preservative butylhydroxytoluene (BHT) from the rubber material into the oily MCT diluent was observed. Thus, the applicant has agreed to undertake a post-authorisation measure to address the quality concern with regards to leaching of the preservative butylhydroxytoluene and other organic compounds from the rubber stopper into MCT diluent. It was concluded that the amount of BHT is highly unlikely to be a causative factor for the observed higher antibody incidence (compared to daily somatropin preparations). Since no safety concern arises from this small amount of BHT, the CHMP considered that the above mentioned request is considered and kept as a recommendation (see section 2.2.6).

No quality aspects impacting on the Benefit-Risk balance have been identified for Somatropin Biopartners.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the assessment of the data package provided in the quality dossier it is concluded that the development, manufacture and control of somatropin drug substance and Somatropin Biopartners drug product are adequate to ensure the production of a medicinal product of sufficient quality in a consistent manner. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to:

    a) gather capillary electrophoresis data for subsequent drug substance batches and revise the limits based on batch analysis;

    b) tighten the drug product release and shelf life limits for total impurity and deamidated rhGH forms by capillary electrophoresis when more batch analysis data are available;

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c) set drug product release and shelf life limits for the maximum amount of any non-deamidated rhGH impurity when more batch analysis data are available.

2. The applicant is recommended to:

a) evaluate swelling of the rubber stopper by MCT diluent and assess migration of additional semi-volatile organic compounds;

b) search for a more suitable stopper and evaluate the potential leachables (BHT as well as other organic compounds) from the candidate;

c) assess both the current and new candidate stopper and choose the rubber stopper with a more suitable leachable profile.

Subsequently, it is recommended that a Type II variation be submitted for the implementation of the new rubber stopper together with the first 6 months stability data including the outcome of the leaching testing.

2.3. Non-clinical aspects

2.3.1. Introduction

Somatropin Biopartners (also referred to as LB03002), is a new prolonged-release formulation of an established recombinant human growth hormone (somatropin, rhGH) drug substance, intended for once weekly subcutaneous injection. Somatropin is formulated in the drug product with the excipients sodium hyaluronate, lecithin, and sodium phosphate buffer in microparticles.

The active substance somatropin (recombinant human growth hormone, rhGH) is produced in S. cerevisiae by recombinant DNA technology. It consists of a single chain, non-glycosylated polypeptide of 191 amino acids with a molecular weight of 22 kD. Two disulfide bonds are formed between Cys53-Cys165 and Cys182-Cys189 and determine a stable three-dimensional protein structure. The active substance is identical to the one of Valtropin, authorised in the EU in 2006 (EMA/H/C/000602) and subsequently withdrawn in 2012 for commercial reasons.

The pharmacological and toxicological effects of somatropins are well known; thus the focus of the non-clinical studies relied on the comparison of LBD-009 (Valtropin) and the new formulation LB03002, which is acceptable given the product characteristics.

GLP aspects

The safety studies on LB03002 and LBD-009/Valtropin and sodium hyaluronate conducted in Korean laboratories were in accordance with the "Good Laboratory Practice Regulations for Non-Clinical Studies" issued by the Ministry of Health and Social Affairs, Korea in October 1987 or the later version issued by the Korea Food and Drug Administration in 2000. The only exceptions where this cannot be verified are (i) the reproductive toxicity studies with LBD-009 where only summary reports are available, lacking individual animal data and relevant certification, and (ii) the safety pharmacology package with LBD-009 where the results are only available as a publication (Lee at al, 1992). Additional safety studies with LB03002, Valtropin and sodium hyaluronate were carried out to GLP standards in USA and EU laboratories.

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2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacological profile of LB03002 has been established through studies using rhGH extracted from LB03002 (the prolonged release formulation) and injected into rats in weight gain and tibia assays and through monitoring the response, in terms of IGF-I and IGFBP-3 levels, of dogs and monkeys to administration of LB03002.

Somatropin extracted from LB03002 shows similar biological activity in a pharmacopoeial rat weight gain assay and almost similar activity in a rat tibia assay when compared with a NIBSC standard. These assays also show similar activity when rhGH extracted from LB03002 is compared with LBD009, which is the same rhGH used in an immediate release formulation authorised under the name Valtropin. However, LB03002 formulation itself has not been tested in the rat weight gain assay.

In dogs and monkeys, plasma IGF-I level was used as a surrogate PD parameter to assess and compare PD activity of LB03002. In dogs and juvenile rhesus monkeys, it was shown that IGF-I plasma levels appear constant or gradually increase after daily injection of aqueous solution of rhGH (LBD-009). In contrast, after administration of LB03002, IGF-I levels peak two-fold (compared to daily administration) on day 2-3 after which these levels drop to approximately base-line levels on day 6-7. A similar pattern of plasma IGF-I levels was shown in cynomolgus monkeys (4 week toxicity study), but IGFBP-3 levels are less consistently elevated when these animals are given doses up to 2 mg/kg/week. In the 4-week study it appears that a tendency to increased IGF-I Cmax levels can be observed with time. Whereas the peak level after day 1 in females in the 2.0 mg/kg group was 2206 ng mL^{-1}, the peak level observed in this group after day 22 was 3836 ng mL^{-1}. IGF-I was not measured in the 26-week study in cynomolgus monkeys and it is not known if a further increase could be expected.

Secondary pharmacodynamic studies

The secondary pharmacodynamics has been established using LBD-009 (Valtropin), the immediate release formulation of rhGH manufactured by LG Life Sciences Ltd.

Besides the effect on weight gain growth plates, hGH also promotes glucose transport into muscles and increased lipogenesis in adipose tissues. The potential effects on LB03002 on glucose levels and epinephrine-induced lipolysis have been evaluated through studies with LBD-009 (Lee et al. 1992; see table 3). No special studies with LB03002 have been performed.

Table 3: Secondary pharmacodynamics evaluation of LBD-009

Parameter	Test Animal/Material	Dose/route	Effect
Blood glucose	Adrenalectomised rats	80 IU/kg, i.v.	20% decrease 20 min. after injection, normal after 40 and 60 min, decrease after 120 min
Glucose tolerance	Rat	40 IU/kg, i.v.	Significant increase in blood glucose 30-120 min. after injection; decrease in glucose tolerance
Lipolysis *in vitro*	Rat Sprague Dawley, Epididymal fat pads	2IU/mL incubation medium	Slight inhibition (33% not significant) of glycerol release in an *in*

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			vitro assay
Epinephrine induced lipolysis	Rat Sprague Dawley, epididymal fat pads	2 IU/mL incubation medium	55% inhibition of glycerol release in an *in vitro* assay

Administration of LBD-009 led to a significant increase in blood glucose levels. The blood glucose concentration was much higher than in the control group indicating a suppressive effect on the glucose tolerance. Administration of LBD-009 was found to suppress the epinephrine-induced lipolysis similar to insulin. The absence of studies with the new formulation LB03002 is acceptable since the pharmacological effects of somatropin are well known.

Safety pharmacology programme

The safety pharmacology has also been established using LBD-009, although the cardiovascular impact was investigated using LBD03002.

Safety pharmacology studies in mice with LBD-009 showed no effect on locomotor activity, rotarod activity, acetic acid induced writhing or the convulsions induced by strychnine or pentylenetetrazole and no effect on hexobarbital-induced sleeping time was observed; in rats, no effect on body temperature was observed; and no intrinsic activity on isolated organs – guinea-pig ileum, rat stomach fundus or rat uterus – could be measured. In contrast to these findings, another study in the literature reported a reduction of hexobarbital-induced sleeping time, which was suggested to be caused by a GH-mediated decrease of CYP450 activity.

Intravenous injection of LBD 009 (5, 10 or 20 IU/kg (1.7, 3.3 or 6.7 mg/kg)) to anaesthetised rabbits did not affect blood pressure, heart rate or respiration. In conscious telemetered male cynomolgus monkeys, subcutaneous doses of 0.2, 0.6 and 2.0 mg/kg of LB03002 had no notable effect on blood pressure, heart rate or the electrocardiogram (RR, PR, QT, QTc intervals; QRS duration), with the exception of one animal showing a large number of premature ventricular complexes (PVC's). The latter observation was considered inherent to this animal, but as there was a dose-related increase in the incidence, a relationship with the administration of the test substance could not be fully ruled out.

Table 4: Safety pharmacology evaluation of LBD-009 and LB03002

Parameter	Test Animal/Material	Test substance	Dose/route	Effect	Reference
Central nervous system	Mouse	LBD-009	20,40 IU/kg, s.c.	No effect	Lee et al 1992
Rectal temperature	Rat	LBD-009	20,40 IU/kg, s.c.	No effect	Lee et al 1992
Writhing test	Mouse	LBD-009	20,40 IU/kg, s.c.	No effect	Lee et al 1992
Antiepileptic effect	Mouse	LBD-009	20,40 IU/kg, s.c.	No effect	Lee et al 1992
Isolated organs	Guinea pig (ileum/trachea)	LBD-009	3×10^{-4}, 1×10^{-3} IU/mL	No effect	Lee et al 1992

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	Rat (fundus/uterus)		1 x 10^{-3} IU/mL		
Respiration and blood pressure	Anaesthetised rabbit	LBD-009	5, 10, 20 IU/kg, i.v.	No effect	Lee et al 1992
Blood pressure, heart rats and ECG	Telemetered monkey	LB03002	0.2, 0.6, 2.0 mg/kg s.c.	No effect	DHJH1002

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed with somatropin, which is acceptable since the pharmacological effects of somatropin are well known. The most relevant pharmacodynamic interactions of growth hormone with other medicinal products have been described in the SmPC.

2.3.3. Pharmacokinetics

Pharmacokinetic data comprise a limited number of comparative assays in dogs where administration of an aqueous solution of rhGH (LBD-009) and LB03002 and different batches of LB03002 are compared, and toxicokinetic data from toxicity studies in juvenile rhesus monkeys and adult cynomolgus monkeys. Additional supportive data are presented consisting of a pharmacokinetic study in rabbits with LBD-009. Furthermore, literature data on distribution, metabolism and excretion of GH are discussed.

The pharmacokinetics of sodium hyaluronate and MCT was not addressed except for a single dose and a repeated dose toxicity study with sodium hyaluronate in dogs where an attempt was made to measure plasma levels of hyaluronate. In these studies all samples were considered to be below the detection limit of 1 µg/mL. Apparently, systemic exposure after subcutaneous administration is very low, which is not unexpected.

GH was measured using ELISAs. Validation reports for these methods were presented and discussed as requested. The validation procedures addressed an appropriate range of features within the assays – including precision, accuracy, linearity, lower and upper limits of quantification and recovery as well as the stability of hGH in serum under the conditions of the storage procedures used.

In pivotal toxicology studies measurement of somatropin and anti-drug antibodies (ADA) was performed using ELISA. The provided data indicate that the presence of GH in the samples has no or a negligible influence on the assay. Although false negative results cannot be ruled out they appear unlikely since monkeys usually do not form antibodies against hGH.

In dogs, the serum concentration curves for the immediate release and the prolonged release formulations clearly demonstrate the slower release and maintained serum levels after administration of LB03002. Respective Cmax values were 109.9 and 77.2 ng/mL for Valtropin and LB03002 with corresponding AUC(0-t) values of 326 and 2158 ng.h/mL, respectively.

In juvenile rhesus monkeys, when the AUC values for comparator groups treated with Genotropin are multiplied by 7, it appears that total exposure was more or less comparable in the Genotropin and LB03002 groups. Cmax levels were also in the same range. In both groups exposure increased less than dose-proportional. Non-linearity was more pronounced in the LB03002 groups.

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In cynomolgus monkeys only LB03002 was investigated (see toxicokinetic data below), both in a 4-week study and in a 26 week study. In general exposure increased with dose, but less than dose-proportional.

Literature data show that in all species investigated (rat, guinea pig, rabbit, sheep and humans), GH is absorbed by the proximal tubules of the kidneys and Kupffer cells of the liver, where it is presumably degraded by lysosomal proteases and subsequently fragments are either released into the circulation or excreted into the urine.

No specific studies have been performed with LBD-009 or LB03002 to investigate possible effects on cytochrome P450 activity but there is no reason to assume that that these entities behave different from other somatropin preparations.

2.3.4. Toxicology

A number of toxicology studies have been submitted. These have been conducted with LB03002 itself and also with the drug substance, LBD-009, or the formulated immediate release product, Valtropin. Studies with sodium hyaluronate produced by LG Life Sciences Ltd. have also been conducted. For LBD-009/Valtropin, these comprise studies on single- and repeat-dose toxicity, genotoxic potential, reproductive toxicity and antigenicity. Studies on single- and repeated dose toxicity have been conducted with LB03002. Single- and repeated-dose studies have been conducted with sodium hyaluronate, which has also been studied for its potential antigenicity and in vitro cytotoxicity.

Single dose toxicity

Table 5: Single dose toxicity studies with LBD-009, LD03002 and sodium hyaluronate

Study ID/ Test article	**Species/ Sex/Number/ Group**	**Dose/Route (Vehicle/formulation)**	**Approx. lethal dose / observed max non-lethal dose**	**Major findings**
S-228/ LBD-009	Mouse (ICR)/ 5/sex/group	0, 5, 10, 20, 40, 80 IU/kg s.c.	>80 IU/kg	None
S-232/ LBD-009	Mouse (ICR)/ 5/sex/group	0, 2.5, 5, 10, 20, 40 IU/kg i.m.	>40 IU/kg	None
S-229/ LBD-009	Rat (Sprague-Dawley)/ 5/sex/group	0, 5, 10, 20, 40, 80 IU/kg s.c.	>80 IU/kg	None
S-233/ LBD-009	Rat (Sprague-Dawley)/ 5/sex/group	0, 2.5, 5, 10, 20, 40 IU/kg i.m.	>40 IU/kg	None
HJH1000/ LB03002	Rat (Sprague-Dawley)/ 5/sex/group	0, 5.0 mg/kg s.c. (medium chain triglyceride)	>5 mg/kg	None
S-328/ Sodium hyaluronate	Rat (Sprague-Dawley)/ 5/sex/group	0, 300 mg/kg s.c.	>300 mg/kg	Swelling at the injection site occurred until day 2.
S-567/ Sodium hyaluronate +TK	Dog (Beagle)/ 1/sex/group	100 mg/kg s.c.	-	Swelling or edema at the injection site until day 3 were observed

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The majority of single dose toxicity studies in rats and mice with rhGH have been conducted with the drug substance LBD-009. Only one study in rats was conducted with LB03002. LBD-009 and LB03002 were both well tolerated after single administration.

Single dose toxicity studies have also been performed with sodium hyaluronate in rats and dogs. The only effects observed were injection site reactions.

Repeat dose toxicity

Table 6: Repeat dose toxicity studies with LBD-009, Vatropin, LB03002 and sodium hyaluronate

Study ID/ Test article/ GLP	**Species/Sex /Number/ Group**	**Dose/ Route**	**Duration**	**NOEL/ NOAEL**	**Major findings**
S-234/ LBD-009 GLP: yes	Mouse (ICR)/ 15/sex/group	0, 1, 3, 10 IU/kg/day s.c.	90 days 28 day interim sacrifice (5 animals/ sex/group)	3 IU/kg	No effects were observed in intermediate or low-dose mice. In the high dose group there was an increase in body weight in male and female animals. Toxicity at the high dose included mortality (2 females), decreased activity, piloerection, decreased respiratory rate, difficulty in breathing and unconsciousness during the second and third weeks of administration. In males at 90 days, increased red blood cell count, haemoglobin and haematocrit, decreased alkaline phosphatase and chloride and increased glucose, total cholesterol, total protein, and albumin were observed. Ninety-day females showed only increased total cholesterol. There were no abnormal gross necropsy findings except for one female that died early on that had white spots on the adrenal gland. Changes in male organ weights at 90 days consisted of increased absolute liver, kidney and spleen weights, increased relative weight of liver and decreased relative weights of brain and testes. In females at 90 days, changes consisted of increases in absolute liver and heart weights, increased relative liver and decreased relative brain weights. Chromosome polyploidy in the liver (both sexes) at 90 days was the only histopathological finding.
S-235/ LBD-009 GLP: yes	Rat (Sprague-Dawley)/ 15/sex/group	0, 1, 3, 10 IU/kg/day s.c.	90 days 28 day interim sacrifice (5 animals/sex/group)	3 IU/kg	In the high-dose males, there was an increase in body weights, absolute spleen, heart and adrenal gland weights, relative spleen weights, and decreased relative brain weight. In the high-dose females, there was an increase in body weights, absolute spleen, ovary, lung, thyroid gland, liver, and kidney weights, and decreased relative heart and brain weights. Haematological findings in males included decreased RBC at 1 and 10 IU/kgday, increased mean corpuscular volume in all dose groups and increased mean corpuscular haemoglobin at 3 and

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Study ID/ Test article/ GLP	Species/Sex /Number/ Group	Dose/ Route	Duration	NOEL/ NOAEL	Major findings
					10 IU/kg/day. No haematological alterations were observed in the females at any dose.
S821/ Valtropin GLP: yes	Rat (Sprague-Dawley)/ 10/sex/group	Control: vehicle Valtropin: 0.2, 2 IU/kg/day Humatrope: 0.2, 2 IU/kg/day s.c.	4 weeks	2 IU/kg	All animals survived until the scheduled sacrifice and there were no treatment-related adverse effects on clinical observations, food consumption, haematology, blood biochemistry, or organ weight data. No gross lesions or histopathological findings indicative of test article effects were observed. Increased bodyweight gain was observed during the first week of treatment in males and females receiving 2 IU/kg/day of Valtropin and females receiving the same dose of Humatrope. Adrenal weights were increased in male animals receiving the high dose of Valtropin and both doses of Humatrope, with adrenal hypertrophy in males. These findings were considered to be related to the primary pharmacological actions of rhGH. Minimal to slight subcutaneous haemorrhage and/or inflammatory cell infiltration were observed microscopically in most injection sites, including control animals. Overall, no toxicologically significant effects were observed following administration of Valtropin, and no differences from Humatrope were observed.
LKY150/002246/ LB03002 GLP: yes +TK	Monkey (cynomolgus) /3/sex/group	0, 0.2, 0.6, 2.0 mg/kg/ week s.c.	4 weeks 4 week recovery	2 mg/kg/ week	All monkeys survived until their scheduled sacrifice. Localised swelling at the injection sites resolved between injections and during the recovery period, however the swelling took longer to resolve in the high-dose group. Aside from the injection site swelling, there were no treatment-related clinical signs of toxicity at any dose level. Similarly, there were no effects of treatment on body weight changes, food consumption, ophthalmoscopic findings, electrocardiogram (ECG) (heart rate), haematological or clinical chemistry values. Urinalyses measurements were unaffected by the test article as were organs weights and macroscopic pathology findings. Microscopic pathology findings were limited to inflammation-related changes at injection sites in all treated and control monkeys. Most of these changes were reduced after the 4-week recovery period. Measurement of circulating growth hormone levels confirmed comparable and dose-related increases in both C_{max} and AUC. No anti-hGH antibodies were detected in this study.
7263-100	Monkey	0, 0.2,	26 weeks	2	All monkeys survived until their scheduled

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Study ID/ Test article/ GLP	Species/Sex /Number/ Group	Dose/ Route	Duration	NOEL/ NOAEL	Major findings
/ LB03002 GLP: yes +TK	(cynomolgus) /4/sex/group	0.6, 2.0 mg/kg/ week s.c.	8 week recovery	mg/kg/ week	sacrifice. There were no treatment-related ophthalmic, electrocardiographic, body weight, serum chemistry, urinalysis, urine chemistry, organ weight, or microscopic changes. Treatment related clinical changes were limited to localised injection site irritation, primarily at the high dose (2.0 mg hGH/kg once weekly) and infrequently at other doses. Elevated total leukocyte, neutrophil, and lymphocyte counts were observed primarily in mid and high-dose groups (males only) at both evaluation periods (weeks 14 and 27). This is consistent with the inflammation noted at the injection sites. Macroscopic and microscopic alterations were restricted to inflammatory changes at the injection site in all groups, including control. The injection sites of the recovery animals were normal. Relative organ weight changes were noted in the reproductive systems of the males, however, these changes were not statistically significant. Microscopic findings were normal in these organs, and the author concluded that these findings were not of biological significance. Measurement of circulating growth hormone levels confirmed comparable and dose-related increases in both C_{max} and AUC. No antibodies were detected in any animal apart from one mid dose female which exhibited antibodies at the end of the study but not at previous sampling times.
7263-130 / LB03002 GLP: yes +TK	Monkey (rhesus, juvenile)/ 3M/group	0.6, 7.0 mg/kg/week Genotropin: 0.086, 1.000 mg/kg/ day s.c.	4 weeks	7 mg/kg/ week	All monkeys survived to scheduled sacrifice on Day 30. Reactions at the injection sites were observed in animals receiving high-dose LB03002. This correlates histopathologically with inflammatory changes at the injection sites (moderate to moderately severe granulomatous inflammatory response with multinucleated giant cells and large vacuoles). There were slight increases in heart and thymus and decreased thyroid/parathyroid weights in these animals. No haematological, blood biochemistry or histological signs of toxicity were observed with either treatment. Circulating hGH and IGF-I levels increased after both treatments, although there was no clear relationship of the latter to either overall dose or the formulation administered. Overall exposure to hGH was similar after LB03002 and Genotropin. No antibodies were detected in response to either LB03002 or Genotropin.

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Study ID/ Test article/ GLP	Species/Sex /Number/ Group	Dose/ Route	Duration	NOEL/ NOAEL	Major findings
S331/ Sodium hyalurona te GLP: yes	Rat (Sprague Dawley)/ 10/sex/group	0, 10, 25, 50 mg/kg/ day s.c.	1 month	25 mg/kg	There were no adverse effects on either bodyweight or food consumption and no clinical signs were observed. Swelling at the injection sites was noted in high-dose animals, probably due to prolonged absorption of the test article, but had subsided prior to the subsequent injection. These swellings correlated on histopathology with mixed inflammatory cell infiltration of the subcutaneous tissue: there was no difference in the degree of inflammation between sodium hyaluronate and Hyruan treated animals. Slight changes in haematological and blood biochemistry parameters were noted in both sodium hyaluronate and Hyruan treated animals, but in the absence of any histopathological correlates, these changes were considered to be of no toxicological importance
P097/ Sodium Hyaluron ate GLP: yes +TK	Dog (Beagle)/ 1/sex/group	0, 5, 10 mg/kg/ day	1 month	10 mg/kg	Clinical signs were restricted to swelling at the injection sites in treated animals, attributed to the slow absorption of the test article, and macroscopic examination showed residues of injected material at the injection sites.

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The 90-day repeat-dose toxicity studies in mice and rats were conducted with the drug substance, LBD-009, after daily s.c. administration. In these studies body weight increased in male and female mice and rats in the highest dose groups without a significant increase in food consumption. This reflects the pharmacological activity of growth hormone. More toxic effects were observed in mice compared to rats. These included changes in haematological (increase in erythrocyte numbers, haemoglobin and haematocrit) and biochemical (increase in cholesterol, glucose, protein and albumin, decrease in alkaline phosphatase and chloride) parameters and changes in organ weights (increase of kidneys, adrenals, liver and ovaries weights, decrease in brain weight). Histopathological effects in mice included liver cell polyploidy. No histopathological changes were observed in rats. Effects in rats included haematological changes in males (decreased RBC, increase in mean corpuscular volume and mean corpuscular haemoglobin), increase and body weight and changes in organ weights. No toxicokinetic data have been generated in these studies and, therefore, no exposure margins to the human exposure could be calculated. The NOAELs in these studies were 3 IU/kg/day for both mice and rats.

The sustained release formulation LB03002 as intended for human use was tested in cynomolgus monkeys (see also section on toxicokinetic data below).

In the 4-week and 26-week repeat dose toxicity studies in cynomolgus monkey the only toxic effect were injection side reactions primarily in the high dose groups, but also occurred in lower dose groups as well as in the vehicle control group. These included swelling at the injection site and histopathologically inflammatory changes at the injection site. The NOAELs for systemic effects in the 4-week and 26-week studies were 2 mg/kg/week and > 2mg/kg/week, respectively.

In the 4-week study in male juvenile rhesus monkeys the weekly administration of LB03002 was compared to daily administration of Genotropin. This study did not include a control group. Swelling at the injection site which correlates histopathologically with inflammatory response was observed in animals receiving the high dose of LB03002. Only minor changes at the injection site were observed in the other groups, including the groups receiving Genotropin. The NOAEL for systemic effects for LB03002 in this study was > 7mg/kg/week.

Cmax exposure comparisons to adult humans at the NOAELs in the adult cynomolgus monkeys studies were in the range 29.3 to 76.4 with the corresponding range based on AUC of 26.0 to 56.6. In children, taking also the study in juvenile rhesus monkeys into consideration, exposure margins based on Cmax ranged from 2.2 to 9.3 with corresponding AUC-based margins in the range 2.1 to 10.3.

Two 4-week repeat dose toxicity studies after s.c. administration were performed with sodium hyaluronate in rats and dogs. In both studies the only substance-related toxic effect were swelling at the injection site which correlates histopathologically with inflammatory changes.

No anti-hGH antibodies were detected in repeat dose toxicity studies in monkeys with LB03002. In anaphylaxis studies with LBD-009 positive results were only seen in guinea pigs.

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Genotoxicity

Table 7: Overview of genotoxicity studies with somatropin (as Valtropin or LBD009) or hyaluronic acid:

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Studies with somatropin			
Gene mutations in bacteria/S-258/yes/LBD009	Salmonella strains TA 98, 100, 1535, 1537	+/- S9: 0-1.6 IU/plate	Negative
Gene mutations in bacteria/S-822/yes/Valtropin	Salmonella strains TA 98, 100, 1535, 1537, E.coil WP2uvrA	+/- S9: 0-3 IU/plate	Negative
Chromosome aberrations in mammalian cells/S259/yes/ LBD009	CHO-cells	+/- S9: 0-1.6 IU/plate	Negative
Chromosome aberrations in mammalian cells/S823/yes/ Valtropin	Chinese hamster lung cells (CHL)	+/- S9: 0-3 IU/plate	negative
Chromosomal aberrations in vivo/S260/yes/LBD009	Mouse ICR, 6/sex/dose group, micronuclei in bone marrow	0, 40, 80, 160 IU/kg/d i.p., for 3 days, sampling 24h post last dose	negative
Chromosomal aberrations in vivo/S824/yes Valtropin	Mouse ICR, 6/sex/dose group micronuclei in bone marrow	0, 2, 5, 10 IU/kg/d, i.p., sampling 24h post last dose	negative
Studies with hyaluronate			
Gene mutations in bacteria/S-944/yes/	Salmonella strains TA 98, 100, 1535, 1537, E.coil WP2uvrA	+/- S9: 0-1000 µg/plate	Negative

Gene mutations in mammalian cells/1405/43- D 6173/yes	L5178Y cells	+/- S9: 0-1000 µg/ml	Negative

LBD009 has been tested *in vitro* and *in vivo* for genotoxic potential with negative results and the matrix substance of the formulation sodium hyaluronate was tested *in vitro* for genotoxicity with also negative results.

Carcinogenicity

Carcinogenicity studies with the API have not been performed because antibody formation against this human material can be expected in rodents. There are life time carcinogenicity studies in rodents available in public literature employing recombinant rat and mouse growth hormone (Farris et al. 2007). These long term studies did not provide any evidence for a biologically relevant tumorigenic potential of recombinant growth hormone.

Reproduction Toxicity

A full range of reproductive toxicity studies with LBD-009 have been submitted. In these studies no pharmacodynamic effects, especially increase in body weights in parent animals, were observed. Overall, no significant differences between non-treated and treated animals and their offspring were seen. In contrast to LBD-009, LB03002 also contains hyaluronate, lecithin and medium chain triglycerides. However, these substances are not expected to adversely affect pregnancy outcome.

Animal studies with this medicinal product are not sufficient to fully assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin products there is no evidence of an increased risk of adverse reactions to the embryo or foetus. Doses in excess of human therapeutic doses have shown adverse effects on reproductive function in male and female rats and male dogs, possibly through disruption of hormonal regulation. In rabbits and monkeys no adverse effects were observed.

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Table 8: Reproduction toxicity studies with LBD-009

Study type/ Study ID / GLP	**Species; Number Female/ group**	**Dose &route**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Male fertility Female fertility/ SNUV 92-001	Rat, Sprague-Dawley 80 F 40 M	0, 1, 3, 10 IU/kg/ day s.c.	Males – from day 60 premating Females – from day 14 premating to day 7 of gestation	slight increase in the number of dead foetuses (1, 2, 3 and 4% at 0, 1, 3 and 10 IU/kg/day, respectively)	NR
Embryo-fœtal development SNUV 92-002	Rat, Sprague-Dawley 120 F	0, 1, 3, 10 IU/kg/ day	GD 7-17	slight increase in the number of dead foetuses (0.54, 3.88, 4.85 and 4.72% at 0, 1, 3 and 10 IU/kg/day, respectively)	NR
Embryo-fœtal	Rabbit, New	0, 1, 3, 10	GD 6-18	None	NR

Study type/ Study ID / GLP	Species; Number Female/ group	Dose &route	Dosing period	Major findings	NOAEL (mg/kg &AUC)
development	Zealand White 48 F	IU/kg/ day			
Peri & postnatal	Rat, Sprague-Dawley 80 F			None	NR

NR = not reported

Toxicokinetic data

Table 9: Toxicokinetic studies with LB03002 and sodium hyaluronate

Study ID	Test article	Day (d)/week (w)	Daily Dose (mg/kg/ week)	Cmax (ng/ml))		Tmax (h)		Animal AUC (ng.h/ml)		Animal:Human Exposure Multiple	
				♂	♀	♂	♀	♂	♀	♂	♀
4-week cynomolgus monkey/ LKY 150/002246	LBD03002	1 (d) 1 (d) 1 (d) 22 (d) 22 (d) 22 (d)	0.2 0.6 2.0 0.2 0.6 2.0	39.6 76.9 167.1 77.6 74.9 133.8	46.2 77.7 131.9 46.8 90.94 162.6	6 6 12 24 6 12	12 12 12 6 72 12	2050 2138 5315 3257 3170 5706	2509 3330 5557 1423 5772 5812	ND	ND
26-week cynomolgus monkey/ 7263-100	LBD03002	1 (d) 1 (d) 1 (d) 13 (w) 13 (w) 13 (w) 26 (w) 26 (w) 26 (w)	0.2 0.6 2.0 0.2 0.6 2.0 0.2 0.6 2.0	42.5 108 248 74.1 99.1 344 44.5 84.2 252	64.5 130 225 97.9 113 140 97.8 136 181	4.5 7.5 10.0 22.5 6.0 9.0 22.5 7.5 10.0	6.0 6.0 8.0 39.0 6.0 7.0 27.0 6.0 10.0	746 1942 5882 2425 2597 8103 1679 2175 8723	865 2180 5014 4305 3215 4005 3497 4704 5885	ND	ND
4-week juvenile rhesus monkey 7263-130	LBD03002	1 (d) 1 (d) 22 (d) 22 (d)	0.6 7.0 0.6 7.0	99.9 658 94.1 331	NA NA NA NA	4.0 10.0 4.0 14.0	NA NA NA NA	3791 16782 2027 11013	NA NA NA NA	ND	ND
Single dose dog/ S567	Sodium Hyaluronate		100	All levels below LLOQ						NA	NA
4-week dog/ P-097	Sodium Hyaluronate		5 10	All levels below LLOQ						NA	NA

ND = not determined; NA = not applicable; LLOQ = lower limit of quantification

In the 4-week monkey study with LB03002, the rate and extent of systemic exposure of the monkeys to hGH appeared to be characterised by non-linear (dose-dependent) kinetics over the dose level range 0.2-2.0 mg hGH/kg once weekly. At the two higher dose levels (0.6 and 2.0 mg/kg once weekly) on days 1 and 22, the maximum concentration (Cmax) and area-under-the-curve (AUC) from zero to 168 h values of hGH were consistently higher than those values in the control group (data not shown).

Toxicokinetic evaluations of the 26-week monkey study administered LB03002 demonstrated that hGH serum levels increased across all three dose levels although the variability within groups was large. The increases in hGH mean Cmax and AUC (over 0-72 hours) values were less than proportional to the increase in dose on the three collection days. Generally, concentrations of hGH declined slowly and were above the pre-dose levels 72 hours postdose. There were neither consistent differences between sexes, nor changes due to multiple dosing with regard to mean Cmax and AUC(0-72h) values. The author

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stated that the results should be interpreted with caution due to the presence of variable baseline concentrations of growth hormone in these animals.

In the 4-week juvenile monkey study with LB03002, exposure to rhGH generally increased as the dose level increased with both test articles, although levels increased more slowly with LB03002 than with Genotropin. Cumulative exposure is expected to be similar if LB03002 is given once a week compared with daily administration of Genotropin.

The data for LB03002 show some variability between doses within a single study, with a clear dose-response relationship not always reflected in these mean AUC values, and between studies in that the same dose did not always produce the same effect in different studies. The applicant argues that the reasons underlying these variations remain obscure though are not unexpected given the differences in species and ages of the animals used in the studies. Overall, however, the data show that repeated weekly administration of LB03002 provides a plasma level of growth hormone which is maintained with successive administrations.

Local Tolerance

Local tolerance of LB03002 has been tested as part of repeat dose toxicity studies in monkeys. In these studies some signs of irritation at the injection site were observed, primarily in the high dose groups, but were also observed in lower dose groups as well as in the vehicle control groups. In addition, local tolerance was also tested for hyaluronic acid as part of the repeat dose toxicity studies in rats and dogs. In these studies slight swelling of the injection site with inflammatory changes was observed in animals treated with hyaluronic acid probably due to prolonged absorption of the test material. The presence of (vacuolated) macrophages, multinucleated giant cells, inflammatory cell infiltrate, fibrosis, epidermal hyperplasia and ulceration were in line with an inflammatory response of the subcutis to tissue damage and/or presence of foreign material.

Other toxicity studies

Antigenicity

The potential antigenicity of sodium hyaluronate was investigated in mice and guinea pigs. Apart from a weak positive result in the skin sensitisation test in guinea pigs, no antigenicity was observed in mice and guinea pigs in the PCA assay and in guinea pigs in the active systemic anaphylaxis test. No cytotoxicity was observed for sodium hyaluronate in an *in vitro* study in L929 cells

2.3.5. Ecotoxicity/environmental risk assessment

LB03002 is a prolonged release formulation of recombinant human growth hormone (hGH). The protein is identical to the naturally occurring pituitary-derived hGH and is rapidly and completely degraded in humans by enzymatic hydrolysis. Thus, the therapeutically administered compound is not released into the environment. Moreover, as the peptide structure of hGH renders it readily susceptible to microbial hydrolytic processes, inadvertent release of waste material would also not cause any environmental problems.

CHMP guidelines on environmental risk assessment (Guideline on the environmental risk assessment of medicinal products for human use: EMEA/CHMP/SWP/4447/00) recognise the particular situation of protein-based medicinal products in that they are unlikely to result in significant risk to the environment. Consequently, and taking into account the rapid breakdown on hGH after administration, no environmental risk can be expected from the introduction of LB03002 into therapy.

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2.3.6. Discussion on non-clinical aspects

The pharmacological and toxicological effects of somatropins are well known; thus the focus of the non-clinical studies relied on the comparison of LBD-009 (Valtropin) and the new formulation LB03002, which is acceptable given the product characteristics.

GH pharmacokinetics of the retarded formulation LB03002 differed from the unretarded product as expected and intended. Assay validations were comprehensive in defining the parameters of the assays and can be considered suitable for the measurement of samples from the toxicology studies: the resulting bioanalytical results can be concluded to be valid.

The pharmacodynamic effects of the active substance of the preparation were as expected for GH. Retardation led to a somewhat different temporal pattern of the resulting IGF-I plasma levels in animals. The same phenomenon was observed in humans (see clinical section below).

Toxicity studies did not reveal unexpected findings.

2.3.7. Conclusion on the non-clinical aspects

The results of non-clinical studies do not raise safety concerns.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

During the assessment no issues of concern with respect to GCP were detected in the clinical studies. A routine GCP inspection initiated by the EMA concerning study BPLG-004 was performed and did not reveal findings that would question the validity and reliability of the pivotal clinical data.

- Tabular overview of clinical studies

The clinical development programme of LB03002 comprises the following studies to assess clinical pharmacology, efficacy, and safety of LB03002.

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Table 10: Overview of clinical studies

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
SHCL-001	Phase I, single-dose, single-centre, double-blind, randomized, placebo-controlled, dose escalation to investigate the safety, tolerability and PK of LB03002 pharmacokinetic profile of three ascending single doses of LB03002	healthy adult volunteers	randomized: 24 treated: 18 6 volunt.: 0.2 mg/kg 6 volunt.: 0.4 mg/kg 6 volunt.: 0.6 mg/kg 6 volunt.: Placebo	24 male volunteers	10 days (single dose study)
BPLG-002	Phase II, single-centre, single-arm, non-randomized, uncontrolled to determine the safety and PK/PD profile of an individualized dose of LB03002 based on the pt's previous daily rhGH dose	adults with GHD	9 (all treated) 8 evaluable (1 outlier)	6 male patients 3 female patients	5 weeks
BPLG-003	Phase II/IIIa, Assessor Blinded (Partially Blinded), Randomised, Active-Controlled, Multicentre, Parallel-Group Study of the Safety, Efficacy and Pharmacokinetics / Pharmacodynamics of LB03002 patients and assessors blinded to the dose level of LB03002	paediatric patients with GHD	51 enrolled (37 analysed, one centre excluded)	51 prepubertal children with GHD	12 months comparative Phase for PK/PD-parameter (3 years in total)
BPLG-004	Phase III, multi-centre, open-label, randomized, parallel-group study of a sustained release formulation of rhGH (LB03002) in pre-pubertal, treatment naïve children with insufficient secretion of endogenous growth hormone. open label extension BPLG-004 EXT	pre-pubertal, treatment naïve children with insufficient secretion of endogenous growth hormone	178 (91 in the LB03002 group 87 in the comparator Genotropin group)	178 pre-pubertal children with GHD	12 months
BPLG-005	Phase III, double-blind, randomized, placebo-controlled, parallel-group, multi-centre study to assess efficacy and safety of LB03002 administered weekly in adults with GHD	adults with GHD	151	Male or female patients with GHD of either adult onset (AO), or failure which occurred at least 1 year before study entry	26 weeks
BPLG-005-RO	Phase III, open-label, uncontrolled, multi-centre, rollover study to assess safety and efficacy of LB03002, administered weekly in adults with GHD	adults with GHD	136	136 adults patients with GHD were carried over from study BPLG-005 into this rollover study	26 weeks

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2.4.2. Pharmacokinetics

PK and PD data were derived from the following studies:

SHCL-001: Phase I in healthy adults

BPLG-002: Phase II in adults with GHD

BPLG-003: Phase II/IIIa in children with GHD

Bioanalytical methods

Four methods were used in total: one for somatropin, one for IGFBP-3 and two for IGF-I (chronologically: until 2006 and from 2006 onwards). The assays were based on commercial kits. Appropriate validation by the applicant was performed.

Pharmacokinetic and statistical data analysis

PK parameters were derived from concentration-time data, and were estimated by non-compartmental methods using software WinNonlin Version 3.0, Pharsight Corporation, Mountain View, CA, USA, 1999. PK data were obtained from three clinical pharmacology studies. For descriptive statistics of PK and PD parameters, N, geometric mean, geometric CV%, arithmetic mean, SD, SEM, CV%, minimum, median and maximum values were calculated. Effect of treatment on LB03002 PK and PD parameters (rhGH, IGF-I, IGFBP-3) has been performed on log-transformed, dose-normalized values (C_{max} and AUC) using ANOVA. The PK data analysis and statistical data analysis are considered appropriate.

Absorption

Following repeated weekly subcutaneous administration of a mean dose of 4.4 mg prolonged release somatropin to adults with GHD the C_{max} and t_{max} of serum hGH were about 4.5 ng/mL and 15 h respectively. The apparent terminal half-life was about 16.8 h in adults, presumably reflecting slow absorption from the site of injection.

Table 11: Summary of PK results (somatropin) (ND, not done)

Parameter	Somatropin dose	SHCL001			BPLG-002		BPLG-003			
		0.2 mg/kg	0.4 mg/kg	0.6 mg/kg	4.7 ± 1.5 mg / 4.4 ± 1.2 mg	Daily rhGH 0.6 ± 0.3 mg	0.2 mg/kg /w	0.5 mg/kg /w	0.7 mg/kg /w	Daily rhGH 0.03 mg/kg /d
C_{max} (ng/mL)	1st dose	35.5 (11.3)	52.0 (27.3)	145 (64.6)	6.1 (3.2)	ND	32.8 (21.1)	81.9 (41.7)	87.4 (51.9)	ND
	Steady state	ND	ND	ND	4.5 (2.2)	2.7 (2.2)	37.2 (12.7)	63.6 (19.9)	109 (103)	21.3 (5.53)
t_{max} (h)	1st dose	3.00 (3, 12)	7.50 (3, 24)	3.00 (1, 6)	7.5 (3.2, 15)	ND	10.5 (3, 36)	10.5 (3, 24)	24.0 (3, 36)	ND
	Steady state	ND	ND	ND	15 (9, 48)	3.5 (2.0, 4.1)	12.0 (3, 24)	12.0 (3, 36)	24.0 (3, 24)	3.0 (2, 4)
$AUC_{0-\infty}$ (µg•h/mL)	1st dose	0.827 (0.104)	2.004 (0.318)	3.780 (0.331)	0.184 (0.078)	ND	0.67 (0.24)	2.05 (0.84)	2.68 (0.69)	ND
	Steady state	ND	ND	ND	0.154 (0.055)	0.023 (0.015)	0.79 (0.11)	1.84 (0.33)	2.66 (0.65)	0.15 (0.03)
AUC/Dose µg•h /mL /(mg/kg)	1st dose	ND	ND	ND	3.47[1]	ND	3.72 (1.30)	4.11 (1.68)	3.83 (0.99)	ND
	Steady state	ND	ND	ND	3.08[1]	3.29[1]	3.95 (0.56)	3.68 (0.66)	3.80 (0.93)	5.14 (1.41)
$t_{½}$ (h)	1st dose	9.22 (1.89)	10.9 (3.25)	17.2 (5.08)	11.9 (4.5)	ND	8.83[5] (7.20)	6.83[5] (1.72)	9.26[5] (2.01)	ND
	Steady state	ND	ND	ND	16.8 (12.6)	5.1 (2.6)	6.10[5] (1.32)	7.56[5] (1.73)	10.7[5] (6.44)	2.60 (0.83)

*Median (Min, Max), otherwise: mean (SD) is depicted

Since the cumulative per body weight doses of LB03002 and Genotropin in children differ from each other (0.5 kg/kg/wk vs. 7∗0.03 mg/kg/d = 0.21 mg/kg/wk), the applicant provided a direct comparison of the exposure data for the LB03002 preparation and the reference product Genotropin (taken from the paediatric study BPLG-003). Due to a recently published French population-based registry-study (Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE), Carel et al., J Clin Endocrin Metab, 2012, 97: 416-425), daily GH doses of above 0.05 mg/kg are not recommended. Thus, the applicant also compared the GH exposure due to weekly LB03002 treatment with the (calculated) GH exposure which can be expected with daily dosing of 0.05 mg/kg Genotropin. The results are provided in the table below.

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Table 12: Comparison of GH PK data of measure and calculated values

Product	LB03002	Genotropin	Max. rec. daily dose*	Ratio	
				LB03002 / Genotropin	LB03002 / max. rec. daily dose
Conditions					
Dose (mg/kg)	0.5	0.03	0.05		
Frequency	weekly	daily	daily		
Sampling time point	Week 13	Day 7	Extrapolated from Genotropin (0.03 mg/kg daily)		
Measure / calculated data					
Weekly dose (mg/kg)	0.5	0.21	0.35	2.38	1.43
GH AUC**tau** [µg*h/mL]	1.81 (18.4)	0.166 (29.7)			
GH AUC**ss(7d)** [µg*h/mL]	1.81 (18.4)	1.162**	1.94	1.56	0.93
GH C**max** [ng/mL]	60.7 (34.1)	25.8 (51.9)	43	2.35	1.41

*Max. rec. daily dose = maximum recommended daily dose (EMA/110423/2012)
** AUCss(7d)[1.162] = AUCtau[0.166]x7
Figures are geometric means , values in brackets are CV%.

It can be derived from the table that the weekly exposure ratio of LB03002 at the proposed dose of 0.5 mg/kg/week vs. Genotropin at a dose of 0.03 mg/kg/day is 1.56. The dose ratio is 2.4 (see above), hence the bioavailability of GH from LB03002 is around 35% lower than of GH from Genotropin. With these data it can be calculated that the exposure following one dose of LB03002 equals the exposure that would result from seven doses of 0.047 mg/kg Genotropin. Hence, LB03002 leads to an extent of exposure towards GH that lies below the maximally recommended daily dose of 0.05 mg/kg.

Distribution and Elimination

Distribution as well as elimination of LB03002 was not investigated. The applicant justifies this by claiming that the aim of PK/PD investigations of LB03002 was to generate data in support of the once-weekly administration as a suitable substitute to the immediate-release rhGH formulations. Based on the same justification, no gender comparisons, drug interaction studies, renal impairment studies, and hepatic impairment studies were conducted. Current scientific evidence assumes somatropin is hydrolysed after receptor binding and internalisation of the ligand-receptor complex. Afterwards, somatropin is subject of the protein catabolic enzyme-machinery in both the liver and the kidney. Thus, the applicant decided that no studies on genetic polymorphism are necessary. After i.v. injection, somatropin has a biphasic clearance curve with a half-life of 9.0 ± 3.5 min for the first phase over 60 min, and 30.7 ± 10.8 min for the second phase between 60 and 120 min. The mean terminal half-life after i.v. administration in healthy adult males is estimated to be 19.5 ± 3.1 min. Currently, eight somatropin-containing medicinal products are approved in the EU all of which share the same primary structure. Therefore, the difference to this MAA to a large extend is of pharmacokinetic nature and the argumentation of the applicant can be agreed.

Dose proportionality and time dependencies

Time dependency was investigated in two multiple dose studies, where PK-parameters from first-dose administration were compared with steady state. These two studies were: BPLG-002 for comparison in adults and BPLG-003 for comparison in the paediatric population. Sustained release form of LB03002 in these studies shifts t_{max}:

- from 7.5 h (1st week) to 15 h (5th week), in study BPLG-002 in adults;

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- from 10.5 h (1st week) to 12 h (13th dose after 3 months) for the 0.5 mg/kg/w in study BPLG-003 in children.

For means of comparison: after s.c. injection of daily applied somatropin (comparative arm of studies BPLG-002 and BPLG-003), peak serum levels were achieved after 3.5 hours (adults with GHD) and 3 hours (children with GHD), respectively.

In all populations under investigation, dose-dependency could be demonstrated. In healthy adults it appears to be however slightly greater than a linear dose proportional manner at 0.6 mg/kg: for LB03002 dose ratios of 1:2:3, the corresponding AUC_{0-t} and C_{max} ratios were 1 : 2 : 4.5 and 1 : 1.5 : 4.1, respectively. In children, C_{max} and AUC_{tau} increased approximately proportionally with dose at both time-points under investigation: at the beginning and after 3 months of weekly administration.

Special populations

Studies in special populations were not conducted (hepatic or renal impaired patients). Specially designed studies to investigate distribution, metabolism, elimination, and influence of genetic polymorphism on drug metabolism or PK parameters in general were not conducted. In view of the long experience and the regulatory status of the active compound Somatropin this is acceptable.

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies were conducted, which is acceptable given the product characteristics.

Pharmacokinetics using human biomaterials

Human biomaterial studies were not conducted, since the active ingredient of LB03002 is identical to the immediate-release rhGH in many marketed products.

2.4.3. Pharmacodynamics

Mechanism of action

All known pharmacodynamic effects of somatropin result from binding to and activating the somatropin receptor. This receptor protein is a widely distributed cell-surface receptor and belongs to the cytokine receptor superfamily. Somatropin exerts its effects by a dual mechanism including direct effects via the GH-receptor and indirect action mediated by IGF-I, which is produced in response to GH stimulation both in the liver and locally in various tissues. Somatropin has two main effects on body composition: Lipolysis and protein anabolic effects. Lipolysis is triggered indirectly and directly by somatropin receptors on the surface of lipocytes. In contrast, anabolic effects are mainly triggered via IGF-I. IGF-I measured in the blood is biosynthesised in the liver and released into the blood stream upon somatropin acting upstream of this biochemical axis. IGF-I in plasma is usually bound to IGFBP-3 and acid-labile-subunit (ALS), resulting in a tripartite bound form acting as a pharmacokinetic compartment in reducing free IGF-I plasma levels. The insulin-like growth factor type 1 receptor as well as the somatotropin receptor is a membrane anchored, hetero-tetrameric tyrosine kinase. Both receptor types (GH and IGF-I) are involved in transducing macroscopic clinical effects. However, 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 IGF-I. For this reason, the

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applicant apart from analysing GH blood concentrations also decided to analyse IGF-I and IGFBP-3 levels (at least in part) as a pharmacodynamic endpoint, which is considered appropriate.

Primary and Secondary pharmacology

Primary pharmacology

Somatropin accelerates the growth of bones and stimulates muscle growth while body fat is reduced by lipolysis. It also stimulates soft tissue and organ growth by promoting cell proliferation and amino acid turnover. However, a switch in influencing blood glucose levels occurs in a time-dependent manner. The comprehensive physiological effects may serve to explain the need for somatropin substitution in GH-deficient children and adults. Throughout this MAA no clinical trials were conducted with a specialized focus on the investigation of new pharmacological properties of somatropin itself, which is considered acceptable.

Relationship between dose and effect

The profiles of IGF-I and IGFBP-3 were investigated in the three studies SHCL-001, BPLG-002 and BPLG-003 (IGF-I only in Phase I study SHCL-001). IGF-I plasma / serum levels were determined 96 hours after administration of LB03002. The pharmacodynamic results from these studies are depicted in the following table.

Table 13: Summary of IGF-I results (ND, not done)

Parameter	Somatropin dose	SHCL001			BPLG-002		BPLG-003			
		0.2 mg/kg	0.4 mg/kg	0.6 mg/kg	4.7 ± 1.5 mg / 4.4 ± 1.2 mg	Daily rhGH 0.6 ± 0.3 mg / d	0.2 mg/kg /w	0.5 mg/kg /w	0.7 mg/kg /w	Daily rhGH 0.03 /kg/d
C_{max} (ng/mL)	1st dose	927.3 (188.4)	908.3 (164.3)	1191.3 (51.8)	236 (51)	ND	81.0 (106)	67.9 (44.3)	164 (118)	ND
	Steady state	ND	ND	ND	199 (46)	215 (78)	113 (130)	165 (99.2)	109 (103)	51.4 (44.3)
t_{max}* (h)	1st dose	48.0 (NC)	48.0 (NC)	72.0 (NC)	48 (24, 48.1)	ND	36.0 (36,168)	48.0 (36, 48)	72.0 (48, 72)	ND
	Steady state	ND	ND	ND	48 (48, 72)	15.0 (9.1, 24)	36.0 (24, 48)	36.0 (36, 48)	48.0 (36, 48)	12.0 (0, 24)
$AUC_{0-\infty}$ (µg•h/mL)	1st dose	ND	ND	ND	18.23 (4.16)	ND	7.54 (10.0)	5.54 (4.48)	9.86 (5.36)	ND
	Steady state	ND	ND	ND	16.04 (3.91)	4.3 (1.6)	9.38 (11.8)	13.8 (9.29)	13.6 (9.44)	4.24 (4.02)
AUC/Dose µg•h /mL /(mg/kg)	1st dose	ND	ND	ND	344	ND	37.7 (50.2)	11.1 (8.96)	14.1 (7.65)	ND
	Steady state	ND	ND	ND	321	614	46.9 (58.8)	27.6 (18.6)	19.5 (13.5)	141 (134)

*Median (Min, Max), otherwise: mean (SD) is depicted

Study SHCL001 shows that plasma IGF-I levels appear to increase with a prolonged kinetic profile in a dose-dependent manner. However, limited interpretation should be based on a single dose administration.

In general, plasma $t_{1/2}$ of IGF-I is longer compared to that of somatropin. However, as can be expected, this difference only becomes evident when the prolonged weekly formulation is given. The fluctuation range of IGF-I, thus, is higher in LB03002-treated patients compared to that observed with daily somatropin administration. However, the mean plasma-level does not differ substantially in daily and weekly given formulation.

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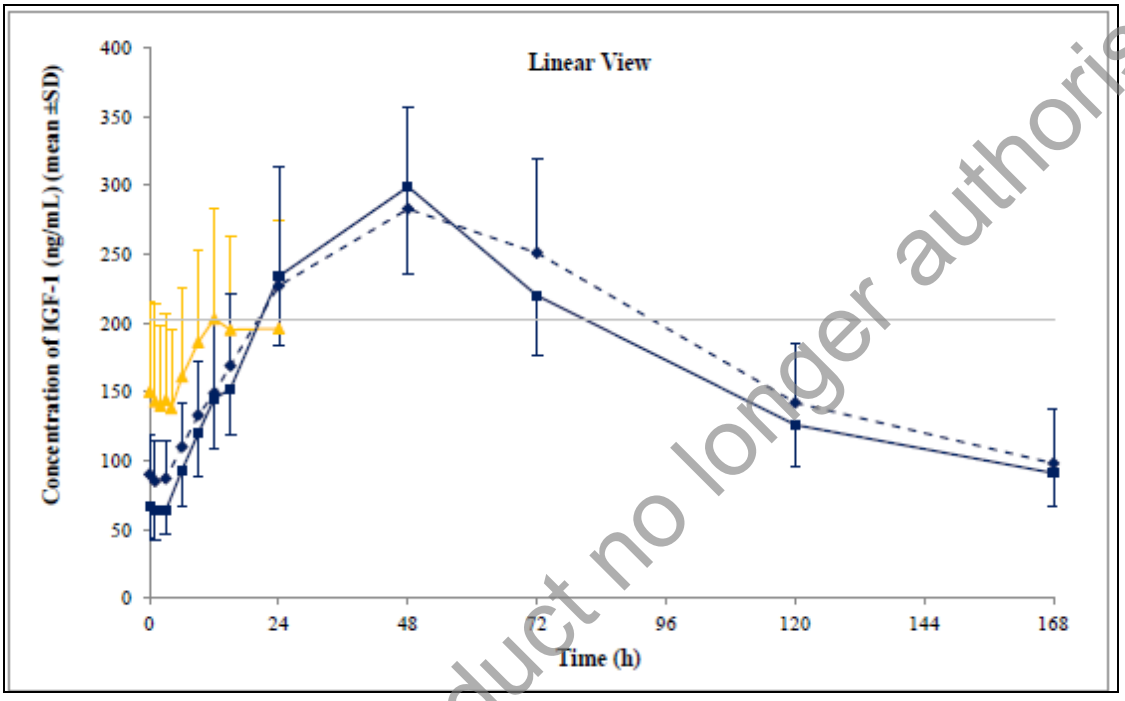
Two clinical studies were conducted, from which direct comparisons can be derived between daily and weekly administration with respect to IGF-I levels: BPLG-002 and BPLG-003:

Study BPLG-002

In this Phase 2 study in 8 evaluated adults with GHD, somatropin doses were calculated on an individual level based on the pre-existing daily somatropin therapy regime over a 7-day-period. Study duration was 5 weeks and PD-measurements were conducted for the first and last week of administration compared to daily injection. Pharmacodynamic biomarkers in this study were both, IGF-I and IGFBP3. Pooled results for IGF-I are depicted in the figure below.

Figure 1: Mean IGF-I serum concentrations after LB03002 administration in adults with GHD



The grey line shows that the IGF-I concentration for LB03002 at 96h (at which blood samples were drawn) is close to the concentration of daily somatropin after 12h (dotted blue line: 5th dose, blue line: 1st dose). From this Figure it becomes evident that the fluctuation range in IGF-I serum levels is higher in LB03002-treated than in Genotropin-treated patients.

Due to this inconstant serum level, IGF-I temporarily reaches higher serum concentrations with LB than with standard Genotropin therapy. However, the applicant demonstrated that the peak levels lie in the mid-normal range (IGF-I SDS of 0 represents the age- and gender adjusted mean in healthy subjects) and did not exceed the upper normal range (+2 SD), see figure below.

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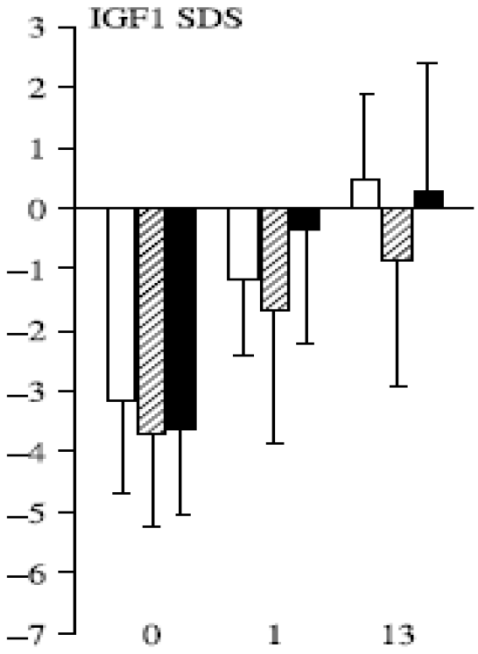

Figure 2: BPLG-003 mean peak IGF-I SDS values at baseline and after the first and last (at 3 months) once-weekly administration of LB03002, at doses of 0.2 (open bars), 0.5 (hatched bars) and 0.7 mg/kg (closed bars). 0, 1 and 13 indicate the study week.

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The reason why the peak levels did not exceed the normal range is shown in the figure below. Mean IGF-I levels always remained somewhat below the normal level (0 SDS) during therapy with LB as well as with Genotropin.

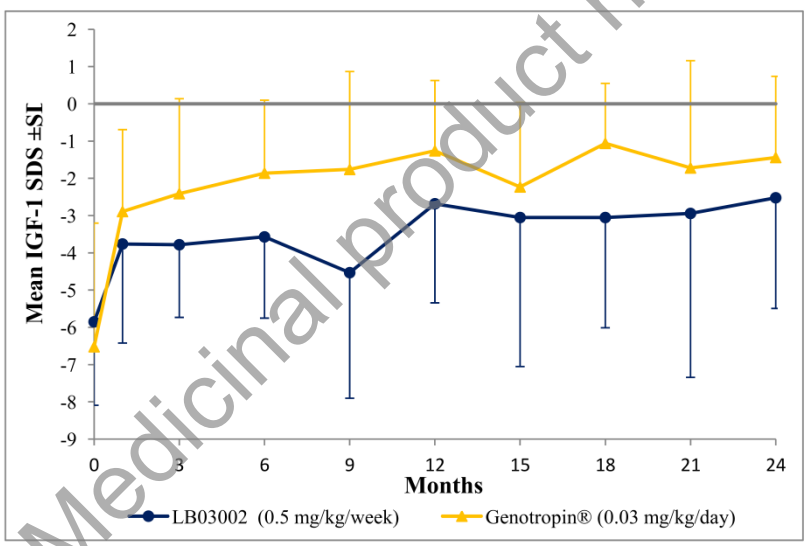

Figure 3: IGF-I SDS over 24 months in study BPLG-003

The serum concentration profile of IGFBP-3 is similar to the one of IGF-I. However, a tendency to decreased values from the first to the last observation (C_{max}, AUC) becomes evident pointing to a possible adaptation process, as shown in the table depicted below.

Table 14: PD-parameters derived from study BPLG-002

		IGFBP3 [ng/mL]		ALS [mU/mL]		GHBP [pmol/L]	
Parameter	**N***	**Day 0**	**Day 28**	**Day 0**	**Day 28**	**Day 0**	**Day 28**
T_{max} [h]	9	69.3 ±22.3	66.7 ±23.3	53.4 ±10.7	56.0 ±24.0		
	8	72.0 ±22.2	69.0 ±23.8	54.1 ±11.2	57.0 ±25.5	92.6 ±35.1[#]	125 ±60.0[&]
$C_{max,Cor}$ [Unit/mL]	9	1136 ±483	738 ±335	937 ±310	815 ±260	64.7 ±68.9	117 ±135
	8	1095 ±499	749 ±357	915 ±324	837 ±268	72.8 ±69.0	132 ±136
$AUC_{t,Cor}$ [Unit•h/mL]	9	118.0 ±59.9	67.3 ±33.5	89.0 ±41.6	58.2 ±20.3	4.16 ±4.83	6.31 ±7.91
	8	112.8 ±61.9	69.8 ±34.9	86.7 ±43.8	59.6 ±21.3	4.68 ±4.89	7.10 ±8.07

Study BPLG-003

Study BPLG-003 was a Phase II/IIIa study in 37 prepubertal children with GHD evaluated for PKPD, which was active-controlled by daily administration of Genotropin. After an initial lead-in phase with daily administered Genotropin for one week and a wash-out phase of three weeks, PD measurements were performed after the 1st and 13th dose of LB03002 (i.e. 1st dose and after 3 months, respectively). According to current patient care guidelines, the target concentration of serum IGF-I concentrations in children from 1-8 life years is 50-300 ng/mL.

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Table 15: PD-parameters derived from study BPLG-003, IGF-I serum concentrations after 1st and 13th LB03002-dose

Data excl. Centre 14	0.2 mg/kg/week LB03002	0.5 mg/kg/week LB03002	0.7 mg/kg/week LB03002	0.03 mg/kg/day Genotropin®
N	10	10	8	9
Pre-Treatment [ng/mL]	7.5 (292.4)	12.0 (226.0)	10.1 (140.2)	9.7 (203.5)*
Lead-in (0.03 mg/kg Genotropin)				
t_{max} [h]	3 (0, 24)	14 (0, 24)	14 (0, 24)	0 (0, 16)
C_{max} [ng/mL]	29.8 (163)	34.6 (82.6)	45.1 (72.5)	40.9 (118)
$AUC_{0\rightarrow last}$ [µg*h/mL]	2.51 (179)	2.81 (75.4)	3.22 (83.2)	3.34 (115)
$AUC_{tau(24h)}$ [µg*h/mL]	0.577 (180)	0.678 (96.6)	0.919 (81.0)	0.815 (127)
AUC_{tau}/dose [µg*h/mL/(mg/kg)]	19.2 (180)	22.6 (96.6)	30.6 (81.0)	27.2 (127)
Visit 1 (1st dose of LB03002)				
t_{max} [h]	36 (36, 168)	48 (36, 48)	72 (48, 72)	
C_{max} [ng/mL]	38.7 (236)	59.8 (51.9)	98.6 (72.1)	
$AUC_{0\rightarrow last}$ [µg*h/mL]	2.34 (322)	4.58 (65.2)	8.52 (65.3)	
$AUC_{tau(168h)}$ [µg*h/mL]	3.69 (214)*	4.58 (65.2)	8.52 (65.3)	
AUC_{tau}/dose [µg*h/mL/(mg/kg)]	18.4 (214)*	9.16 (65.2)	12.2 (65.3)	
Visit 3 (13th dose of LB03002)				
t_{max} [h]	36 (24, 48)	36 (36, 48)	48 (36, 48)	
C_{max} [ng/mL]	68 (140)	145 (55.7)	134 (77.7)	
$AUC_{0\rightarrow last}$ [µg*h/mL]	5.18 (161)	11.9 (58.1)	11.1 (79)	
$AUC_{tau(168h)}$ [µg*h/mL]	5.18 (161)	11.9 (58.1)	11.1 (79)	
AUC_{tau}/dose [µg*h/mL/(mg/kg)]	25.9 (161)	23.9 (58.1)	15.9 (79)	

t_{max} - median (min, max), other parameters - Geometric mean (%CV)
*n=8

From these data it becomes evident, that LB03002 after repeated dose administration shows no significant difference between 0.5 and 0.7 mg/kg/week strengths. In contrast, a remarkably greater difference between 0.5 and 0.7 mg/kg/week strengths is observed after the 1st administration (C_{max}, AUC). Thus an adaption process appears possible. As a result, however, it should be mentioned that all

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C_{max} values are within the age-adjusted target range. The serum concentration profile of IGFBP-3 again is very similar to the one of IGF-I. It is even in line with the IGF-I data in terms of reflecting no difference in IGFBP3 values between the 0.5 and 0.7 mg/kg/week strengths after 3 months of treatment. However, when looking at individual patient data, it becomes evident, that there is huge inter-subject variability in IGF-I C_{max}-levels, ranging from <12 ng/mL up to >200 ng/mL.

Thus, study BPLG-003 showed no substantial difference in IGF-I serum concentrations for the 0.5 and 0.7 mg/kg/week strengths after 3 months of treatment. Taken together with the similar growth rates obtained with both dosages (as referred to in the clinical efficacy section) it was reasonable to choose the lower dosage for the following pivotal study. IGF-I and IGFBP-3 in both studies (BPLG-002 and BPLG-003) showed a very similar profile with IGFBP-3 increasing slightly later.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

PK analysis revealed that the bioavailability of GH from LB03002 is around 35% lower than availability of GH from Genotropin. Hence, one LB03002 dose of 0.5 mg/kg as recommend in children leads to a 1.56-fold higher cumulative exposure than seven daily doses of 0.03 mg/kg Genotropin. Vice versa, the cumulative GH exposure resulting from LB03002 treatment would correspond to a daily Genotropin dose of 0.047 mg/kg. This is in line with the current recommendation that the daily GH dose (of a standard preparation) should not exceed 0.05 mg/kg/day for safety reasons.

In the steady state after sc injection of weekly applied somatropin (studies BPLG-002 and BPLG-003), peak serum levels are achieved after 15 hours (adults with GHD) and 12 hours (children with GHD), respectively. The measurements conducted by the applicant appear appropriate. However, due to the fact that a biphasic curve with two consecutive t_{max}-values is observed, not too much attention should be paid to pure numerical t_{max}-values.

Studies in special populations were not conducted (hepatic or renal impaired patients). Specially designed studies to investigate distribution, metabolism, elimination, and influence of genetic polymorphism on drug metabolism or PK-parameters in general were not conducted. In view of the long experience and the regulatory status of the active compound somatropin this is acceptable.

In all populations under investigation, dose-dependency of rate and extent of absorption could be demonstrated. In healthy adults it appears to be however slightly greater than a linear dose proportional manner. In children, C_{max} and AUC_{tau} increased approximately proportionally with dose at both time-points under investigation: at the beginning and after 3 months of weekly administration.

Pharmacodynamics

Somatropin in general is a well-known substance and marketed in the EU (and many other regions of the world) for many years. The basic principles of somatropin pharmacodynamic action are long established medicinal knowledge. Studies conducted for this MAA aimed to investigate IGF-I and IGFBP-3 as pharmacodynamic markers; this is considered acceptable. Somatropin exerts its effect by a dual mechanism, i.e. directly through GH-receptors and indirectly through IGF-I. Thus, measuring IGF-I plasmaconcentration and its main binding hormone IGFBP-3, which is also stimulated by GH, is reasonable. This MAA refers to a new, prolonged formulation of a well-known active substance. Thus, restriction of pharmacodynamic target parameters to IGF-I and IGFBP-3 levels, which are standard parameters in assessing somatropin pharmacodynamics, is acceptable. Lipolytic, anabolic, and diabetogenic effects have been investigated in study BPLG-005 with respect to DXA on body composition (Dual X-Ray Absorptiometry to Determine Body Composition changes), HbA1c, FPG and fasting insulin which is acceptable.

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2.4.5. Conclusions on clinical pharmacology

The most important difference in PK parameters between LB03002 and the once daily administered comparator Genotropin is the 2.4-fold higher weekly dose leading to an approximately 1.56-fold higher exposure required to yield comparable results in efficacy. Furthermore, with LB03002 but not with Genotropin the serum IGF-I levels undulate within the dosing interval. The mean IGF-I levels achieved with LB03002 and Genotropin, respectively, are similar.

Pharmacodynamics was measured using standard parameters (IGF-I, IGFBP3). No studies designed to investigate other pharmacodynamic properties are required or conducted. Some differences in IGF-I parameters were observed, in particular the above mentioned marked periodical (weekly) fluctuation. This, however, is a consequence of the different formulation and the weekly dosing scheme and is not due to alterations in the active substance (hGH) of LB03002.

The CHMP concluded that all aspects regarding clinical pharmacology are satisfactory and that there are no outstanding issues.

2.5. Clinical efficacy

The clinical development program aimed to support the proposed use of LB03002 in children and adults with GHD was as follows:

In **paediatric subjects**, pre-pubertal growth hormone (GH) treatment naïve children with primary (idiopathic) or secondary (organic) insufficiency of growth hormone were investigated. The objective of the clinical development programme for LB03002 was to demonstrate that LB03002 administered once-weekly by s.c. injection is comparable in terms of efficacy and safety to an approved daily somatropin product. For this purpose Genotropin was chosen as comparator. In the supportive paediatric clinical studies, Eutropin Inj. was used as comparator product. Eutropin Inj contains the same active drug substance (somatropin) as LB03002 and Valtropin and is approved and marketed as a 4 IU formulation in South Korea.

In **adult subjects**, the studies were conducted in patients with GHD of either adult onset (AO), resulting from pituitary ablation or failure or childhood onset (CO), either idiopathic or secondary to pituitary disease. The aim was to demonstrate efficacy and safety of LB03002 as compared to placebo in adults with childhood or adulthood onset of GHD.

Overall data from 9 clinical studies were provided as reports. For an overview see Figure 4 and Table 16 below.

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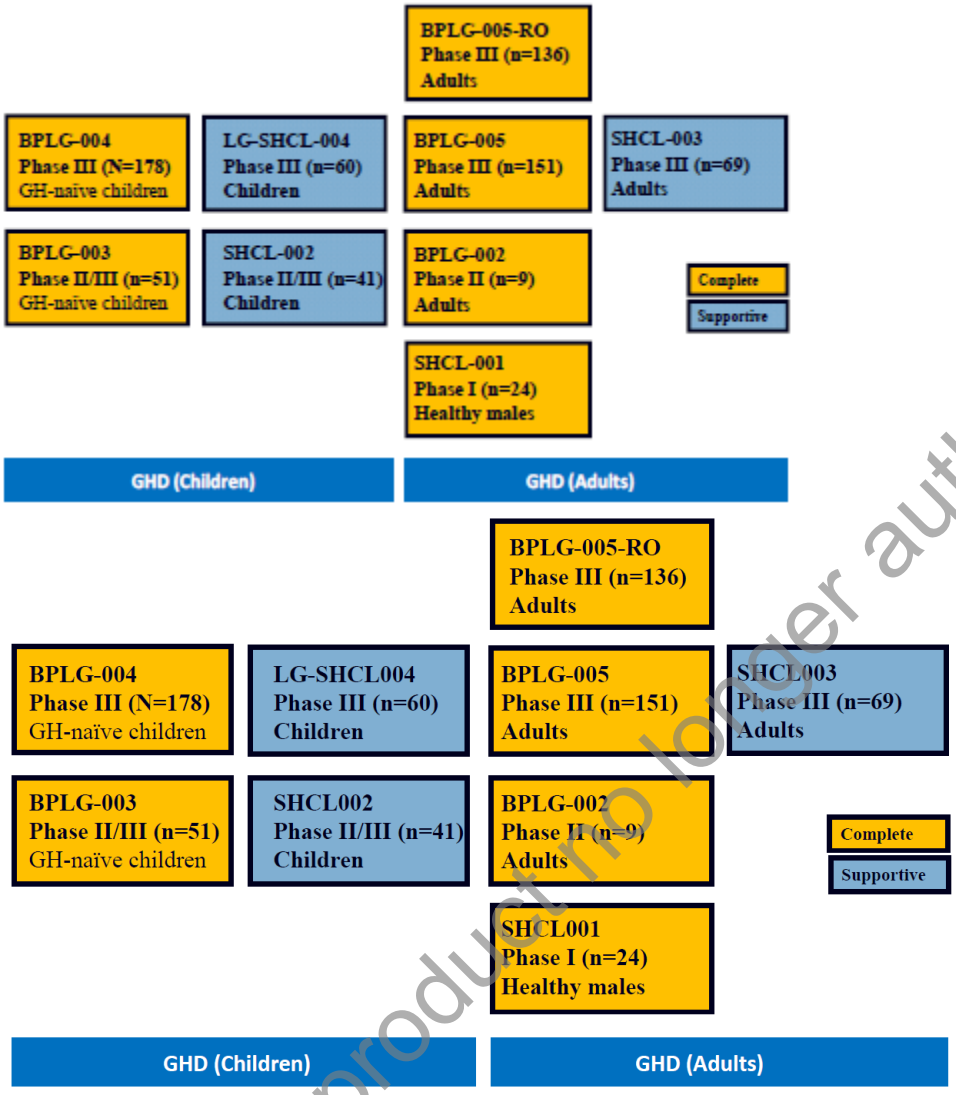
Figure 4: Overview of the clinical development program of LB03002



Dose-response studies and main clinical studies

The following table summarises the studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see sections below).

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Table 16: Overview of the complete study programme with LB03002

Study No./ Study Phase	Title of the Study	Country	No. of Study Centres	Number of Patients
Paediatric studies				
BPLG-003/ Phase II/IIIa	A Phase II/IIIa, assessor blinded (partially blinded), randomized, active-controlled, multi-centre, parallel-group study of the safety, efficacy and pharmacokinetics/ pharmacodynamics of LB03002 administered weekly in children with growth failure due to growth hormone deficiency.	Europe	9 centres in Hungary, Poland Romania, Russia, Serbia/ Montenegro, Ukraine	51
BPLG-004/ Phase III	Phase III, multi-centre, open-label, randomized, parallel-group study of a sustained release formulation of rhGH (LB03002) in pre-pubertal treatment naïve children with insufficient secretion of endogenous growth hormone. Open label extension BPLG-004-EXT	World-wide	49 centres	178 167
SHCL002/ Phase II	An open-label, randomized, parallel-group, multi-centre study to assess efficacy and safety after 6 months administration of LB03002 (sustained-release human growth hormone) 0.3 mg/kg/wk or 0.5 mg/kg/wk and Eutropin™ Inj. (human growth hormone) 0.3 mg/kg/w (given as 6 daily injections per week) to improve growth failure in pre-pubertal children with growth hormone deficiency.	Korea	10 centres	41
LG-SHCL004/ Phase III	An open-label, active controlled, randomized, parallel-group, multi-centre study to assess efficacy and safety after 6 months-administration of SR-hGH (sustained-release human growth hormone) 0.5 mg/kg/wk and Eutropin™ Inj. (immediate-release human growth hormone) 0.21 mg/kg/w (given as 6 daily injections per week) to improve the growth failure in pre-pubertal children with growth hormone deficiency (Phase III).	Korea	14 centres	60
Adult studies				
SCHCL001/ Phase I	A single centre, Phase I, double-blind, randomized, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics of LB03002, a sustained release formulation of recombinant human growth hormone, in healthy male subjects	UK	1 centre	24
BPLG-002/ Phase II	Open, single arm, uncontrolled Phase II study to evaluate safety and pharmacokinetics/pharmacodynamics of a five-week treatment with LB03002 in adults with growth hormone deficiency.	Germany	1 centre	9
BPLG-005/ Phase III	A Phase III, double-blind, randomized, placebo-controlled, parallel-group, multi-centre study to assess efficacy and safety of LB03002 administered weekly in adults with growth hormone deficiency.	Western Europe/ Central Eastern Europe/ USA	31 centres in total	151
BPLG-005-RO/ Phase III	A Phase III, open-label, uncontrolled, multicentre, rollover study to assess safety and efficacy of LB03002 administered weekly in adults with growth hormone deficiency	Western Europe/ Central Eastern Europe/ USA/	28 centres in total	136
SHCL003/ Phase III	A Phase III, double- blind, randomized, parallel-group, placebo controlled, multi-centre study to assess efficacy and safety of LB03002 (SR-hGH, sustained-release human growth hormone) with dose adjusted from starting weekly	Korea	7 centres	69

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Study No./ Study Phase	Title of the Study	Country	No. of Study Centres	Number of Patients
	dose of 6 IU following 24-week subcutaneous administration and additional 24-week extension Phase in adults with growth hormone deficiency.			

2.5.1. Dose response study(ies)

While rGH dose is based on kg bodyweight in children, an IGF-I based titration scheme is standard in adult patients with GHD.

Dose finding in the paediatric population

One supportive study from South Korea (SHCL-002) and one key study (BGLP-003) were conducted in pre-pubertal growth hormone (GH) naïve children with primary (idiopathic) or secondary (organic) insufficiency of growth hormone to decide on the dose to be investigated in the pivotal study.

In Study **SHCL002** two different doses of LB03002 were compared in children with GHD to a comparator licensed in South Korea (Eutropin) that is qualitatively identical to Valtropin, which had been licensed in the EU but was recently withdrawn by the MAH for commercial reasons, and contains the same drug substance as LB03002. When comparing 0.3 mg/kg/week and 0.5 mg/kg/week of LB03002 to Eutropin 0.3 mg/kg/week, a dose that is higher than the dose-range recommended for daily injectable somatropins in the EU (0.175 to 0.245 mg/kg/week) for children with GHD, the effect of Eutropin on height velocity (HV) was numerically higher than the effect of both doses of LB03002. A dose of 0.5 mg/kg/week of LB03002 was more effective than 0.3 mg/kg/week. Although the trial was formally successful since the predefined non-inferiority margin of -2.7 cm/year was met, this margin is considered too wide to conclude on non-inferiority.

The key study for dose finding was **BPLG-003.** Three doses of 0.2, 0.5, and 0.7 mg/kg/week of LB03002 were compared to 0.21 mg/kg/week of Genotropin in prepubertal children with GHD over twelve months. In this multicenter study, a dose relation (albeit flat in the upper part) was seen in both primary endpoints (height velocity (HV) and height velocity standardised for age and gender (HV-SDS)). Efficacy of the lowest dose was clearly inferior to the comparator. Efficacy of 0.5 and 0.7 mg/kg/week was in the range of Genotropin with the 0.5 mg dose being numerically slightly lower. Non-inferiority regarding HV was not formally demonstrated for any of the doses due to the narrow predefined non-inferiority margin of -1 cm/year. A non-inferiority margin had not been pre-specified for the endpoint HV SDS.

Since efficacy of both the 0.5 mg and 0.7 mg/kg/week dose of LB03002 was numerically in the range of the comparator, the applicant chose the lower dose due to safety considerations, which is acceptable.

Table 17: Summary of efficacy for trial Study BPLG-003

Title: A Phase II/IIIa, Assessor blinded (partially blinded), Randomized, Active-controlled, Multicentre, Parallel-group Study of the Safety, Efficacy and Pharmacokinetics / Pharmacodynamics of LB03002 administered weekly in Children with Growth Failure due to Growth Hormone Deficiency	
Study identifier	BPLG-003

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Design	This was a Phase II/IIIa, Assessor blinded (partially blinded), Randomized, Active-controlled, Multicentre, Parallel-group Study of LB03002 administered weekly in pre-pubertal growth hormone (GH) naïve children (boys aged 4-10 years or girls aged 4-9 years) with primary (idiopathic) or secondary (organic) insufficiency of growth hormone secretion were included	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months each (period 2, 3, 4) 28 days (period 1) not applicable
Hypothesis	Non-inferiority LB03002 3 doses compared to Genotropin	
Treatments groups	LB03002 0.2 mg/kg/week	12 months, switched to 0.5 mg/kg/week for 24 months
	LB03002 0.5 mg/kg/week	36 months
	LB03002 0.7 mg/kg/week	12 months, switched to 0.5 mg/kg/week for 24 months
	Genotropin 0.03 mg/kg daily (0.21 mg/kg/week)	24 months, switched to LB03002 0.5 mg/kg/week for 12 months
Endpoints and definitions	Primary endpoints	Height velocity (HV) and HV standard deviation score (HVSDS) after 12 months, non-inferiority margin -1 cm/year for HV
	Secondary endpoints	Height Standard Deviation Score (HTSDS), Height gain (HTG), Predicted adult height (PAH), Bone maturation (BM) Levels of insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3)
Study period	First Patient Enrolled: Last Patient Completed:	15 August 2003 21 June 2007

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Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	A total of 138 patients were screened for entry into the study. Of these, 51 were randomised (FAS: 51, Safety population: 51, PP set 46 (at month 12), 45 at month 36)
Primary endpoint: HV and HV SDS at 12 months.	

Analysis of adjusted mean differences in HV (cm/year) between the different treatments and daily rhGH at 12 months (FA population)

Randomisation groups	LB03002 0.2 mg/kg/week minus daily rhGH	LB03002 0.5 mg/kg/week minus daily rhGH	LB03002 0.7 mg/kg/week minus daily rhGH
Visit 6 (12 months)			
Adjusted mean difference	-2.347	-0.178	-0.143
95% CI for mean difference	-4.152, -0.541	-2.039, 1.683	-2.073, 1.788

Analysis of adjusted mean differences in HV (cm/year) standardised by gender and chronological age, between the different treatments and daily rhGH at 12 months (FA population).

Randomisation groups	LB03002 0.2 mg/kg/week minus daily rhGH	LB03002 0.5 mg/kg/week minus daily rhGH	LB03002 0.7 mg/kg/week minus daily rhGH
Visit 6 (12 months)			
Adjusted mean difference	-2.973	-0.688	-0.341
95% CI for mean difference	-5.837, -0.110	-3.636, 2.260	-3.409, 2.728

Summary of HV (cm/year) at Visits –2, 6, 11 and 17 (FA population) by randomised treatment group

Randomisation groups	LB03002 0.2 mg/kg/ week	LB03002 0.5 mg/kg/ week	LB03002 0.7 mg/kg/ week	daily rhGH 0.03 mg/kg /day
Visit -2 (screening)				
N	13	13	13	12
Mean (SD)	3.54 (1.45)	3.98 (1.59)	3.16 (1.37)	3.81 (1.49)
Min, Max	1.47, 5.81	1.27, 7.35	0.84, 5.06	0.23, 5.71
Visit 6 (12 months)				
N	13	13	13	12
Mean (SD)	9.67 (1.51)	11.75 (1.88)	12.44 (2.34)	12.17 (1.34)
Min, Max	7.14, 11.74	8.51, 15.40	9.16, 18.98	9.71, 13.77
Visit 11 (24 months)				
N	13	13	13	12
Mean (SD)	9.05 (0.97)	9.89 (1.45)	10.28 (1.61)	10.44 (0.86)
Min, Max	7.26, 10.49	7.23, 12.40	7.97, 14.48	9.31, 11.63
Visit 17 (36 months)				
N	12*	13	13	12
Mean (SD)	8.54 (0.97)	9.01 (1.33)	9.30 (1.22)	9.18 (0.76)
Min, Max	6.95, 10.01	6.84, 11.34	7.44, 12.23	8.40, 10.40

* Patient withdrew consent due to relocation

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Summary of height velocity (cm/year) standardised by gender and chronological age at Visits –2, 6, 11 and 17 (FA population) by randomised treatment group

Randomisation groups	LB03002 0.2 mg/kg/ week	LB03002 0.5 mg/kg/ week	LB03002 0.7 mg/kg/ week	daily rhGH 0.03 mg/kg/ day
Visit -2 (screening)				
N	13	13	13	12
Mean (SD)	-3.26 (1.34)	-2.56 (1.78)	-3.42 (1.68)	-2.65 (2.06)
Min, Max	-5.31, -0.77	-5.11, 1.34	-6.39, -1.49	-7.24, 0.14
Visit 6 (12 months)				
N	13	13	13	12
Mean (SD)	5.40 (2.60)	8.14 (3.23)	9.55 (3.49)	8.97 (3.30)
Min, Max	1.87, 9.81	3.88, 14.78	5.74, 19.85	3.15, 14.30
Visit 11 (24 months)				
N	13	13	13	12
Mean (SD)	4.98 (2.19)	6.02 (2.33)	6.73 (2.01)	6.71 (2.10)
Min, Max	1.43, 9.14	3.55, 10.69	4.67, 12.65	3.34, 10.64
Visit 17 (36 months)				
N	12*	13	13	12
Mean (SD)	4.45 (2.20)	4.99 (2.21)	5.23 (1.67)	5.01 (2.10)
Min, Max	1.16, 8.71	2.72, 9.83	2.20, 7.77	2.93, 9.71

*patient withdrew consent at Visit 17 due to relocation

Notes

Please note that after 12 months all patients randomised to LB03002 switched to 0.5 mg/kg/week and after 24 months also patients randomised to Genotropin switched to LB03002 0.5 mg/kg/week

Analysis description

Secondary analysis

Mean (SD) Height Velocity Standardized for Gender and Bone Age (HVSDSB) (Greulich-Pyle) at 12 months: 1.27 (1.54) for the LB03002 0.2 mg/kg/week group, 3.74 (3.06) for the 0.5 mg/kg/week group, 4.01 (2.98) for the 0.7 mg/kg/week group, 3.66 (2.54) for the daily rhGH group.

The results obtained based on mean HVSDSB (Tanner-Whitehouse) values were similar

At baseline the mean (SD) height of subjects in the LB03002 0.2 mg/kg/week group was 98.9 (11.1) cm, for the 0.5 mg/kg/week group 104.7 (10.5) cm, for the 0.7 mg/kg/week group 103.9 (9.0) cm and for the daily rhGH group 103.0 (12.9) cm. After 12 months, mean (SD) height gains ranged from 9.66 (1.51) cm in the LB03002 0.2 mg/kg/week group to 12.39 (2.39) cm in the LB03002 0.7 mg/kg/week group.

Similar results were obtained for Height standardised by gender and chronological age (HTSDS), Height standardised by gender and bone age (HTSDSB) (Greulich-Pyle), Height standardised by gender and bone age (HTSDSB) (Tanner-Whitehouse), Standardised predicted adult height, Standardised predicted adult height calculated from chronological age, Predicted adult height calculated from bone age (Greulich-Pyle), Predicted adult height calculated from bone age (Tanner-Whitehouse).

In all of these analyses the values for the LB 03002 0.2 mg/kg/week group were at least numerically lower at 12 months and (after switching to 0.5 mg/kg/week) after 24 and 36 months as compared to daily rhGH 0.03 mg/kg/day.

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Dose finding in the adult population

No dose finding study based on clinical endpoints was conducted in the population of adults with GHD. Information about efficacy of different doses on clinical endpoints is not available. Instead, dosing in the key studies in these patients was based on IGF-I levels at day 4 after dosing. Albeit correlation between GH secretion and IGF-I levels or between IGF-I levels and clinical effect is weak in adults, guidance by IGF-I levels is state of the art, mainly for safety reasons. Starting at a low level with individual dose adaptation based on IGF-I levels has been approved for other medicinal products indicated for GH replacement therapy in adults.

2.5.2. Main study(ies)

Pivotal study BPLG-004 for the paediatric indication

The pivotal study BPLG-004 was a multicentre, randomised, active-control, parallel-group, and open-label study. Blinding would have required additional placebo-injections, which was not considered ethical in a paediatric population. Pre-pubertal rhGH naive children (boys age: >3 and <12 years or girls: age >3 and <11 years) with established organic or idiopathic GH deficiency were included. Diagnosis of GH insufficiency was determined by two different GH provocation tests, defined as a peak serum GH level of ≤ 7 ng/mL, HV of at least 1 SD (HVSDS ≤ -1) below the mean HV for CA and gender according to the standards of Prader, and baseline IGF-I level of at least 0.5 SD (IGF-I SDS ≤ -0.5) below the mean IGF-I level standardised for age and gender according to the central laboratory reference values. Mainly children from Eastern Europe and India and few children from Western Europe were included.

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Table 18: The main baseline characteristics of the study population

	LB03002 (N=91)	Genotropin (N=87)	Overall (N=178)
Age (years)			
Median	7.80	7.80	7.80
Mean (SD)	7.82 (2.54)	7.78 (2.53)	7.80 (2.53)
Minimum, maximum	3.0, 12.4	3.0, 11.9	3.0, 12.4
Body weight (kg)			
Median	16.10	16.40	16.10
Mean (SD)	17.02 (6.14)	17.15 (6.05)	17.08 (6.08)
Minimum, maximum	5.1, 36.0	6.2, 34.6	5.1, 36.0
Height (cm)			
Median	104.0	102.70	103.05
Mean (SD)	102.15 (14.92)	101.75 (15.05)	101.95 (14.95)
Minimum, maximum	60.1, 129.3	67.0, 129.3	60.1, 129.3
BMI (kg/m^2)			
Median	15.50	15.50	15.50
Mean (SD)	15.72 (2.05)	16.00 (1.85)	15.86 (1.95)
Minimum, maximum	12.2, 24.0	12.4, 23.6	12.2, 24.0
HV at baseline (cm/year)			
Median	2.580	2.930	2.745
Mean (SD)	2.691 (1.150)	2.934 (1.087)	2.810 (1.123)
Minimum, maximum	0.51, 5.11	0.67, 6.62	0.51, 6.62
HVSDS at baseline			
Median	-3.130	-3.290	-3.175
Mean (SD)	-3.163 (1.573)	-3.054 (1.539)	-3.110 (1.553)
Minimum, maximum	-7.20, -0.30	-6.79, 0.59	-7.20, 0.59

A dose of 0.5 mg/kg/week of LB03002 was compared to 0.21 mg/kg/week of Genotropin, the middose of the dose range (0.175 to 0.245 mg/kg/week) recommended for treatment of children with GHD in the EU.

Annualised HV at 12 months was chosen as the primary endpoint for efficacy, consistent with the recommendations of the EMA/CHMP Note for Guidance on Similar Medicinal Product Containing Somatropin (EMEA/CHMP/BMWP/94528/2005). Although LB03002 is not a biosimilar medicinal product, the recommendations are also relevant for this application. Since catch-up growth is most pronounced during the first treatment year, this time period is considered most sensitive to detect differences in efficacy between two somatropin-containing products. During the procedure, the applicant provided up to 4 years of growth data. Further, the applicant has agreed to provide final height data post-marketing.

A non-inferiority margin of -1.8 cm/year was set at an alpha level of 5% corresponding to about 20% of the expected HV at 12 months. Overall, this margin is considered acceptable. So far, non-inferiority margins of -1.5 to -2.0 cm/year in HV have been accepted.

HVSDS was a key secondary endpoint, data on IGF-I and IGFBP-3 levels were obtained as important PD markers, although IGF-I levels upon GH treatment may not predict efficacy in an individual child. Due to

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their undulating pattern during the dosing interval, IGF-I and IGFBP-3 were determined at day 4 after once weekly administration of the prolonged release formulation of LB03002 and compared to IGF-I and IGFBP-3 levels obtained approximately 12 hours after the last injection in patients receiving Genotropin.

BA was determined by X-ray according to the method of Greulich and Pyle.

All analyses were performed in the FAS and in the PP set using ANCOVA. Overall the results showed no major differences in these two sets. The statistical approach was considered acceptable.

Results

The efficacy results of study **BPLG-004** are summarized in Table 21 below.

Although the point estimate regarding HV was numerically slightly lower for LB03002 compared to Genotropin, the primary efficacy goal (non-inferiority of LB03002 vs. Genotropin for annualised HV at month 12) was achieved for the FAS and the PP set. Even the 99% CI was within the predefined margin of 1.8 cm/year. As the lower bounds of the 95% CIs and the 99% CIs were also ≥ -1.5, non-inferiority of LB03002 was even demonstrated under the more stringent assumption of a non-inferiority margin of -1.5 cm/year, again for both the FAS and PP sets.

Results for secondary analyses supported the primary analysis. The data showed a parallel time course of efficacy in all relevant analyses with pronounced effects after initiation of therapy and slow attenuation of efficacy over time. This time course is consistent with other studies on GH replacement therapy in GHD children.

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Table 19: Summary of efficacy for trial BPLG-004

Title: A Phase III, Multi-centre, Randomised, Parallel Group Study of Safety and Efficacy of the LB03002, a New Sustained Release Formulation of Human Recombinant Growth Hormone, as Compared to Standard Daily Therapy with Genotropin in Treatment Naïve Children with Growth Failure due to Insufficient Secretion of Endogenous Growth Hormone		
Study identifier	**BPLG-004**	
Design	This was a Phase III, multi-centre, open-label, randomised, parallel-group study of a sustained release formulation of rhGH (LB03002) in pre-pubertal treatment naïve growth-deficient children with insufficient endogenous GH secretion.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 year not applicable 1 year and 2 additional years follow up.
Hypothesis	Non-inferiority	
Treatments groups	LB03002 0.5 mg/kg/week	1 year and 1 year extension period
	Genotropin 0.03 mg/kg/day or 0.21 mg/kg/week	1 year, followed by LB03002 0.5 mg/kg/week for another year
Endpoints and definitions	annualised HV in cm/year at month 12	The primary objective of this study was to demonstrate that the LB03002 was clinically comparable (non-inferior) to daily Genotropin in terms of its safety and efficacy features.
	- HV Standard Deviation Score (HV SDS) - IGF-I - IGFBP-3	HV Standard Deviation Score (HV SDS) was determined after 12 months of treatment IGF-I and IGFBP-3 after 1, 3, 6, 9 and 12 months treatment

Study period	First Patient Enrolled: 16 November 2005 Last Patient Completed: 04 June 2009

Results and Analysis

Analysis description — **Primary Analysis**

Analysis population and time point description

Pre-pubertal children (boys age: >3 and <12 years or girls: age >3 and <11 years) with isolated GH insufficiency, GH insufficiency as part of multiple pituitary hormone deficiencies, or organic GH insufficiency were included.

Screened: 490, randomized: 180, 91 patients to LB03002, 89 patients to Genotropin (FAS), PP Set included 169

Descriptive statistics and estimate variability

Primary efficacy parameter: Summary of Annualised Height Velocity at Month 12 (FAS)

	LB03002 (N=91)	Genotropin (N=87)
Annualised HV at baseline (cm/year)		
n	91	87
Mean (SD)	2.691 (1.150)	2.934 (1.087)
Median	2.580	2.930
Minimum, maximum	0.51, 5.11	0.67, 6.62
Annualised HV at month 12 (cm/year)		
n	91	87
Mean (SD)	11.630 (2.599)	11.974 (3.089)
Median	11.370	12.090
Minimum, maximum	5.93, 21.81	3.33, 19.90
Change from baseline (cm/year)		
n	91	87
Mean (SD)	8.939 (2.908)	9.040 (3.187)
Median	8.330	8.540
Minimum, maximum	1.50, 20.69	1.90, 16.63
ANCOVA factor/covariate [A]	**p-Value [A]**	**Estimate [B]**
Treatment	0.2765	
Age group	0.9660	
Gender	0.1524	
Region	0.0091	
Baseline HV	0.1548	0.268
Baseline HT	0.0080	-0.055
Least square means and treatment difference	**Estimate [B]**	**95% CI**
LB03002	10.953	10.227, 11.680
Genotropin	11.382	10.676, 12.088
LB03002 – Genotropin	-0.429	-1.205, 0.347

ANCOVA = analysis of covariance; CI = confidence interval; HT = height; HV = height velocity; N = number of patients in group; n = number of patients with data; SD = standard deviation.
[A] ANCOVA with fixed effects for treatment, age group, gender and region with baseline HV and baseline HT as covariates.
[B] Least-squares (type III) estimates derived from the ANCOVA. For the covariates: estimate of the regression coefficient.
Non-inferiority of LB03002 can be concluded if the lower bound of the 95% CI is ≥ -1.8.

Analysis description — **Secondary analysis**

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Main Secondary Efficacy Analyses

Summary of Height Velocity Standard Deviation Score at Month 12 (FAS).

	LB03002 (N=91)	Genotropin (N=87)
HVSDS at □aseline		
n	91	87
Mean (SD)	-3.163 (1.573)	-3.054 (1.539)
Median	-3.130	-3.290
Minimum, maximum	-7.20, -0.30	-6.79, 0.59
HVSDS at month 12		
n	91	87
Mean (SD)	5.678 (3.325)	6.127 (3.596)
Median	5.070	5.600
Minimum, maximum	0.71, 21.42	-2.54, 13.42
Change from baseline		
n	91	87
Mean (SD)	8.841 (4.128)	9.181 (4.385)
Median	8.540	9.270
Minimum, maximum	1.01, 27.63	1.80, 19.22
ANCOVA factor/covariate [A]	**p-Value [A]**	**Estimate [B]**
Treatment	0.2757	
Age group	0.7989	
Gender	0.3805	
Region	0.3464	
Baseline HVSDS	0.2017	-0.229
Baseline HT	0.0004	-0.097
Least square means and treatment difference	**Estimate [B]**	**95% CI**
LB03002	5.351	4.494, 6.209
Genotropin	5.857	5.035, 6.680
LB03002 – Genotropin	-0.506	-1.420, 0.408

ANCOVA = analysis of covariance; CI = confidence interval; HT = height; HVSDS = height velocity standard deviation score; N = number of patients in group; n = number of patients with data; SD = standard deviation

[A] ANCOVA with fixed effects for treatment, age group, gender and region with baseline HVSDS and baseline HT as covariates.

[B] Least-squares (type III) estimates derived from the ANCOVA. For the covariates: estimate of the regression coefficient.

A relevant and stable increase in IGF-I and IGFBP-3 levels was seen with LB03002 with a profile over time similar to that observed with Genotropin (see Figures 5 and 6 below), demonstrating pharmacological activity of LB03002 and supporting maintenance of the effect. IGF-I SDS levels also showed the expected increase with GH treatment in either group but indicated that IGF-I levels remained below the reference values for healthy children of the same age and gender in a substantial number of patients. This is of no concern as long as growth rate is sufficient. In fact, children with true GHD often grow well with rather small doses of GH. Since patients had a relevant retardation of bone age, IGF-I SDS levels for bone age could have been provided which may have shifted the values into the normal range. However, this is considered of more academic interest than relevance to the assessment of this application.

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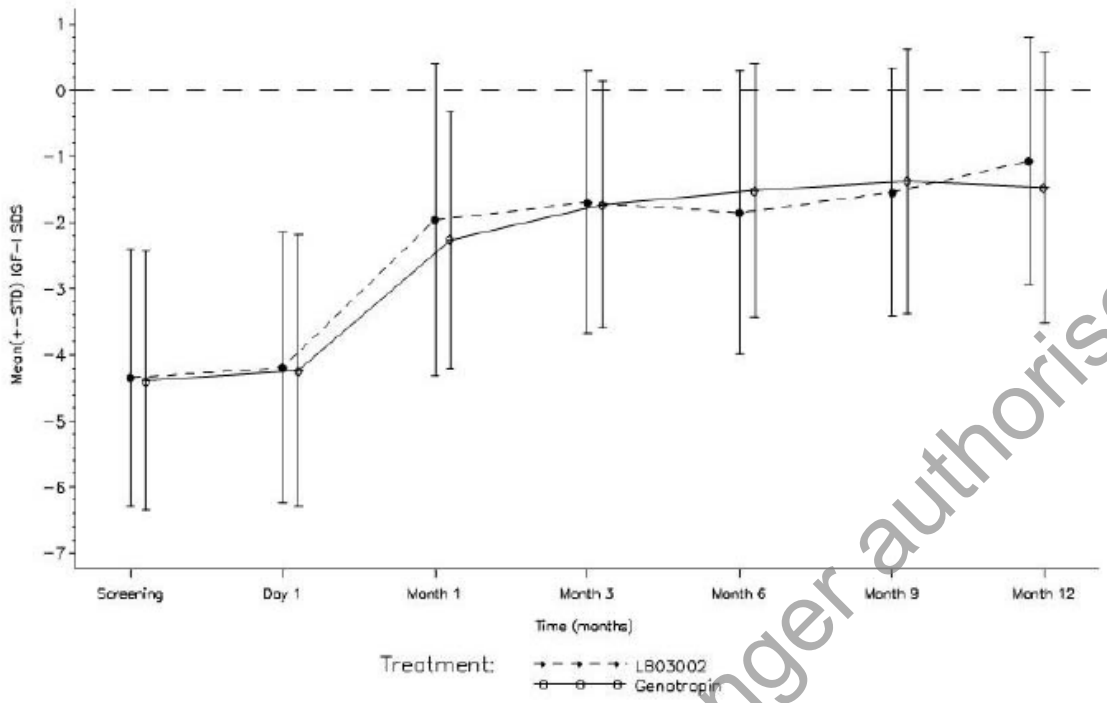
Figure 5: Mean Plot of IGF-I Standard Deviation Scores Over Time: Full Analysis Set



IGF-I = insulin-like growth factor-I; SDS = standard deviation score
Source: Figure 3.1, Section 14.1.

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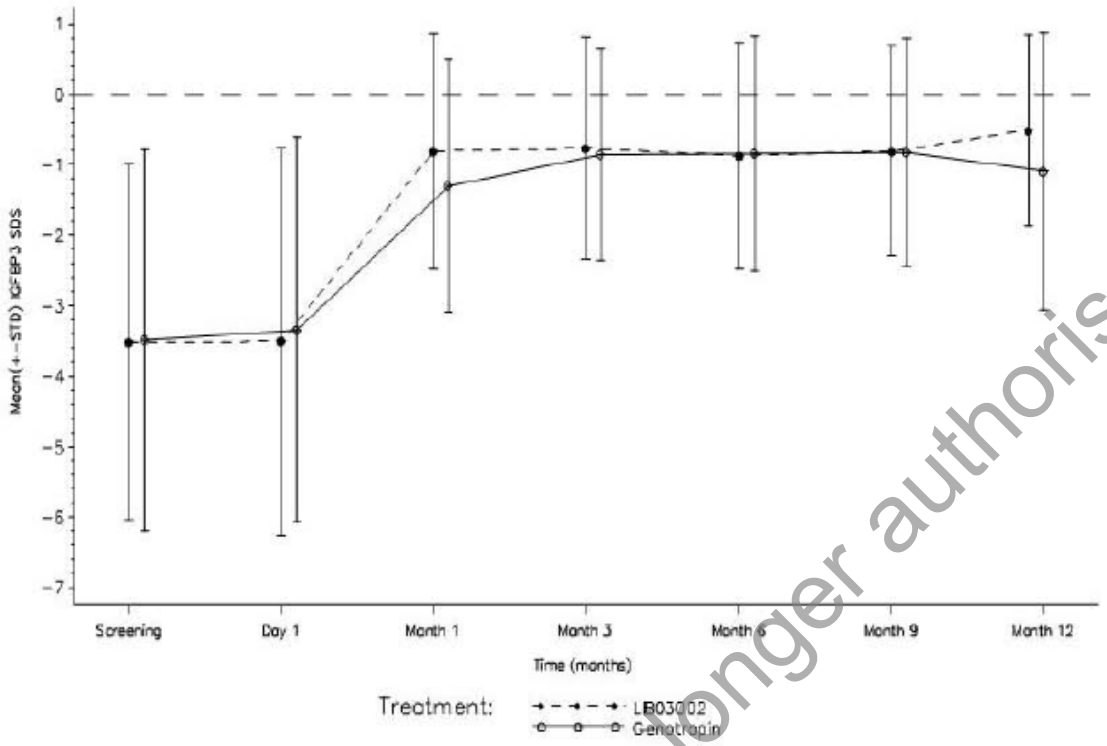
Figure 6: Mean Plot of IGFBP-3 Standard Deviation Scores Over Time: Full Analysis Set



IGFBP-3 = insulin-like growth factor binding protein 3; SDS = standard deviation score
Source: Figure 3.2, Section 14.1.

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Extension study BPLG-004-EXT

The 24-month efficacy results of the study BPLG-004-EXT are summarized in Table 22 and the 24-month IFG-1 SDS levels in Figure 7 below.

Albeit uncontrolled, the extension study to BGLP-004 indicated maintenance of the effect of LB03002 over 24 months with respect to growth parameters and IGF-I/IGFBP-3 levels in 86 patients. In 75 patients it was documented that switching from Genotropin to LB03002 was feasible with few patients discontinuing the treatment due to tolerability reasons. However, annualised HV from month 12 to month 24 was somewhat lower in the group that switched from Genotropin to LB03002 compared to the LB03002 « throughout » group raising concerns of reduced efficacy of LB03002 once weekly in patients previously treated with Genotropin daily. The observation was not consistent with the results after switching in study BPLG-003. In study BPLG-003, after 36 months, annualised HV was similar in the respective groups. This issue has been addressed by the applicant by submitting 3-year data from study BPLG-003 and preliminary 4-year data from study BPLG-004-FUP (see below). These data suggest a chance finding of transiently reduced HV after switch from Genotropin to LB03002.

Table 20: Summary of efficacy for trial BPLG-004 Extension study

Title: A Phase III, Multi-centre, Randomised, Parallel Group Study of Safety and Efficacy of the LB03002, a New Sustained Release Formulation of Human Recombinant Growth Hormone, as Compared to Standard Daily Therapy with Genotropin in Treatment Naïve Children with Growth Failure due to Insufficient Secretion of Endogenous Growth Hormone	
Study identifier	BPLG-004 Extension study

Design	This is an uncontrolled, open-label extension of study BPLG-004. Patients were given the option to participate in a 12-month extension period after completing the 12-month comparative treatment period. All patients received LB03002 during this extension period. Patients who received LB03002 during the comparative period of the study continued their treatment unchanged. Patients who received Genotropin in the comparative period were switched over to treatment with LB03002 (0.5 mg/kg/week).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable 12 months
Hypothesis	Exploratory	
Treatments groups	LB03002 Throughout	LB03002 0.5 mg/kg/week Throughout 12 months, 87 patients
	LB03002 Switched	LB03002 0.5 mg/kg/week Switched from Genotropin, 12 months, 80 patients
Endpoints and definitions	Endpoints	Annualised HV, Annualised HV-SDS for chronological age, Height Velocity Standard Deviation Score for Bone Age at Month 12 and Month 24, IGF-I and IGFBP-3 at Months 12, 18 and 24, Gain in height

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population	FAS 167 patients, Per protocol 159 patients

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Annualised HV at baseline, at month 12 and at month 24

	Measured Values (cm/year)		
	LB03002 Throughout (N=87)	**Switched to LB03002 (N=80)**	**Overall (N=167)**
Annualised HV at baseline (cm/year)			
n	87	80	167
Mean (SD)	2.639 (1.112)	2.868 (1.040)	2.749 (1.081)
Median	2.570	2.905	2.690
Minimum, maximum	0.51,4.96	0.67,6.62	0.51, 6.62
Annualised HV from baseline to month 12 (cm/year)			
n	87	80	167
Mean (SD)	11.724 (2.575)	12.161 (3.094)	11.933 (2.835)
Median	11.450	12.275	11.780
Minimum, maximum	7.51, 21.81	3.33, 19.90	3.33, 21.81
p-value[B]			0.322
Annualised HV from month 12 to month 24 (cm/year)			
n	87	80	167
Mean (SD)	8.325 (1.923)	7.281 (2.335)	7.825 (2.187)
Median	8.390	7.535	8.210
Minimum, maximum	0.00 [D], 13.89	0.00[D], 12.29	0.00[D], 13.89
p-value[B]			0.002

HV = height velocity; N = number of patients in group; n = number of patients with data; SD = standard deviation.
[A] For month 12 changes from baseline, for month 12 to subsequent visits changes from month 12.
[B] P-value of the two-sample t-test for treatment comparison.
[C] Annualised HV was calculated on the available HT measurements during the respective period. Six patients had no HT measurements at Month 24 but the HV was calculated from the remaining time points, i.e., month 15, 18 and 21.
[D] This patient was included in the analysis set as they dropped out due to a treatment-related adverse event and their height in the following visit was the last observation carried forward.

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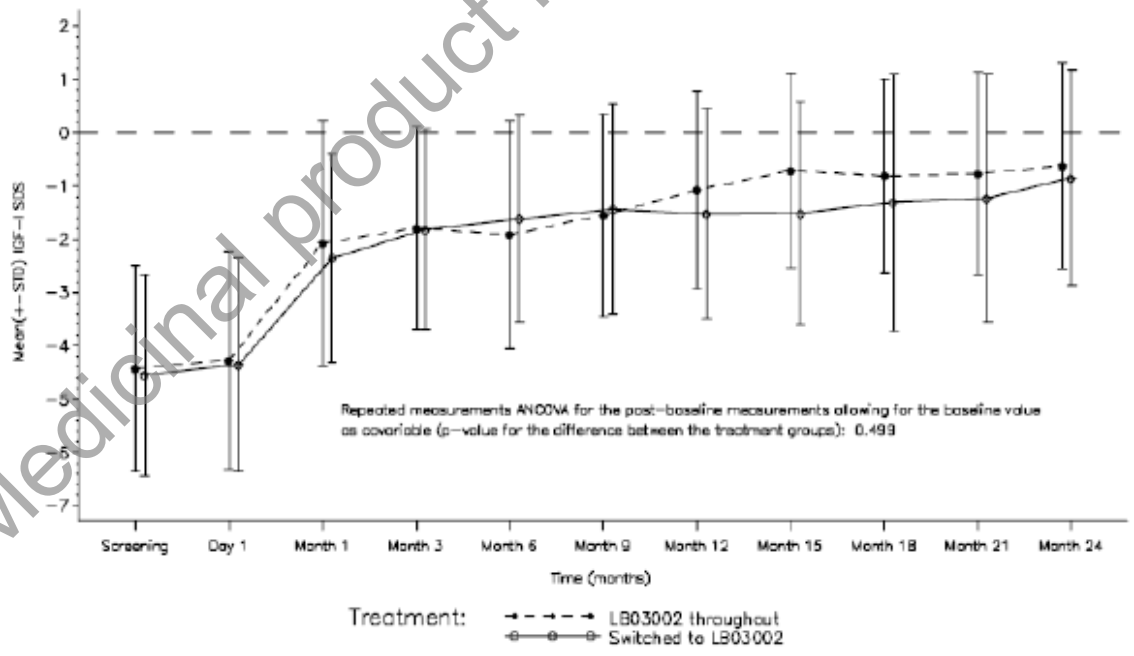
Annualised HV-SDS for chronological age

	Measured Values		
	LB03002 Throughout (N=87)	**Switched to LB03002 (N=80)**	**Overall (N=167)**
HVSDS for CA at baseline			
n	87	80	167
Mean (SD)	-3.226 (1.518)	-3.092 (1.524)	-3.161 (1.518)
Median	-3.140	-3.300	-3.180
Minimum, maximum	-7.20, -0.66	-6.79, 0.59	-7.20, 0.59
HVSDS for CA at month 12			
N	87	80	167
Mean (SD)	5.737 (3.351)	6.259 (3.660)	5.987 (3.502)
Median	5.070	5.925	5.290
Minimum, maximum	1.11, 21.42	-2.54, 13.42	-2.54, 21.42
p-value[B]			0.337
HVSDS for CA at month 24			
N	87	80	167
Mean (SD)	2.208 (1.886)	1.466 (1.918)	1.852 (1.932)
Median	2.170	1.315	1.790
Minimum, maximum	-3.44, 8.70	-3.57, 7.90	-3.57, 8.70
p-value[B]			0.013

CA = chronological age; HVSDS = height velocity standard deviation score; N = number of patients in group; n = number of patients with data; SD = standard deviation.
[A] For month 12 changes from baseline, for month 12 to subsequent visits changes from month 12.
[B] P-value of the two-sample t-test for treatment comparison.

Fig. 7: Mean Plot of IGF-I Standard Deviation Scores Over Time (FAS)



Source: Figure 4.1, Section 14.1.

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Additional long-term efficacy data

To provide further reassurance regarding long-term efficacy of LB03002, the applicant submitted 3-year data from study BPLG-003 as a publication (Péter et al., J Clin Endocrinol Metab 2012), and preliminary 4-year data from study BPLG-004-FUP during the procedure.

Study BPLG-003 was the pivotal dose finding study in children with GHD (described above) with a main comparative phase of 12 months. After the first year of treatment all patients were switched to 0.5 mg/kg/wk LB03002, the dose applied for. A total of 51 patients provided 3-year data. Patients continued to grow well regardless of their treatment assignment during the first year and without acceleration of bone maturation. The following Table is copied from the publication by Péter et al. and summarizes the main results.

TABLE 2. Height growth and bone maturation during treatment with once-weekly LB03002 or daily GH in prepubertal children with GH deficiency

	LB03002			Daily rhGH, 0.03 mg/kg/d, and then LB03002, 0.5 mg/kg/wk
	0.2 and then 0.5 mg/kg/wk	0.5 mg/kg/wk	0.7 and then 0.5 mg/kg/wk	
N	13	13	13	12
HV (cm/yr)[a]				
Baseline	3.31 ± 1.45	3.77 ± 1.51	3.18 ± 1.48	3.66 ± 1.34
12 months	9.67 ± 1.51	11.75 ± 1.88	12.44 ± 2.34	12.17 ± 1.34
24 months	9.05 ± 0.97	9.89 ± 1.45	10.28 ± 1.61	10.44 ± 0.86
36 months	8.54 ± 0.97	9.01 ± 1.33	9.30 ± 1.22	9.18 ± 0.76
HSDS				
Baseline	−5.02 ± 1.56	−3.92 ± 0.81	−4.53 ± 1.27	−4.53 ± 1.38
12 months	−3.97 ± 1.28	−2.55 ± 0.61	−3.03 ± 1.11	−3.06 ± 1.27
Gain from baseline	1.05 ± 0.38	1.37 ± 0.39	1.50 ± 0.44	1.47 ± 0.29
24 months	−3.10 ± 1.24	−1.87 ± 0.59	−2.22 ± 1.13	−2.17 ± 1.08
Gain from baseline	1.91 ± 0.53	2.05 ± 0.63	2.30 ± 0.65	2.36 ± 0.49
36 months	−2.56 ± 1.26	−1.49 ± 0.75	−1.86 ± 1.26	−1.89 ± 1.05
Gain from baseline	2.50 ± 0.74	2.43 ± 0.78	2.67 ± 0.66	2.64 ± 0.68
BA/CA				
Baseline	0.46 ± 0.17	0.48 ± 0.13	0.44 ± 0.17	0.43 ± 0.14
12 months	0.56 ± 0.18	0.61 ± 0.16	0.57 ± 0.19	0.53 ± 0.18
24 months	0.70 ± 0.17	0.70 ± 0.15	0.64 ± 0.19	0.69 ± 0.18
36 months	0.79 ± 0.18	0.78 ± 0.14	0.72 ± 0.16	0.75 ± 0.17

Values are mean ± SD.

[a] HV was calculated as change in height from baseline to each time point/time.

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Four-year follow-up data in a subset of patients from the pivotal **study BPLG-004-FUP** have also been submitted. The results summarized in Table 23 below show that the growth pattern was similar in children treated with either LB03002 for 4 years or Genotropin for one year followed by LB03002 for another 3 years.

Table 21: Growth parameters in study BPLG-004 over 4 years of treatment

Parameter	Time point	LB03002 throughout	Switched to LB03002	Overall
HV ±SD (cm)	Baseline	2.39 ±1.00	2.56 ±0.74	2.47 ±0.88
	12 months	12.34 ±2.45	12.87 ±2.37	12.61 ±2.41
	24 months	8.13 ± 1.62	8.07 ±2.07	8.10 ±1.84
	36 months	6.87 ±2.4	7.44 ±1.98	7.15 ±2.19
	48 months	5.97 ±2.18	6.57 ±2.03	6.24 ±2.12

Gain in height (cm)	0-12 months 12-24 months 24-36 months 36-48 months	12.19 ±2.30 8.16 ±1.67 6.86 ±2.44 5.93 ±2.17	12.88 ±2.35 8.03 ±2.02 7.39 ±1.89 6.62 ±2.01	12.53 ±2.33 8.09 ±1.83 7.12 ±2.18 6.27 ±2.10
Δ HSDS	Baseline 12 months 24 months 36 months 48 months	NA 1.61 ±0.74 2.17 ±1.08 2.43 ±1.29 2.58 ±1.32	NA 1.65 ±0.67 2.17 ±0.98 2.53 ±1.15 2.83 ±1.21	NA 1.63 ±0.71 2.17 ±1.01 2.48 ±1.20 2.71 ±1.26

As shown in Table 15-2 and Figure 15-1 below, the HV in children treated with LB03002 or Genotropin/LB03002 for 4 years is similar to published growth rates of daily administered rGH.

Table 15-2: Comparison of HV in children over 4 years of treatment with rhGH

Source		Average dose (mg/kg/wk)	Mean HV ±SD (cm)			
			12 months	24 months	36 months	48 months
De Muinck Keizer Schrama, 1994		0.21	11.0 ±3.0	8.0 ±2.2	7.0 ±0.5	
Mac Gillivray et al, 1996		0.33	11.4 ±2.5	9.0 ±1.9	8.0 ±1.5	7.5 ±1.4
Ranke et al, 1999	KiGS	0.2	9.2 ±2.4	7.4 ±1.8	6.7 ±1.5	6.1 ±1.3
	OZGROW	0.2	11.1 ±2.7	8.0 ±1.9	7.0 ±1.3	6.6 ±0.7
	Tübingen	0.2	9.7 ±1.9	8.2 ±1.6	6.8 ±1.5	6.8 ±1.0
BPLG-004	LB03002 throughout	0.5	12.3 ±2.5	8.1 ±1.6	6.9 ±2.4	6.0 ±2.2
	Switched to LB03002	0.21	12.9 ±2.4	8.1 ±2.1	7.4 ±2.0	6.5 ±2.0
	Overall	LB03002 throughout and Switched to LB	12.6 ±2.4	8.1 ±1.8	7.2 ±2.2	6.2 ±2.1

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In the listed study cohorts daily GH dosages were in the same range as or slightly higher (study by Mc Gillivray) than the Genotropin dose used for the non-inferiority comparison with LB03002 in study BPLG-004.

Figure 15-1 shows that 4-year HV data for study BPLG-004 are comparable with data for Genotropin and Omnitrope as published by Romer et al (Horm Res 2009). At the end of the fourth treatment year the mean HV in children in study BPLG-004 was 6.2 cm ± 2.1 cm and bone maturation was 0.85 ± 0.17 demonstrating further growth potential in these children.

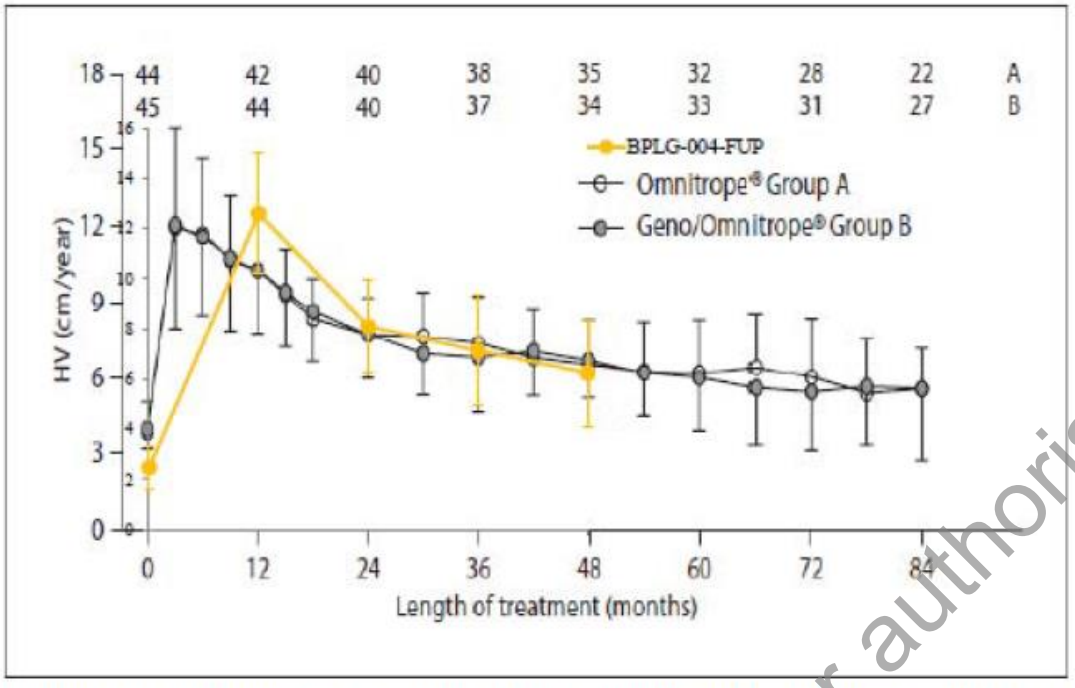

Figure 15-1: HV (cm, mean ±SD) in Indian and Egyptian children treated for 4 years with 0.5 mg/kg/week LB03002 or with 0.21 mg/kg/week Genotropin® for 1 year followed by 3 years with 0.5 mg/kg/week LB03002 ( ) compared to Figure 3 from Romer et al, 2009.

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Efficacy in adults based on study BPLG-005 and its extension BPLG-005-RO

BPLG-005 was the pivotal study to support an indication for the treatment of adults with GHD. In order to obtain additional data for the long-term use a roll over study, BPLG-005-RO was conducted.

BPLG-005 was a phase III, randomized, placebo-controlled, double-blind, parallel-group, multicenter study to evaluate efficacy and safety of LB03002. The patients included (male or female patients (23 – 70 y) were representative for the target patient population. Patients with GHD of either adult onset (AO), resulting from pituitary ablation or failure, or childhood onset (CO), either idiopathic or secondary to pituitary disease, were included.

Table 22: Main baseline characteristics of the study population

	LB03002 (N=101)	Placebo (N=50)	Overall (N=151)
Age (years)			
Median	47.0	41.0	44.0
Mean (SD)	45.5 (12.9)	41.8 (14.1)	44.3 (13.3)
Minimum, maximum	24, 69	23, 68	23, 69
Body weight (kg)			
Median	77.90	76.50	77.40
Mean (SD)	79.25 (21.21)	76.35 (18.03)	78.29 (20.20)
Minimum, maximum	32.5, 129.7	39.0, 115.0	32.5, 129.7
Height (cm)			
Median	166.0	169.5	168.0
Mean (SD)	166.3 (10.6)	166.3 (12.8)	166.3 (11.4)
Minimum, maximum	130, 186	128, 196	128, 196
BMI (kg/m^2)			
Median	27.90	26.30	27.60
Mean (SD)	28.32 (5.89)	27.53 (5.60)	28.06 (5.78)
Minimum, maximum	16.1, 43.0	17.3, 45.6	16.1, 45.6
Onset of GHD n (%)			
Adult	71 (70.3)	37 (74.0)	108 (71.5)
Child	30 (29.7)	13 (26.0)	43 (28.5)
Sex n (%)			
Male	56 (55.4)	29 (58.0)	85 (56.3)
Female	45 (44.6)	21 (42.0)	66 (43.7)

[A] = Number of non-missing values in LB03002 group was 100.
BMI = body mass index; GHD = growth hormone deficiency; N = number of patients in group; n= number of patients with data; SD = standard deviation.

LB03002 was individually dosed based on IGF-I levels obtained at day 4 in order to achieve and maintain -0.5 ≤ IGF-I SDS ≤ +1.5 or +1 increase from baseline in IGF-I SDS. Dosing by IGF-I levels has previously been shown to be superior to dosing by weight with respect to adverse events.

The primary efficacy endpoint was the decrease in Fat Mass (FM) after treatment for 26 weeks as assessed by DXA scan. The primary endpoint has been used in previous GH treatment studies in adults and is considered acceptable. DXA scans are considered an appropriate method to determine body composition. Assessment in the roll over study was performed after 52 weeks.

Secondary efficacy endpoints included Lean Body Mass (LBM), other body composition parameters, IGF-I, IGFBP-3, QoL and lipid profile. The statistical analysis (ANCOVA) testing for superiority for change in FM between the two treatment groups at 26 weeks with fixed effects for treatment, region, gender and onset type with Baseline FM and IGF-I as covariates is acceptable.

Results

The efficacy results of study **BPLG-005** are summarized in Table 25 below.

There was a statistically significant treatment effect after 26 weeks. FM decreased by 1.05 kg in the treatment group and increased by 0.52 kg in the placebo group in the FAS. In the PP set there was no

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increase in FM in the placebo arm. Therefore, at 6 months of treatment patients lost about 1 – 1.6 kg FM compared to placebo, depending on the analysis.

After another 6 months of treatment no additional effect was seen on FM in BPLG-005-RO but the effect achieved at month 6 was maintained (see Table 25 below). Similarly in the supportive Korean study SHCL003 (see below) the change in FM after 24 weeks was -1.1 kg on LB03002 and -0.4 on placebo, respectively. After 48 weeks the difference between LB03002 and placebo was smaller.

The placebo corrected increase in LBM was 1.4 kg. No beneficial effects on Quality of Life and no effects on Lipid status were observed.

Most patients achieved IGF-I levels in the target range (see Figure 8 below). There was no correlation between IGF-I levels at end of treatment and effect on FM but such correlation has also not been established for other somatropins. The aim of dose selection according to IGF-I levels is mainly to reduce long term side effects of overtreatment.

Furthermore, the dose was adjusted to reach normal IGF-I levels (± 2 SDS) in the extension phase. Although a large proportion of the patients were within these borders, some apparently had IGF-I above the normal range. As for other somatropin-containing products, the SmPC includes a clear statement that IGF-I levels should be maintained in the normal range.

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Table 23: Summary of efficacy for trial BGLP-005

Title: A phase III, double-blind, randomized, placebo-controlled, parallel-group, multicenter study to assess efficacy and safety of LB03002 administered weekly in adults with growth hormone deficiency		
Study identifier	BPLG-005	
Design	This was a phase III, randomized, placebo-controlled, double-blind, parallel-group, multicenter study to evaluate efficacy and safety of a sustained-release formulation of recombinant human growth hormone (rhGH), LB03002, in adults with GHD.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks not applicable 2 weeks
Hypothesis	Superiority	
Treatments groups	LB03002	26 weeks, 101
	Placebo	26 weeks. 50
Endpoints and definitions	Primary endpoint	Fat Mass Change from Baseline at Visit 8
	Secondary endpoint	Lean Body Mass (LBM), other body composition parameters, IGF-I, IGFBP-3, QoL and lipid profile
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Screened: 198, FAS 151, Per protocol 128, safety set 151	

Primary endpoint	Fat Mass Change from Baseline at Visit 8

	LB03002 (N=101)	Placebo (N=50)
Screening (Visit 1)		
n	101	50
Mean (SD)	27.470 (10.1222)	26.716 (10.0699)
Median	27.037	25.606
Minimum, maximum	9.079, 72.276	9.310, 54.791
Change from Baseline (Visit 2) at Visit 8		
n	100	47
Mean (SD)	-1.050 (2.2500)	0.519 (2.5450)
Median	-1.274	0.411
Minimum, maximum	-9.130, 4.695	-5.523, 7.976
ANCOVA Factor/Covariate [A] at Visit 8		**p-Value [A]**
Treatment		0.0005
Treatment*Region		0.0780
Least Square Means and Treatment Difference at Visit 8	**Estimate [B]**	**95% CI**
LB03002	-1.052	-1.614, -0.491
Placebo	0.570	-0.205, 1.345
LB03002 – Placebo	-1.622	-2.527, -0.717

Note: Units of Fat Mass are kilogram.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients in group; n= number of patients with data; SD = standard deviation.
[A] ANCOVA with fixed effects for treatment, region, gender and growth hormone deficiency onset type and with fat mass and Insulin-like Growth Factor-I at Baseline as covariates. Interactions of treatment with any of the other fixed effects are included in the model only if $p < 0.1$ for such interaction.
[B] Least-squares (type III) estimates derived from the ANCOVA.

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Key secondary endpoint

Summary of Lean Body Mass (FAS)

	LB03002 (N=101)	Placebo (N=50)
Screening (Visit 1)		
n	101	50
Mean (SD)	48.778 (13.8378)	46.611 (11.6946)
Median	47.487	48.321
Minimum, maximum	21.292, 84.898	22.493, 69.011
Change from Baseline (Visit 2) at Visit 6		
n	100	48
Mean (SD)	1.579 (2.1315)	0.350 (2.0865)
Median	1.518	0.178
Minimum, maximum	-7.027, 9.913	-3.585, 6.565
ANCOVA Parameter [A] at Visit 6		**p-Value [A]**
Treatment		0.0159
Gender		0.0338
Least Square Means and Treatment Difference at Visit 6	**Estimate [B]**	**95% CI**
LB03002	1.351	0.859, 1.843
Placebo	0.313	-0.427, 1.053
LB03002 – Placebo	1.038	0.197, 1.879
Change from Baseline (Visit 2) at Visit 8		
n	100	47
Mean (SD)	2.001 (2.2882)	0.749 (2.2143)
Median	2.047	0.318
Minimum, maximum	-5.802, 7.920	-2.558, 9.244
ANCOVA Parameter [A] at Visit 8		**p-Value [A]**
Treatment		0.0005
Least Square Means and Treatment Difference at Visit 8	**Estimate [B]**	**95% CI**
LB03002	2.087	1.569, 2.605
Placebo	0.695	-0.016, 1.405
LB03002 – Placebo	1.393	0.614, 2.171

Source: Tables 4.2.1, 4.2.3 and 4.2.5, Section 14.1
Note: Units of Lean Body Mass are kilogram.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients in group; n= number of patients with data; SD = standard deviation.
[A] ANCOVA with fixed effects for treatment, region, gender and growth hormone deficiency onset type and with lean body mass and Insulin-like Growth Factor-I at Baseline as covariates. Interactions of treatment with any of the other fixed effects are included in the model only if $p < 0.1$ for such interaction.
[B] Least-squares (type III) estimates derived from the ANCOVA.

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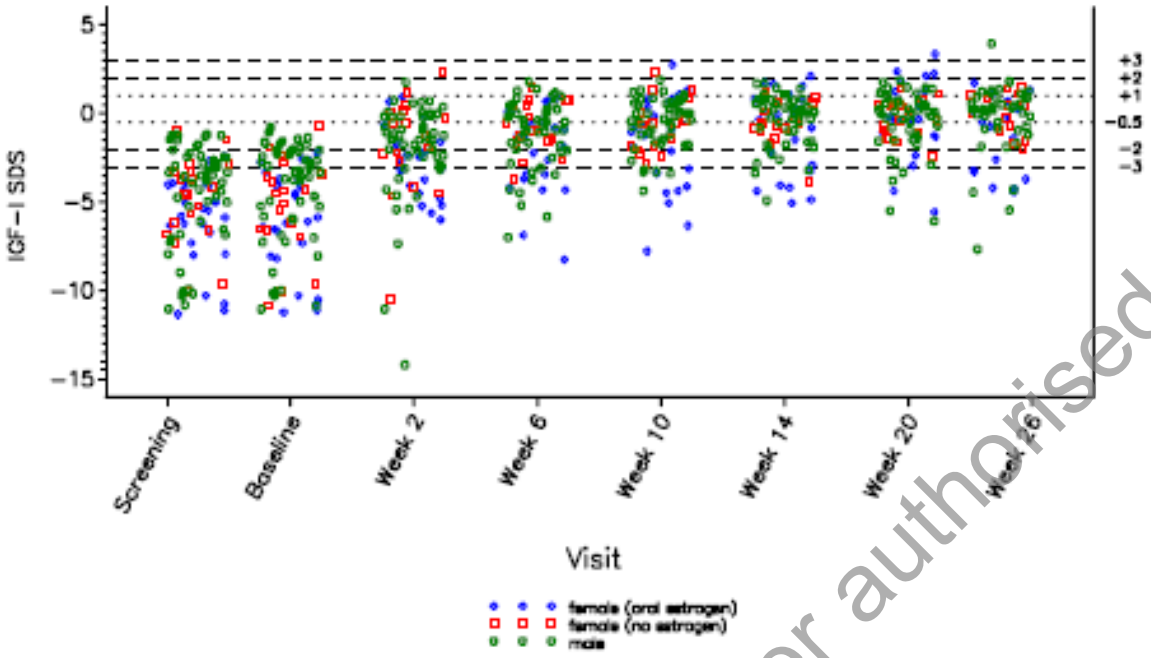
Figure 8 Course of IGF-I SDS – LB03002 Patients (FAS)



Source: Figure 2.1.1, Section 14.2
IGF-I SDS = Insulin-like Growth Factor-I Standard Deviation Score.

Table 24 Main results for fat mass change in Study BPLG-05-RO

	LB03002 Throughout (12-Month Data) (N=93)	Switched to LB03002 (6-Month Data) (N=43)
Screening Value from Visit in the BPLG-005 Study	**Visit 2**	**Visit 8**
n	93	43
Mean (SD)	27.832 (8.8765)	27.410 (10.9126)
Median	27.758	26.223
Minimum, maximum	9.079, 54.786	10.811, 56.930
Change from Baseline at RO Visit 6 [A]		
n	88	39
Mean (SD)	-1.064 (3.1570)	-1.115 (1.9543)
Median	-1.143	-0.836
Minimum, maximum	-10.317, 8.548	-4.812, 3.842
P-value [B]	0.002	0.001
95% Confidence interval [C]	-1.733, -0.396	-1.749, -0.482

Note: Units of Fat Mass are kilograms.
N = number of patients in group; n= number of patients with data; SD = standard deviation; RO = rollover.
[A] LB03002 throughout group: changes from screening; Switched to LB03002 group: changes from Visit 8 (= RO Visit 0).
[B] P-value of paired t-test for changes within groups.
[C] Standard confidence interval for the mean change using standard error of the mean and upper 97.5 percentile of the t-distribution with N-1 degrees of freedom.

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Table 25 Main results for lean body mass change in Study BPLG-05-RO

	LB03002 Throughout (12-Month Data) (N=93)	Switched to LB03002 (6-Month Data) (N=43)
Screening Value from Visit in the BPLG-005 Study	**Visit 2**	**Visit 8**
n	93	43
Mean (SD)	49.322 (13.5060)	47.168 (11.9831)
Median	47.487	47.433
Minimum, maximum	23.578, 84.898	23.436, 70.099
Change from Baseline at RO Visit 6 [A]		
n	88	39
Mean (SD)	2.229 (2.9008)	1.646 (1.8879)
Median	2.416	1.685
Minimum, maximum	-5.502, 8.412	-1.982, 5.006
P-value [B]	< 0.001	< 0.001
95% Confidence interval [C]	1.615 , 2.844	1.034, 2.258

Note: Units of Lean Body Mass are kilograms.
N = number of patients in group; n= number of patients with data; SD = standard deviation; RO = rollover.
[A] LB03002 throughout group: changes from screening; Switched to LB03002 group: changes from Visit 8 (= RO Visit 0).
[B] P-value of paired t-test for changes within groups.
[C] Standard confidence interval for the mean change using standard error of the mean and upper 97.5 percentile of the t-distribution with N-1 degrees of freedom.

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis across trials was performed. However, in the following table efficacy is compared across trials.

Children

The point estimate for HV was generally numerically slightly lower for LB03002 compared to Genotropin (see Table 26 below). However, the difference is not considered clinically relevant since clinically relevant inferiority has been excluded.

Table 26: Primary efficacy endpoint of HV compared across key studies

	Study BPLG-003		Study BPLG-004	
Efficacy Parameter	**LB03002 0.5 mg/kg/w (N=13)**	**Daily rhGH (Genotropin®) 0.21 mg/kg/w (0.03mg/kg/d) (N=12)**	**LB03002 0.5 mg/kg/w (N=91)**	**Daily rhGH (Genotropin®) 0.21 mg/kg/w (0.03mg/kg/d) (N=87)**
Annualized HV at Baseline Mean (SD), cm/y	3.98 (1.59)	3.81 (1.49)	2.69 (1.15)	2.93 (1.09)
Annualized HV at 12 m Mean (SD), cm/y	11.75 (1.88)	12.17 (1.34)	11.63 (2.60)	11.97 (3.09)

Adults

The key data are based on one study (BPLG-005 and the associated roll over study BPGL-005-RO).

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Study **SHCL-003** was a supportive study (see respective section below. Efficacy on FM was similar in both studies (BPLG-005 and SHCL-003, see Table 27 below).

Table 27: Primary Efficacy Endpoint Comparisons Across Studies (FAS)

	FM (kg)	
	LB03002	**Placebo**
Study BPLG-005, Baseline Mean (SD	27.5 (10.1)	26.7 (10.1)
Change from Baseline to 26 w Mean (SD)	-1.1 (2.3)	0.5 (2.5)
Study SHCL003 Baseline Mean (SD)	21.8 (6.0)	21.7 (7.1)
Change from Baseline at 24 w Mean (SD)	-1.1 (2.3)	-0.4 (2.3)

Long term data over 52/48 weeks of studies BPLG-005 RO/SHCL-003 consistently indicated that the effect on FM, LBM and IGF-I/IGF-BP3 levels persisted.

Clinical studies in special populations

The application concerns an indication in paediatric patients and in adult patients with GHD. The clinical study program did not include special populations outside these two areas, which is acceptable given the product characteristics.

Supportive study(ies)

Supportive studies were conducted in South Korea and were part of the marketing authorisation application for LB03002 in South Korea.

Children

Study **SHCL-002** is discussed above in the context of dose finding in children.

Adults

Study **SHCL-003** was a supportive Phase III, Randomized, 24-week, Double- blinded, Placebo-controlled, Multicenter (South Korea) study to assess the Safety and Efficacy of LB03002 administered subcutaneously to adults with Growth Hormone Deficiency over 24 weeks. This was followed by additional 24 weeks of treatment with LB03002 for all patients in an open label design.

The population in this study was similar to that included in the pivotal adult study with minor differences. Weight and height of the adults in South Korea is generally lower than that in the EU/USA studies.

A starting dose of 6 IU (2mg) of LB03002 was subcutaneously administered once weekly. The dose was subsequently adjusted to achieve IGF-I levels of +1SD of the IGF-I reference range. The primary efficacy endpoint was Change in Fat Mass (FM) from baseline to Week 24. Efficacy is summarised and compared to the results in BPLG-005 in Table 26 in the section "Analysis performed across trials". Efficacy on FM was similar in both studies.

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2.5.3. Discussion on clinical efficacy

Dose finding and efficacy in the paediatric population

The clinical program was conducted in pre-pubertal children with properly diagnosed organic or idiopathic GH deficiency. The study population appropriately reflects the target population. The inclusion of pre-pubertal children is appropriate to avoid confounding effects of the pubertal growth spurt.

Dose finding was based on two studies; one supportive study from South Korea (SHLC-002) and one multicenter key study (BGLP-003). Dose was selected based on body weight, which is appropriate in children.

Study BPLG-003 compared four groups of GH-deficient, GH-naive pre-pubertal children receiving 0.2, 0.5 or 0.7 mg/kg/week LB03002 or daily GH 0.03 mg/kg/day during the first 12 months of treatment. After the first year of treatment all patients were switched to 0.5 mg/kg/week LB03002, the dose applied for. Efficacy of the 0.5 and 0.7 mg/kg/week doses were numerically in the range of that of the comparator Genotropin. The applicant stated that safety considerations have driven the decision to choose the lower dose for the pivotal study despite of slightly lower numerical effects. Considering the safety aspects and the only minor differences in efficacy between the two doses, the dose selection is considered appropriate.

The pivotal efficacy study (BPLG-004) was a multicenter, randomised, active-control trial. Annualised HV at 12 months was chosen as the primary endpoint and HV-SDS was a key secondary endpoint, consistent with the recommendations of the EMA/CHMP Note for Guidance on Similar Medicinal Product Containing Somatropin (EMEA/CHMP/BMWP/94528/2005). Although LB03002 is not a biosimilar medicinal product, the recommendations are at least in part, also relevant for this application. Since catch-up growth is most pronounced during the first treatment year, this time period is generally considered most sensitive to detect differences in efficacy between two somatropin-containing products.

The predefined non-inferiority margin of 1.8 cm/year in HV is considered reasonable. Previously, comparability margins of 1.5 to 2 cm/year have been accepted.

The comparator in the pivotal study was Genotropin at a dose of 0.21 mg/kg/week. CHMP questioned the use of a fixed medium dose of Genotropin instead of an individually titrated dose within the recommended dose range (0.175 to 0.245 mg/kg/week) or a maximally effective dose since the use of a submaximal dose of comparator may have facilitated the demonstration of non-inferior efficacy.

In their response to this question, the applicant provided several examples from the literature indicating that, at least in the upper range of recommended doses, the dose-response relationship of somatropin is rather flat. Indeed, higher doses of somatropin have been shown to result in an improved short-term growth response, especially during the first year of treatment, however without clear improvements in final height, which is probably due to a simultaneous acceleration of bone maturation. Examples of two randomized controlled studies; one in children with GHD [3,4] and one in children born small for gestational age (SGA) (see Section 5.1 of the SmPC of Genotropin and Norditropin) suggest that even a double dose of somatropin may not result in a relevant improvement of final height. Therefore, the arguments of the applicant that a dose increase from 0.21 mg/kg/week (mid-dose used in comparative trials) to 0.245 mg/kg/week (upper-dose of the recommended dose range for children with GHD, 0.175 – 0.245 mg/kg/week) would not result in a relevant improvement in (final) height and that, from a

[3] De Muinck Keizer-Schrama S, Rikken B, Hokken-Koelega A, Wit JM, Drop S: Comparative effect of two doses of growth hormone for growth hormone deficiency. The Dutch Growth Hormone Working Group. Arch Dis Child 1994; 71: 12–18.

[4] Theo C.J. Sas, Maria A.J. de Ridder, Jan M. Wit, Joost Rotteveel, Wilma Oostdijk, H. Maarten Reeser, Barto J. Otten, Sabine M.P.F. de Muinck, Keizer-Schrama. Adult Height in Children with Growth Hormone Deficiency: A Randomized, Controlled, Growth Hormone Dose-Response Trial. Horm Res Paediatr 2010;74:172–181.

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safety aspect, the lowest effective dose should be used, is accepted. Indeed, patients with true GHD, the proposed target population of LB03002, usually respond very well to rather small doses of somatropin and thus, in clinical practice, normally do not require high doses. Based on these considerations, CHMP considered the use of the 0.21 mg/kg/week dose of Genotropin in the clinical trials acceptable.

CHMP also questioned whether a fixed dose of 0.5 mg/kg/week of LB03002 as used in the studies and recommended in the proposed SmPC would be appropriate in clinical practice or whether a dose range allowing some flexibility would be more appropriate. However, based on the responses provided by the applicant, the CHMP considered that in the absence of a universal agreement among endocrinologists on the optimal dose or dose adjustment algorithm in children, the non-inferior efficacy of LB03002 compared to Genotropin with regard to first year growth response, the convincing evidence of long-term efficacy of LB03002 (see below) and the obviously small effects of increased doses on final height (see above), this issue would not be essential for the benefit - risk balance of LB03002 as applied for. Based on efficacy and safety considerations, the proposed dose of 0.5 mg/kg/week appears sufficiently justified. The applicant suggested further exploration of a potential dose adjustment algorithm post-marketing, e.g. based on published growth prediction models, which is supported (Recommendation). Given the conclusions drawn from the SAGhE study that, for currently available daily somatropin preparations, a dose of 0.5 mg/kg/day should not be exceeded, the proposed dose of 0.5 mg/kg/week of LB03002 (which would – by exposure - correspond to a daily dose of 0.047 mg/kg) should be the maximal daily dose to be administered. This is clearly stated in the SmPC (Section 4.2).

In the pivotal efficacy study BPLG-004, LB03002 at a dose of 0.5 mg/kg/week showed non-inferior efficacy compared to Genotropin at a dose of 0.21 mg/kg/week. Even the 99% CI was within the predefined margin of 1.8 cm/year. As the lower bounds of the 95% CIs and the 99% CIs were also ≥ -1.5, non-inferiority of LB03002 was even demonstrated under the more stringent assumption of a non-inferiority margin of -1.5 cm/year, for both the FAS and PP sets. Results were consistent for HVSDS. All analyses were performed in the FAS and in the PP set using ANCOVA. Overall the results showed no major differences in these two sets.

Although LB03002 at a dose of 0.5 mg/kg/week was numerically slightly less effective than the respective comparator across studies, this was not considered relevant since clinically relevant inferiority has been excluded during the first 12-month catch-up growth of study BPLG-004. In addition, the applicant could show that the first and second-year growth results with LB03002 are fully in line with those reported for licensed daily somatropins.

Results for secondary analyses supported the primary analysis. Catch-up growth was most pronounced after initiation of therapy with slow attenuation over time. This observation is consistent with other studies on GH replacement therapy in GHD children.

Although IGF-I levels may not predict efficacy in an individual child, they demonstrate biological activity of a somatropin. IGF-I levels were measured at day 4 of the dosing interval in children receiving LB03002 and compared to the more stable IGF-I levels obtained with daily rGH administration. The reasons for choosing day 4 are the undulating IGF-I pattern induced by weekly LB03002 administration (ratio of Cmax/Cave about 1.6 with LB03002 vs. about 1.2 for daily administered rhGH), and the observation that average weekly IGF-I concentrations are achieved at day 4. The arguments of the applicant are considered acceptable in this regard.

A relevant and stable increase in IGF-I levels at day 4 was seen with LB03002 with concentrations over time similar to those observed with Genotropin. IGF-I levels remained below the reference values for healthy children of the same age and gender in a substantial number of patients. However, low IGF-I levels are of no concern as long as growth rate is sufficient. On the other hand, CHMP questioned whether undulating IGF-I levels as observed with LB03002 may exert different metabolic effects compared to more stable IGF-I concentrations achieved with daily injections. However, there is no

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indication from the clinical trials or from literature that effects on metabolism of more undulating IGF-I levels are different compared to more stable IGF-I concentrations produced by daily somatropin administration (see also safety section below).

Upon a request by the CHMP, the applicant submitted further long-term data on LB03002, including the publication by Péter et al. [5] on the 3-year growth data of study BPLG-003 and preliminary 4-year growth data of study BPLG-004. These data provide convincing evidence of long-term efficacy of LB03002 with growth rates similar to those reported for daily somatropin regimens using dosages within the range recommended for GHD children in the EU (0.175 – 0.245 mg/kg/week). CHMP concluded that LB03002, at a dose of 0.5 mg/kg/week, produces similar growth responses and growth patterns over time (up to 4 years) as daily somatropin regimens at recommended doses without undue acceleration of bone age. Therefore, similar final height gain may be expected with LB03002 as with currently licensed daily somatropins. Nevertheless, final height from ongoing clinical trials should be submitted, once available (Recommendation). In addition, the applicant is encouraged to provide additional long-term efficacy data as part of the PASS (included as an additional Pharmacovigilance activity in the RMP) (see safety section below).

Overall comment on dose finding and efficacy in the adult population

No dedicated dose finding study was conducted in the population of adults with GHD. Dosing in the key studies in these patients was based on IGF-I levels at day 4 after dosing. Although the correlation between GH secretion and IGF-I levels or between IGF-I levels and clinical effect is weak in adults, guidance by IGF-I levels is state of the art for safety reasons. Starting at a low level with individual dose adaptation based on IGF-I levels has been approved for other medicinal products indicated for GH replacement therapy in adults.

For these reasons, IGF-I based dosing of LB03002 is considered appropriate, but CHMP questioned whether dose adaptation based on IGF-I levels at day 4 with the prolonged release formulation administered once weekly is equivalent to dose adaption based on IGF-I levels upon daily administered GH preparations. It has to be taken into account that a prolonged release formulation of GH does not mirror the physiological pulsatile pattern of GH secretion and rather stable IGF-I profile (which is better but not fully mimicked by daily GH administration). With LB03002, IGF-I levels are undulating, exhibiting increased levels for some days after LB03002 administration but subsequently declining and decreased levels for several days every week. Again, the applicant argued for choosing IGF-I levels at day 4 as appropriate for dose adjustments based on the undulating IGF-I pattern induced by weekly LB03002 administration and the observation that average weekly IGF-I levels are achieved around day 4.

Study BPLG-005 was the pivotal trial including patients with a properly confirmed diagnosis of profound GHD of childhood or adult onset. The study population can be considered representative for the target population. BPLG-005 was a placebo controlled trial, which is acceptable since it is not unethical to withhold GH treatment in this patient population for a limited duration of time and because a non-inferiority margin for change in body composition may be difficult to define. In addition, a non-inferiority trial may not be feasible with a reasonable number of patients. However, an inclusion of a daily GH treatment arm as internal control could have been valuable for the interpretation of the results.

The primary efficacy endpoint was the decrease in fat mass (FM) after treatment for 26 weeks as assessed by DXA scan. This endpoint has been used in previous studies with daily somatropin regimens

[5] Péter F, Bidlingmaier M, Savoy C, Ji HJ, Saenger P. Three-year efficacy and safety of LB03002, a once-weekly sustained-release growth hormone (GH preparation, in prepubertal children with GH deficiency (GHD). J Clin Endocrinol Metab 2012; 97(2):400-407.

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and is thus acceptable. The secondary efficacy endpoints included lean body mass (LBM), other body composition parameters, IGF-I, IGFBP-3, QoL and lipid profile.

Compared to placebo, LB03002 led to a statistically significant reduction in fat mass (FM) after 26 weeks. The difference was 1.6 kg in the primary FAS analysis and about 1 kg in the PP analysis. The treatment effect observed in this study is considered to be of borderline clinical relevance and was smaller than that reported in several previously published studies. Published data indicated decreases by 4 – 6 kg in FM during 6 months of treatment accompanied by increases in LBM by 2.2 – 5 kg (Bengtsson BA et al., J Clin Endocrinol Metab 1993; 76: 309. Salomon F et al., N Engl J Med 1989; 321: 1797; Jorgensen JO et al., Lancet 1989;i:1221–1225.; Jorgensen JO, J Clin Endocrinol Metab 1989; 69: 1127;Cuneo RC et al. J Clin Endocrinol Metab 1998; 83: 107). However, such impressive results were achieved with rather high fixed GH doses. The applicant could show that the results achieved with LB03002 in study BPLG-005 are in line with those obtained with daily somatropin, when dose is adapted based on IGF-I (Maison at al., 2004, Pastuszak et al., 2012). Of note, in contrast to the present trial none of the published studies using IGF-I-based titration of somatropin dose included a placebo control.

After another 6 months of treatment no additional effect was seen on FM in BPLG-005-RO but the effect was maintained in line with findings for other somatropin-containing products. The impression of a small effect was supported by the supportive study SHCL-003 in Asian patients with similar effects on FM after 24 and 48 weeks of GH treatment.

There was no correlation between absolute IGF-I levels at end of treatment and effect on FM. Female patients needed relatively more GH than their male counterparts to obtain the same results. Accordingly, higher GH doses were needed in women taking oral estrogens vs. women not taking estrogens. This was expected since estrogens are known to influence GH sensitivity.

The placebo corrected increase in LBM in study BPLG-005 was 1.4 kg and therefore rather small. Furthermore, there were no beneficial effects on QoL or on lipid status, although an effect, at least on serum lipids, may have been expected. The applicant was therefore asked to provide evidence of treatment benefit beyond that on fat mass. The applicant pointed out that no placebo-controlled study has so far been performed with individualized (IGF-I based) dose regimens, and reports on long-term improvements are exclusively based on open single centre studies or on surveillance databases. The applicant highlighted that inconsistent results have been reported regarding the (long-term) effect of GH treatment on serum lipids (meta-analysis by Maison et al. 2004; Murray et al 2002). In addition, the patient population included in study BPLG-005 was relatively healthy with either well-controlled lipids on medication before starting GH treatment, or their GHD dependent lipid abnormalities were limited. Since the most pronounced effect of GH treatment can be expected in patients with the most adverse lipid profiles at baseline (Murray et al 2002), the lack of a significant effect on lipids in the overall cohort of study BPLG-005 may not be unexpected.

Published data suggest beneficial effects of somatropin replacement therapy on intima media thickness, inflammatory markers, bone mineralisation, energy expenditure, muscle strength and quality of life. Most of these parameters have not been investigated in the clinical development programme of LB03002 but this is not considered necessary for the purpose of substitution therapy. As with daily somatropin, LB03002 should only be given to adults with profound GHD as per label.

Based on the similar effects on body composition achieved with LB03002 compared to daily somatropin therapy (with IGF-I based dose adjustment) in adults with GHD, and based on evidence from the clinical development programme in children, it can be assumed that LB03002 provides similar beneficial effects in patients with GHD as daily administered somatropin.

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2.5.4. Conclusions on the clinical efficacy

In children with GHD, LB03002 at a dose of 0.5 mg/kg/week demonstrated non-inferior efficacy compared to daily Genotropin at an appropriate dose of 0.21 mg/kg/week during the initial active controlled 12-month treatment period. In addition, short- and long-term efficacy (up to 4 years) was comparable to that published for daily somatropin regimens using dosages within the range recommended for GHD children in the EU (0.175 – 0.245 mg/kg/week). It can be concluded that LB03002, at a dose of 0.5 mg/kg/week, produces the expected growth responses and growth patterns over time without undue acceleration of bone age. Therefore, similar final height gain with LB03002 as compared to currently licensed daily somatropins is likely. Nevertheless, final height from ongoing clinical trials should be submitted, once available (Recommendation). In addition, the applicant is encouraged to provide additional long-term efficacy data as part of the PASS (included as an additional Pharmacovigilance activity in the RMP). The applicant suggested further exploration of a potential dose adjustment algorithm post-marketing, e.g. based on published growth prediction models, which is supported (Recommendation). The maximal dose of LB03002 should not exceed 0.5 mg/kg/week as stated in the SmPC.

In adults with GHD, the effect of IGF-I guided LB03002 therapy on fat mass, although modest, was statistically significant compared to placebo and appears to be within the expected range of IGF-I guided treatment with daily somatropins. Body composition endpoints, particularly fat mass, have been used as main endpoints in previous trials with daily administered somatropin and can be considered the most reliable endpoints in assessing the effect of GH replacement therapy in adults. Therefore, efficacy of LB03002 in adult patients with GHD has been sufficiently demonstrated.

Based on all available data from the clinical development programme, LB03002 can be expected to provide similar beneficial (long-term) effects in patients with GHD as daily administered somatropin. Differences in metabolic effects due to the undulating nature of the IGF-I levels appear unlikely.

2.6. Clinical safety

Two pivotal studies were performed; one in children and one in adults, which constitute the major part of the safety database. For aspects of special interest (e.g. immunogenicity and injection site reactions) the applicant provided summaries across studies which also included data from the smaller, non-pivotal studies. In general, safety conclusions of the smaller trials (albeit strongly limited by the low patient number) were in agreement with the pivotal trials.

Patient exposure

Safety data is available from nine clinical studies with LB03002. The total number of patients exposed to LB03002 is presented in Table 28 below.

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Table 28: Numbers of Patients Exposed to LB03002 Over Time

Study	Children					Adults			
	<6m	6 m	12 m	24 m	36 m	<6m	6 m	12 m	
BPLG-003		51	51	39	39				
BPLG-004*	171	165	164	86					
SHCL002	27	24							
LG-SHCL004		30							
BPLG-005						102	100		
BPLG-005-RO							43	93	
SHCL003						80	69	34	
SUM	198	270	215	125	39	182	212	127	**Total**
								Children	**279**
								Adults	**212**
								Adults incl. Phase I/II**	**239**

* includes BPLG-004-EXT

** Studies SHCL001 and BPLG-002

Adverse events

The incidence of AEs was in general balanced between the treatment groups. An exception was the remarkable difference in incidence of local injection site reactions. There was a very high percentage with these events in the LB03002 group, most pronounced in children (39% vs. 2%). Furthermore, a high percentage of children in the LB03002 group developed antibodies against hGH. The pivotal study in adults was a comparison against placebo so that, as expected, AEs known to be related to hGH were more frequent in the verum group.

Children

The following frequencies of adverse events were observed in the pivotal paediatric trial:

Table 29: Overall Summary of TEAEs: Study BPLG-004

	LB03002 (0.5 mg/kg/w) (N = 91)		Daily rhGH (0.03 mg/kg/d) (N= 87)		
	n (%) pts affected	No. of Events	n (%) pts affected	No. of Events	p-value *
Any TEAE	75 (82)	308	63 (72)	321	0.1503
Any severe TEAE	7 (8)	8	6 (7)	6	1.000
Any Serious TEAE	2 (2)	2	2 (2)	3	1.000
Any TEAE leading to permanent discontinuation of study drug	1 (1)	1	0 (0)	0	1.000
Any TEAE resulting in death	0 (0)	0	0 (0)	0	n/a

* Fischer's exact test comparing the number of affected patients

The high incidence of AEs in both treatment groups is to a large part due to endocrine disturbances, e.g. hypothyroidism and adrenal cortical insufficiency. Endocrine AEs were balanced between LB03002 and Genotropin. This reflects the fact that many participants in this study had further endocrine disorders

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beyond GH deficiency. The imbalance in total AEs (82% vs. 72% as shown above) was mainly due to injection site reactions. The nature of these reactions is summarised in the following table.

Table 30: Summary of Number of Injection Site Reactions: Study BPLG-004

	LB03002 (N = 91)		Daily rhGH (N = 87)		
	n (%) pts affected	**No. of Events**	**n (%) pts affected**	**No. of Events**	**p-value***
Any injection site reaction	**35 (39)**	**86**	**2 (2)**	**6**	**<0.0001**
Injection site swelling	26 (29)	40	0 (0)	0	<0.0001
Injection site pain	8 (10)	15	0 (0)	0	0.0032
Injection site erythema	8 (9)	9	1 (1)	1	0.0348
Injection site discolouration	7 (8)	11	0 (0)	0	0.0140
Injection site nodule	4 (4)	9	0 (0)	0	0.1212
Injection site reaction	1 (1)	1	0 (0)	0	1.0000
Injection site warmth	1 (1)	1	0 (0)	0	1.0000
Injection site bruising	0 (0)	0	1 (1)	1	0.4888
Injection site haemorrhage	0 (0)	0	2 (2)	4	0.2375

* Fisher's exact test comparing the number of affected patients

The incidence and intensity of the injection site reactions over time suggest that the local reactions become attenuated over time (months). Two events were considered severe (one case of swelling and one case of pain); all other events were mild or moderate.

Adults

Five studies make up the adult programme for LB03002. Summary AE data are shown here from the largest adult trial BPLG-005 (placebo-controlled). The other adult studies revealed results that are in accordance with study BPLG-005 but do not allow firm conclusions due to the small patient and event number. The following table provides an overview of AE incidence in BPLG-005.

Table 31: Overall Summary of TEAEs: Study BPLG-005

	LB03002 (N = 102)	Placebo (N = 49)	
	n (%) pts affected	**n (%) pts affected**	**p-value***
Any TEAE	72 (71)	34 (69)	1.0000
Any Severe TEAE	12 (12)	2 (4)	0.2285
Any Serious TEAE	6 (6)	3 (6)	1.0000
Any TEAE leading to permanent discontinuation of study drug	1 (1)	3 (6)	0.1005
Any TEAE resulting in death	0 (0)	0 (0)	NA

* Fisher's exact test comparing the number of affected patients

Among the severe AEs listed in the table above were (LB03002 vs. placebo): Nervous system disorders 4 vs. 0 (the four cases were 3 times headache and one carpal tunnel syndrome), Musculoskeletal and connective tissue disorders 4 vs. 0 (2 times back pain, pain in extremity and arthralgia).

Regarding the nature of the most frequent AEs, there was a marked imbalance in the incidence of peripheral oedema, pain in extremity and back pain. These are established side effects of somatropin therapy. Thus, this pattern in adverse events in the LB03002 group vs. placebo meets the expectations.

In adults there was no difference in injection site reactions between LB03002 and placebo. Most likely, the local reactions were largely due to the excipients which were also present in the placebo preparation.

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Serious adverse event/deaths/other significant events

The overall incidence of serious adverse events (SAEs) was balanced between the treatment groups in adults and children, see previous section.

SAEs in children were often due to infection, e.g. tonsillitis, sepsis, gastroenteritis, pyelonephritis, pneumonia, Dengue fever etc. Nevertheless, overall infections were not more frequent in LB patients than in Genotropin patients.

In adults SAEs were abdominal pain, musculoskeletal pain and adrenal insufficiency (relationship was considered "unlikely" or "unrelated").

Furthermore, there were in total five events related to tumour recurrence or progression. In one paediatric case of suspected tumour progression, no malignant cells could be detected, and hence four cases remain. All these four patients had received LB03002, but two of them also Genotropin during the first treatment year, and consequently it is difficult to assess the contribution (if any) of LB03002 and/or Genotropin. Furthermore, the number of events is too small for any firm conclusions.

Laboratory findings

Beyond standard laboratory tests which revealed no relevant imbalances between groups, some glycaemic parameters were evaluated at every visit in the paediatric study BPLG-004, namely HbA1c, fasting glucose and fasting insulin:

Mean HbA1c increased slightly from baseline to visit 6 by 0.06% in the LB03002 group and by 0.09% in the Genotropin group.

Mean fasting glucose increased from baseline to visit 6 by 0.4593 mmol/L in the LB03002 group and by 0.5609 mmol/L in the Genotropin group.

Mean fasting insulin increased from baseline to visit 6 by 12.90 pmol/L in the LB03002 group and by 28.40 pmol/L in the Genotropin group.

For all these glycaemic parameters similar findings were also obtained at the other visits.

The data presented confirm that somatropin may impair glucose tolerance, but the effect was small in the paediatric population. It is reassuring that no relevant differences between weekly LB03002 and daily Genotropin became obvious.

Lipid parameters (total cholesterol and triglycerides) were also followed. No meaningful differences between LB03002 and Genotropin became obvious in the paediatric studies. In the adult study, the lipid profile did not improve in the LB03002 compared to the placebo arm, although such an effect may have been expected from published data on daily administered hGH.

Safety in special populations

Special populations (e.g. elderly and patients with renal or hepatic impairment) were not studied. This is endorsed in view of the extensive clinical experience with somatropin therapy. It is not expected that weekly vs. daily administration would fundamentally change any safety aspects particular for special populations. Instead, the safety considerations provided here are expected to be valid also for special populations.

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Immunological events

A marked difference in the incidence of antibody formation was observed in children receiving LB03002 vs. Genotropin. Antibodies were mainly of the IgG1 and IgG4 classes. A detailed immunogenicity report on the pivotal paediatric trial BPLG-004 was provided; the antibody outcomes of the other trials were described briefly. The following table provides antibody frequency in the paediatric trial BPLG-004.

Table 32: Incidence of antibodies to hGH over the two year study BPLG-004

Treatment arm (as randomized	LB03002 (N=91) n (%)	Genotropin (N=87) n (%)
Patients developing anti-hGH antibodies	37 (41%)	7 (8%)
Patients with a positive test at two or more consecutive study visits	33 (36%)	4 (5%)

Most antibodies appeared around Month 3 of treatment; about half of the patients that developed antibodies were still antibody-positive at the last visit.

The mean antibody titre reached maximal levels after 6 months and slowly declined thereafter until the last measurement at 24 months, see figure below (data taken from study BPLG-004-EXT).

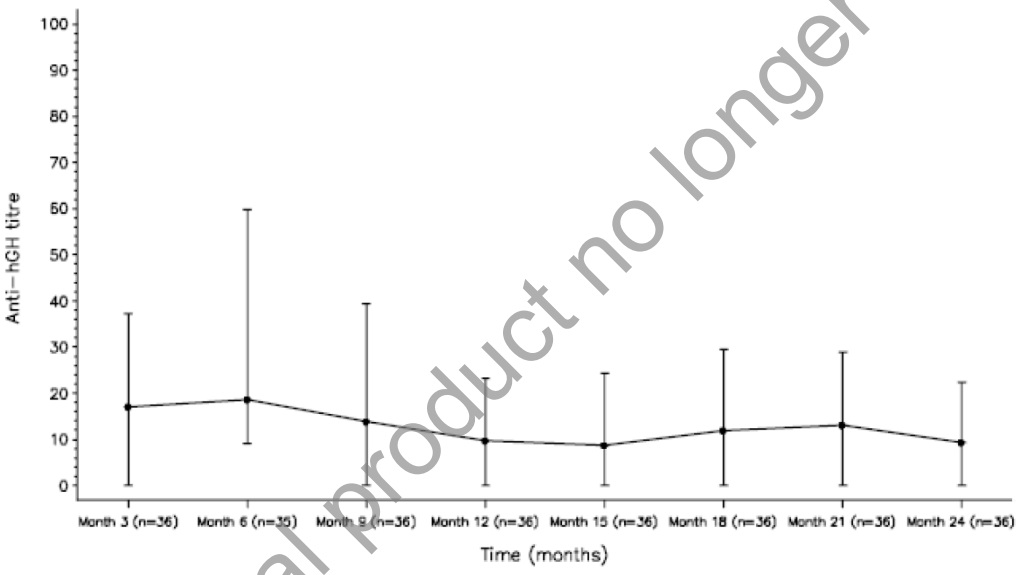

Figure 9: Median, 25% and 75% quartiles for anti-hGH AB titres over 24 months by visit in subjects being treated with LB03002 throughout

The antibodies did not affect growth velocity in a relevant way as determined in trial BPLG-004 as demonstrated by a comparison of HV for children with vs. without antibodies. The result (baseline to month 24) is depicted in the figure below (Figure 10).

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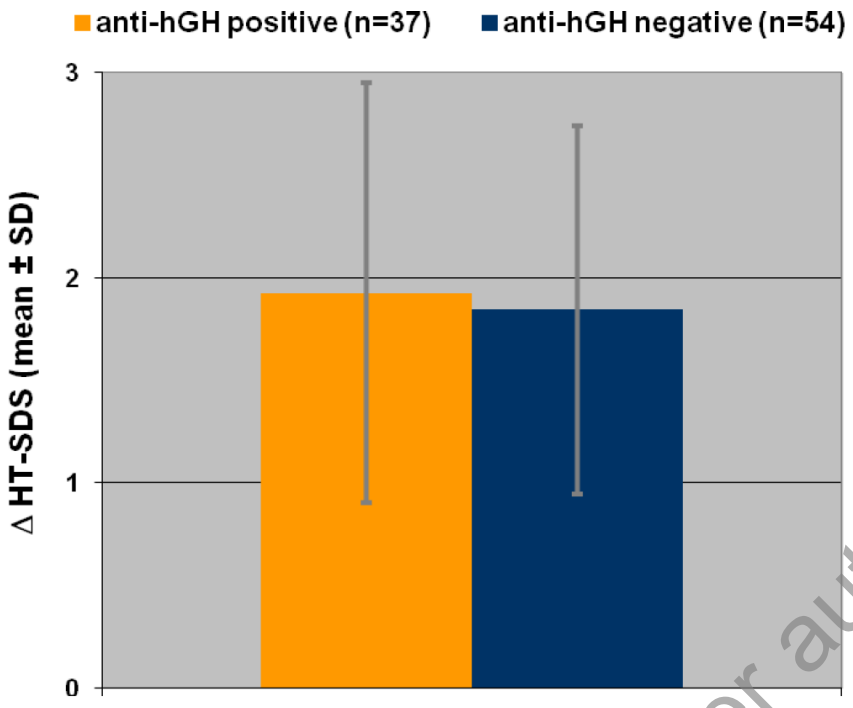

Figure 10: Influence of anti-hGH antibodies on gain in HT-SDS (24 months – baseline) in patients receiving LB03002 Throughout

In trial BPLG-004, there was one patient who reached very high antibody titres, ascending during the whole study period. This patient was found to have a homozygous defect in the GH1 gene which is known to favour formation of neutralising GH antibodies.

Adults developed antibodies much less frequently than children. In the pivotal adult trial BPLG-005 there were 4% of patients antibody-positive in the LB03002 group vs. none in the placebo group. A rate of 4% is well within the range that is expected for rGH preparations.

Discontinuation due to adverse events

Most salient reasons of discontinuation were injection site reactions and neoplasm recurrence/progression. Both aspects were already discussed in previous sections above.

Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most prominent safety findings in LB03002-treated vs. Genotropin-treated paediatric patients were:

- an increased incidence of (usually non-serious) injection site reactions;
- an increased incidence of binding, i.e. not neutralising, antibodies against hGH which, however, had no obvious clinical consequences; the mean titre slowly decreased over time.

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In adults, there was an increased incidence of events known to be related to hGH (e.g. back pain, pain in extremity and peripheral oedema) in the LB03002 as compared to the placebo group. This is expected and does not raise any particular safety concern. In adults, there was no major difference in injection site reactions between LB03002 and comparator (placebo). This was due to the fact that there was a high incidence of local reactions also in the placebo group. This indicates that the uncommon excipients of LB03002 (medium chain triglycerides and hyaluronic acid) may contribute to the local reactions to a large part.

Injection site reactions in children were mostly mild or moderate. In only two cases injection site reactions were regarded as severe in the paediatric pivotal study BPLG-004, namely one case of injection site swelling and one case of injection site pain; no abscesses occurred. However, injection site reactions led to discontinuation of the study drug in three cases and are therefore obviously not always tolerated by the patient. On the other hand, patients that experience some kind of difficulty with the daily injections may prefer weekly injections when these are well tolerated. The injection site reactions did not negatively affect compliance in the clinical trials. It should also be noted that serious local reactions such as abscesses were rare (only one case in an adult).

Since injection site reactions appear manageable and patients not tolerating the depot formulation can switch back to daily injections at any time, local tolerability is considered acceptable given the appropriate labelling in the SmPC.

Antibodies against hGH were frequently observed in children treated with LB03002 but did not appear to have an impact on safety. Neutralising potential was not detected except in one patient harbouring a GH gene deletion. Efficacy was not affected, and there were no adverse events that were clearly linked to the presence of antibodies. On the other hand, it was questioned whether general tolerability of LB03002 may decrease with the presence of antibodies although no specific AEs suggestive of being antibody-mediated became obvious. In order to detect a potentially lower general tolerability of LB03002 in case of antibody formation, the applicant provided an analysis of AE incidence stratified for antibody-positive (ab-pos) and antibody-negative (ab-neg) children in the pivotal paediatric study BPLG-004. In this analysis, injection site erythema, pyrexia, gastrointestinal disorders and headache were numerically more frequent in ab-pos children as compared to ab-neg children. These events are not considered serious, and due to the low absolute number of patients, the significance of this finding is unclear. An uneven distribution by chance of common childhood diseases between the groups would be a plausible explanation. Potential adverse events including such potentially related to the presence of antibodies will be followed post-marketing. It is reassuring that the mean antibody titres did not increase but instead gradually decreased over time (followed over 24 months), from the peak level of 29 at month 6 to 19 at month 24.

The reason for the high incidence of antibody formation in children is unclear. There could be, however, a correlation with the frequent injection site reactions in this patient group. Notably, erythema at the injection site was markedly more frequent in ab-pos children of the pivotal trial BPGL-004 (14.7% vs. 5.3%, ab-pos vs. ab-neg children; otherwise the most frequent local reaction was swelling, independent of the antibody status). This observation is in line with the theoretically conceivable assumption that antibody formation may be enhanced by local inflammation.

A general concern of hGH therapy is that the active substance could promote tumour proliferation. Normally this risk is considered small because hGH is used as substitution therapy so that its levels (or the resulting IGF-I levels) should not exceed the physiological concentrations. In children, around 2.4-times higher doses of somatropin are needed with LB administered weekly as compared to daily Genotropin to achieve similar growth responses. Due to the lower bioavailability of LB03002 this corresponds to a 1.56-fold exposure, which however leads to the same mean serum IGF-I levels as daily GH (see PK/PD sections above). The GH serum levels were not continuously elevated but only during the

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first few days after injection. Thereafter, the serum levels returned to baseline. Due to findings in the French SAGhE study, a maximal daily dose of 0.05 mg/kg is currently recommended. Thus, with the lower bioavailability of LB03002 as compared to standard daily preparations such as Genotropin, the GH exposure following LB03002 administration does not exceed this limit.

Mean IGF-I levels were not increased with LB03002, and peak IGF-I levels remained within the reference range. Therefore, the depot is not expected to be different from daily growth hormone preparations with regard to the tumour promoting effect.

The temporal profile of IGF-I serum concentration is different with LB03002 as compared to Genotropin. This could theoretically alter the action of IGF-I on certain target tissues but to date there is not any indication from existing data that this could be a safety concern. In respect to adverse events of IGF-I the absolute plasma concentration is considered important, not some undulation over time.

According to present data efficacy of LB03002 during catch-up growth is non-inferior to Genotropin, and no adverse events were observed that could be clearly attributed to the differences in kinetics and exposure. In the paediatric studies, fasting blood glucose, fasting insulin and HbA1c were determined in order to assess glycaemic control. Lipid parameters (total cholesterol and triglycerides) were also followed. No meaningful differences between LB and Genotropin were observed.

2.6.2. Conclusions on the clinical safety

Considering all relevant aspects of PK (exposure), PD (IGF-I levels) and AE profile, the safety profile of this long-acting (once weekly) GH preparation Somatropin Biopartners is overall considered acceptable. In order to investigate long-term safety in a larger population in the clinical setting, the applicant has agreed to perform a post-authorisation safety study (PASS), which is included as an additional Pharmacovigilance activity in the RMP (see below).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.5, the PRAC considers by consensus decision that the risk management system for Somatropin (Somatropin Biopartners) is acceptable for the following proposed indication:

Paediatric patients

Somatropin Biopartners is indicated in children and adolescents aged 2 to 18 years for long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone.

Adult patients

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Somatropin Biopartners is indicated for the replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency (GHD).

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 33: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hypothyroidism Hypocorticolism or hypoadrenocorticism
Important potential risks	Benign intracranial hypertension Intracranial aneurysm Intracranial haemorrhage Carpal tunnel syndrome New first neoplasm Second neoplasm in childhood cancer survivors Recurrence or progression of a pre-existing tumour Side effects related to anti-GH antibodies
Important missing information	Long term safety data Final height data Safety in elderly patients Safety in patients with hepatic impairment Safety in patients with renal impairment Pregnancy and breastfeeding Overdose Medication errors Paediatric off-label use The potential for misuse for illegal purposes

- **Pharmacovigilance plans**

Table 34: Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
Collection of data in follow-up part of study BPLG-004 (BPLG-004-FUP) Phase III, Multi-centre, Randomised, Parallel Group Study of Safety and Efficacy	To further investigate the long-term safety and to gain final height data	Missing long term safety and missing final height data	Clinical phase complete	Submission of final report Q2 2013
Observational Post	To further	Missing long term	Planned	To be

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Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
Authorisation Safety Study (PASS), including subgroup analysis to evaluate the growth response/efficacy (PAES)	investigate the long-term safety and to gain final height data	safety data and missing final height data		determined once the full study protocol is submitted (i.e. within 3 months of the Commission Decision)

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Post-authorisation Safety Study

The applicant plans to perform an observational post-authorisation safety study (PASS) to evaluate the long-term safety of LB03002. Final height is going to be addressed as efficacy parameter in a subgroup of patients from the PASS.

The PASS is designed to be a non-interventional multi-centre, open-label, prospective study including children and adolescents receiving Somatropin Biopartners in the clinical practice setting for long-term treatment of growth failure due to insufficient secretion of endogenous growth hormone.

The applicant proposed to include only 500 patients in the PASS and stated that based on the very low incidence rates of the long-term safety issues it is not feasible to address these issues in the PASS. Experience with the existing GH registries has shown that addressing the safety issue of tumour promotion within registries for single products is very challenging. These registries included large numbers of patients but could only provide limited data on these safety issues. Although it would clearly be desirable to address the outstanding concerns that relate to the whole class of GH, the applicant's argumentation on the non-feasibility of a PASS for a single GH product to address these concerns is endorsed. The currently presented data do not allow the conclusion that Somatropin Biopartners will have a different safety profile with regard to the potential risks of new first neoplasm, second neoplasm in childhood cancer survivors, recurrence or progression of a pre-existing tumour than other GH products. Therefore, there are no sufficient grounds to oblige the MAH to address these concerns independently from the overall discussion of these safety concerns for the whole class of GH products.

These safety concerns could only be addressed in an EU-wide mandatory registry for all somatropin-containing products. However, any further discussions on such a registry would rely on the final results of the EU-SAGhE study that are awaited later in 2013.

The applicant has instead proposed to conduct a PASS by monitoring the safety of Somatropin Biopartners that will include 500 patients that will be monitored for at least 10 years. Although this PASS will not allow addressing safety concerns related to the potential of tumour-promotion of the product, it will allow gaining more information on the safety profile of LB03002 in clinical practice and is therefore deemed acceptable at this stage.

- **Risk minimisation measures**

The PRAC, having considered the data submitted, was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

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3. Benefit-Risk Balance

Benefits

Beneficial effects

Paediatric indication

In children with GHD, LB03002 at a dose of 0.5 mg/kg/week demonstrated non-inferior height velocity (HV) compared to daily Genotropin at an appropriate dose of 0.21 mg/kg/week during the initial active controlled 12-month treatment period. IGF-I and IGFPB-3 levels over time as well as bone age (BA) advancement were also similar. In addition, short- and long-term growth rates (up to 4 years) observed with LB03002 were comparable to those published for daily somatropin regimens using dosages within the range recommended for GHD children in the EU (0.175 – 0.245 mg/kg/week). Based on the data available, it can be concluded that LB03002 at the proposed dose of 0.5 mg/kg/week produces the expected growth responses and growth patterns over time without undue acceleration of bone age.

Adult indication

In adults with GHD, the effect of IGF-I guided LB03002 therapy on fat mass, although modest, was statistically significant compared to placebo and appears to be within the expected range of IGF-I guided treatment with daily somatropins. Body composition endpoints, particularly fat mass have been used as main endpoints in previous trials with daily administered somatropin and can be considered the most reliable endpoint in assessing the effect of GH replacement therapy in adults. Therefore, efficacy of LB03002 in adult patients with GHD has been sufficiently demonstrated.

Uncertainty in the knowledge about the beneficial effects

Paediatric indication

Although, based on the short- and long-term data available, similar final height gain can be expected with LB03002 as with currently licensed daily somatropins, final height data from on-going clinical trials should be submitted, once available. In addition, the applicant has agreed to provide additional long-term efficacy data in the clinical practice setting as part of the post-authorisation safety study (PASS), which is included as an additional Pharmacovigilance activity in the RMP.

There is no universal agreement among paediatric endocrinologists about the optimal dose or dose adjustment algorithm for GH treatment in children. The applicant suggested further exploration of a

potential dose adjustment algorithm post-marketing, e.g. based on published growth prediction models, which is supported.

Adult indication

Treatment with LB03002 in adults with GHD did not reveal beneficial effects on lipid status or QoL, although an effect at least on serum lipids may have been expected. The applicant pointed out that no placebo-controlled study has so far been performed with individualized (IGF-I based) dose regimens, and reports on long-term improvements are exclusively based on open single centre studies or on data from surveillance databases. The applicant highlighted that inconsistent results have been reported regarding the (long-term) effect of GH treatment on serum lipids. The lack of a beneficial effect on serum lipids in study BPLG-005 may be due to the study population having been relatively healthy with either well-controlled lipids on medication before starting GH treatment, or limited GHD dependent lipid abnormalities.

Published data suggest beneficial effects of somatropin replacement therapy on intima media thickness, inflammatory markers, bone mineralisation, energy expenditure, muscle strength and QoL. Most of these parameters have not been investigated in the clinical development programme of LB03002. However, this was considered acceptable for the purpose of pure substitution therapy. As with daily somatropin, LB03002 should only be given to adults with profound GHD as clearly stated in the SmPC.

Based on all available data from the clinical development programme, LB03002 can be expected to provide similar beneficial (long-term) effects in patients with GHD as daily administered somatropin. Differences in metabolic effects due to the more undulating nature of the IGF-I levels appear unlikely.

Risks

Unfavourable effects

Generally, the AE profile of LB03002 appears to be similar to the well-known safety profile of daily somatropin regimens with the exception of an increased incidence of injection site reactions and GH antibodies associated with the use of the depot formulation in children.

In paediatric patients frequent injection site reactions, most of them being mild or moderate in severity, were observed with Somatropin Biopartners, but not with Genotropin, which led to discontinuation of the drug in a few cases (not seen in the Genotropin group). Furthermore, one case of skin atrophy due to injection of LB03002 was reported post-marketing (South Korea). Lipoatrophy has also been reported for daily injected somatropins, which emphasizes the necessity to vary the injection site. Guidance has been included accordingly in the SmPC of Somatropin Biopartners.

A higher incidence of antibodies binding to hGH (but not neutralising, except in one patient with GH gene deletion) was found with LB03002 than with Genotropin in children. Antibody titres were low in most patients and slowly decreased over time. About half of the patients developing antibodies remained ab-positive at the last visit (at month 24). These antibodies did not affect efficacy in the clinical trials and were not associated with obvious safety issues.

Cumulative exposure towards GH was around 1.5-fold higher with weekly LB03002 as compared to daily Genotropin administration. Nevertheless, this exposure is not higher than that achieved with the currently recommended maximal daily dose of 0.05 mg/kg and is therefore not considered a concern. In addition, mean IGF-I levels were not higher with weekly LB03002 compared to daily rGH administration and peak IGF-I levels remained within the reference range.

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Uncertainty in the knowledge about the unfavourable effects

From experience with daily administered somatropins and the clinical trials with LB02003, the observed increased incidence of binding antibodies against hGH in children are unlikely to create an efficacy or safety issue, but a generally decreased long-term tolerability cannot be fully excluded at this point in time. Therefore, the long-term safety of LB03002 in clinical practice, including potential long-term effects due to the presence of antibodies, will be followed in a post-marketing safety study (PASS), which is included as an additional Pharmacovigilance activity in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Deficiency in GH may already develop early in (prenatal) life and, if severe, present clinically with micropenis in males, exaggerated jaundice and/or hypoglycaemia but may also develop and/or manifest later during development or in adult life. The indications for, and the aims of therapeutic intervention are different in the paediatric and the adult populations.

The typical symptom of GHD in children is growth failure, and consequently, the main aim of treatment is the normalization of the growth rate during childhood and attainment of normal adult height. The effects of hGH replacement in children can best be evaluated by assessing the increase in height velocity and related auxological parameters as well as bone maturation.

Adult GHD presents with a more subtle and complex syndrome. The clinical features associated with this syndrome are abdominal obesity, decreased lean body mass (LBM), reduced muscle strength and exercise capacity, abnormalities in lipid status, reduced bone mineral density (BMD), dry skin, fatigue and impaired psychological well-being. The increased cardiovascular mortality observed in adult patients with hypopituitarism has been attributed to these metabolic abnormalities. Thus, the aim of treatment of GHD in adults is to reverse the abnormalities in body composition (increased body fat, decreased lean body mass and bone mass), improve lipid status (decrease in serum cholesterol, increase in HDL-cholesterol), exercise capacity and QoL.

For these reasons, somatropin replacement therapy is important for patients with GHD but established preparations for daily dosing exist. Therefore, a formulation for weekly injection is mainly for convenience. Treatment compliance was generally high in the studies and improvement in compliance with the depot compared to the daily hGH formulation cannot be derived from the clinical trial data.

Based on all data available from the clinical development programme, similar efficacy of LB03002 compared to daily somatropin preparations in adults and children with GHD has been sufficiently established.

The convenience of the depot formulation may be limited by the frequent injection site reactions observed in children, although these did not obviously affect compliance in the clinical trials and resulted in only few treatment discontinuations. Patients not tolerating the depot formulation may switch to daily injections at any time.

Benefit-risk balance

Based on the demonstration of non-inferior efficacy of LB03002 in children and adults with GHD and an acceptable safety profile, CHMP considers that the benefit - risk ratio in the indications applied for is favourable.

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Discussion on the benefit-risk balance

Although in children, based on the short- and long-term data available, similar final height gain can be expected with LB03002 as with the currently authorised daily somatropins, final height data from ongoing clinical trials should be submitted once available. In addition, the applicant has agreed to provide additional long-term efficacy data in the clinical practice setting as part of the post-authorisation safety study (PASS).

There is no universal agreement among paediatric endocrinologists about the optimal dose or dose adjustment algorithm for GH treatment in children. The applicant suggested further exploration of a potential dose adjustment algorithm post-marketing, e.g. based on published growth prediction models, which is supported.

The applicant has agreed to further evaluating long-term safety of LB03002 in clinical practice in a PASS, which is included as an additional Pharmacovigilance activity in the RMP.

Conclusions

Taken together, efficacy of LB03002 has been shown to be similar to that of daily GH treatment and the PK (exposure), PD (IGF-I levels) and AE profiles do not raise any safety concerns for this long-acting (once weekly) GH preparation. Thus, the overall benefit-risk balance for Somatropin Biopartners is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Somatropin Biopartners in the long-term treatment of growth failure in children and adolescents aged 2 to 18 years due to insufficient secretion of endogenous growth hormone, and as replacement therapy of endogenous growth hormone in adults with childhood- or adult-onset growth hormone deficiency (GHD), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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