CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

DATE: May 30, 2006

FROM: Robert J. Meyer, M.D.
Director, Office of Drug Evaluation II

TO: NDA 21-426
Omnitrope (somatropin [rhGH] for injection) 5.8 mg & 1.5 mg Lyophilized Powder
Biochemie U.S., Inc. / Sandoz – U.S. Agent
Proposed use: pediatric and adult growth hormone deficiency

SUBJECT: Additional NDA review issues / Conclusions (see Dr. Orloff's memorandum of 8-31-04 for a more in-depth discussion of overall issues)

Background/procedural issues:

I am in substantial agreement with Dr. Orloff's signatory memorandum of 8-31-04 (that memorandum is appended to this memorandum for the reader's reference). On that date, an action letter was sent stating "we [FDA] are unable at this time to reach a decision on the approvability of the application because of unresolved scientific and legal issues related to your NDA." These issues arose from the application being submitted through the approval pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and the implications that this had for follow-on protein product applications. Subsequent to the August 31, 2004, letter, public meetings and other deliberations on follow-on protein products have taken place and informed FDA policy on the "scientific and legal issues" alluded to in our 2004 action letter.

Since somatropin is not a new molecular entity, the original signatory authority for this application was appropriately delegated to the division level per usual CDER policy. However, Dr. Orloff has since left FDA and, as I have been involved in discussions on Omnitrope prior to the 2004 time frame and into the present, I have elected to assume the signatory authority for this action.

Supplemental Analysis:

Limited new data were requested of the sponsor after completion of Dr. Orloff's memorandum. The data requested constituted a final safety update and included relevant new immunogenicity data on the Biochemie-sourced lyophilized product (study EP2K-02-PhIII-Lyo). As per Dr. Orloff's memorandum, the review conclusions from the relevant expert review disciplines were all recommending approval, based on the data submitted in NDA 21-426 and FDA's prior finding of safety and efficacy for Genotropin. The biopharmaceutics review, while recommending approval

over all, did not initially find that there was a viable pharmacokinetics bridge between the two proposed formulations (1.5 mg vs. 5.8 mg), given the differences in the formulations of each, to support a dosage equivalence waiver (biowaiver) for the 1.5 mg product. However, this recommendation was made with the supposition by the reviewer that this drug might be appropriately regarded as a 505(b)(1), where no reliance on data in the public domain (such as literature) or FDA's prior finding of safety and effectiveness for Genotropin could be brought to considered. However, in light of the applicants stated intention of utilizing the 505(b)(2) pathway, this issue was discussed again with the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), including OCPB's Director Dr. Lesko, and after deliberations within OCPB, their final recommendation is that the biowaiver should be granted. I would note that Dr. Orloff's review reached this same conclusion, since Dr. Orloff believed that there was sufficient CMC bridging to allow an inference of equivalence between the formulations despite the minor differences in ingredients (most notably the benzyl alcohol, which would not be expected to change the active substance in a way that would affect bioavailability). He therefore did not believe the differences in the formulations would result in meaningful clinical differences. Thus, OCPB's final recommendation for granting of a biowaiver is concordant with Dr. Orloff's conclusions in his memorandum.

In reviewing this application and Dr. Orloff's memorandum, it is important to bear in mind that this application is for somatropin, a very well characterized single-chain, 191-amino-acid protein hormone. The amino acid sequence of human growth hormone is well known, and it is accepted that the protein is not particularly "complex" (e.g., it is not glycosylated). In addition, non-proprietary reference standards are available for this protein.

The sponsor has supplied sufficient data in NDA 21-426 to support approval of the 5.8-mg formulation of Omnitrope for treatment of pediatric growth hormone deficiency without FDA specifically referring to its previous finding of safety and efficacy for Genotropin (which is the product referenced in this NDA) or to any other approved somatropin. The sponsor relies on FDA's finding of safety and effectiveness for Genotropin pursuant to section 505(b)(2) of the Act to support approval of Omnitrope for treatment of adult GHD, as the sponsor has not provided clinical trial data for Omnitrope in this patient population. This reliance is scientifically appropriate in light of the sponsor's demonstration that the active ingredient in Omnitrope and Genotropin is somatropin, and Omnitrope and Genotropin are highly similar pharmacokinetically, pharmacodynamically, and clinically in the direct comparative trial performed in GH-deficient children. Given the highly comparable clinical results in children and the other similarities demonstrated between these products, there is a firm basis to conclude that the use of Omnitrope in adults with GH deficiency would be safe and effective, based on the previous finding that Genotropin is safe and effective for this use.

Given the current state of knowledge about human growth hormone, our review of the Omnitrope NDA focused on whether the sponsor demonstrated the following:

- The gene construct and biologic system utilized results in a protein that is, by primary amino acid sequence, identical to hGH (somatropin). As stated above, the primary structure of hGH is well-known and there are World Health Organization, European Pharmacopoeia, and, more recently, USP reference standards by which to evaluate the similarity of other relevant characteristics. In this case, the sponsor has demonstrated the similarity of their

drug substance to the WHO and European Pharmacopoeia standards, and to Genotropin as well.[1]

- The sponsor's specified and actual production method leads to an acceptably pure and reproducible supply of drug substance.
- The formulation is tolerated and lacks remarkable short-term local and systemic toxicities, as demonstrated in preclinical animal models. Reaching this conclusion is facilitated if the excipients used in the drug product are not unique to the proposed formulation, but rather have been used in other formulations administered by the same route of administration (in this case, subcutaneously).
- The drug product, administered as proposed, results in reliable drug delivery, as assessed by pharmacokinetics, and drug action as evidenced by relevant short-term measures of pharmacodynamics — such as measures of resultant insulin-like growth factor-1 (IGF-1) levels and measures of IGF binding protein following administration.
- The drug product has acceptable immunogenicity and, specifically, there are neither untoward allergic responses, such as anaphylaxis, nor the development of neutralizing antibodies that would negate further response to exogenous hGH administration and any remaining endogenous GH secretion.
- And, finally, the data in the application demonstrates that the drug product administered as recommended leads to a meaningful clinical action of the drug in terms of the actions expected of hGH (e.g., growth in GH-deficient children).

Given the well-known effects of GH, including the natural "experiment" of GH excess in acromegaly, and given the specificity of immune responses in humans, other than testing for any toxicities of the unique formulation, there is little to be gained from preclinical animal testing of a new native-sequence hGH drug product in terms of general toxicology or immunotoxicology. Therefore, while many 505(b)(2) applications will rely on the finding of safety and efficacy for a reference product as a means of avoiding having to repeat (needlessly) previously conducted animal toxicology studies, the preclinical data submitted in the Omnitrope NDA (including a hypophysectomized rat weight gain assay, a subacute 14-day rat toxicology study, and a local (skin) tolerance study in rabbits) are sufficient without specific reference to the Agency's findings for Genotropin or any other approved somatropin. In fact, the sponsor has provided adequate information for Omnitrope to address all of the above bullets and to therefore obtain approval for the 5.8-mg formulation of Omnitrope for the treatment of pediatric GH deficiency based on these data alone. Although Genotropin was used as a concurrent control in the sponsor's non-inferiority trial, the data from this trial are newly generated and stand on their own (without reliance on the Agency's finding of safety or effectiveness for Genotropin). The comparative data generated from the first 9 months of the Omnitrope phase 3 program, given historical data with hGHs in general,[2] serve as a means of further substantiating the Omnitrope data for the claims proposed in the relevant pediatric population, where the growth effect of Omnitrope not only compares favorably to

[1] It should be noted that use of the term "similarity" in this memorandum encompasses the terms "similarity" and "comparability" as used, often interchangeably, in Dr. Orloff's memorandum and in various memoranda from the relevant expert review disciplines.

[2] The Omnitrope application included historical data on the efficacy of somatropin in children with growth hormone deficiency. The statistical reviewer evaluated this data, approved rhGH labeling, and selected published literature as a supplementary tool. In determining the basis for the statistical reviewers' conclusion regarding the efficacy of Omnitrope for treatment of pediatric GHD, the team leader for this statistical review advised that the approval recommendation was based on the data from Omnitrope's phase 3 clinical program.

historical references, but to the direct active comparator as well.. In fact, as Dr. Orloff (and Dr. Roman in his primary medical officer review) points out, Omnitrope performed quite comparably to Genotropin in this clinical study, with a non-significant numerical advantage over Genotropin in one important attribute, the standard deviation score for height velocity (or HVSDS).

One scientific issue with this application is that in the original trial, the source of the drug substance was from Covance. This drug substance supplier was used for the clinical trial material in the first 9 months of the trial during which there was a direct comparison to Genotropin. This drug substance supply proved in retrospect to have a fairly high amount of host-cell (E. coli)-related antigen and this was associated with high rates of anti-GH antibody production. In fact, at the 9-month time point, 59% of subjects in the Omnitrope arm had developed anti-GH antibodies compared to only 2% having such antibodies with Genotropin treatment. Following the 9-month time point, all patients were switched to Omnitrope formulations, with the drug substance now being sourced from Biochemie. The Biochemie product was shown by in vitro characterization studies to be cleaner in terms of host-cell proteins/antigens. The Omnitrope lyophilized product with the Biochemie-sourced drug substance was used to dose patients previously assigned to the Covance product for the next 6 months. Over these 6 months of treatment, 11 of the 24 patient who were antibody positive following the Covance treatment lost their anti-GH antibodies, which is affirmative evidence that Omnitrope produced with the Biochemie drug substance is much less immunogenic than that from Covance.

In the arm that previously received Genotropin during the initial nine months of the trial, patients were switched to Omnitrope liquid (product that is already in a liquid form rather than a lyophile for reconstitution). This product again was made with the Biochemie drug substance. In this group, the rate of antibody positivity during the next 6 months of treatment was unchanged (2% at 15 months vs. the 2% positivity following Genotropin therapy).

At the end of 15 months, all patients, irrespective of prior treatment, were placed on Omnitrope liquid. Patients were then assessed for anti-GH antibody status through month 36 of the study sequence. In the patients originally on Genotropin, the immunogenicity remained low, between 2 – 5%, with no more than 2 patients showing anti-GH antibody positivity at any given assessment. In the patients first treated with the Covance lyophilized product and then the two formulations of Omnitrope, the antibody positivity continued to decline, with only 6 of 38 patients (16%) remaining antibody positive at month 36. In the final safety update, data out to month 66 showed a leveling off of anti-GH antibodies at this point and beyond in this group of patients reaching 14% at month 42. These data taken together strongly support that drug substance from Biochemie is sufficiently refined with regard to antigens to lead to a product – whether in lyophilized form or liquid – that is acceptable from a clinical standpoint.

Importantly, even considering only the clinical results with the original Covance material, the data during the first 9-month comparative portion of the trial showed that children who developed anti-GH antibodies did not have definable differences in growth rates compared to those who were antibody negative. Therefore, one can conclude that the anti-GH antibodies that were prompted by the higher levels of host-cell proteins were not neutralizing in their effects. It should also be noted that there was slightly more eosinophilia (the blood leukocyte often associated with allergy) seen with the Covance product than with either Genotropin or Biochemie product. However, the

Biochemie treated patients had eosinophilia rates similar to, if not lower than, Genotropin patients. It must also be pointed out that there was not a signal of notable differences related to serious allergic events between the overall Omnitrope experience (including the 9-month use of Covance product) and the experience with Genotropin.

Finally, the final safety update also included data submitted from study EP2K-02-PhIII-Lyo, a study using the lyophilized product proposed for marketing for 24 months of treatment. This study enrolled 51 subjects, 50 of whom contributed data at the 24-month time point. The trial again confirms the efficacy of Omnitrope against a historical control. More to the point, the trial also showed a very low rate of anti-GH antibody development in patients (actually, no patients on Omnitrope developed anti-GH antibodies through month 24 of the trial). This rate is certainly comparable to, if not lower than, historical rates in general or rates reported with Genotropin specifically. This study also assessed anti-HCP (host cell protein) antibody development and showed a very low rate of this as well (one subject showed anti-HCP at several assessments). Finally, no remarkable safety signals were seen in this trial suggestive of anaphylaxis or other important allergic reactions. These data provide final confirmation of the acceptable immunotoxicity profile of the to-be-marketed Omnitrope lyophilized preparation.

One final issue worth noting briefly is that the final composition of the "to-be-marketed" lyophilized product is slightly different from that of the tested product (the level of the [redacted] is marginally lower and the [redacted] marginally higher). These changes in the relative exact compositions of the two sodium phosphate buffers are quite minor, and would not be expected to change product performance, including immunogenicity. Given the minor nature of these changes, one should reasonably conclude that the expected results of therapy with the "to-be-marketed" formulation are fairly represented by the results from the lyophilized product tested in the latter phases of the clinical trials, including EP2K-02-PhIII-Lyo.

I therefore concur with Dr. Orloff's prior opinion that these data are adequate to establish that Omnitrope as proposed for marketing (the lyophilized product) is sufficiently safe and effective with regard to immunogenicity and any resultant consequences. In my mind, how Omnitrope equates to the immunogenicity of Genotropin, while interesting, is immaterial to the approval of Omnitrope through the 505(b)(2) pathway, as the immunogenicity response with Omnitrope (both Covance and Biochemie-sourced substance) was characterized and there were no clinical consequences seen, either in terms of diminished efficacy or in terms of worrisome safety findings in clinical trials. Nevertheless, the results of the EP2K-02-PhIII-lyo study, submitted in the safety update, establish the very acceptable immunogenicity profile of the lyophilized drug product with a rate of immunogenicity at 24 months that is as low, if not lower, than other approved products, including the referenced Genotropin.

For this application, the findings for which we need to refer to the Genotropin approval and to published literature (i.e, data not owned by the applicant or data for which the applicant has not obtained a right of reference) are for the safety and effectiveness of rhGH to treat GH-deficient adults (and, as discussed below, to support the biowaiver for the 1.5-mg dose strength). I find no reason to believe that if Omnitrope and Genotropin are clinically equally efficacious in children (even with the initial, relatively immunogenic Covance drug substance) that the finding of efficacy

of adults with Genotropin could not be inferred as applying to final Omnitrope formulation. This is further bolstered by the evidence regarding somatropins as in the cited publications.

One area where I paid special attention for this review summary was whether FDA could accept the request for a biowaiver of the 1.5 mg product, as suggested by Dr. Orloff's conclusions on the approvability of the 1.5 mg product. This was due to the original biopharmaceutics review stating that there was a need for PK data linking this product to the 5.8 mg product due to differences in the formulation.[3] While I agreed with Dr. Orloff's conclusion that there is in all likelihood no anticipated differences in bioavailability between the two, I had concerns about what the final OCPB recommendation might be. As previously noted, when this issue was further discussed with OCPB (including discussions with Dr. Lesko, the Director), OCPB's final recommendation was for allowing a biowaiver, with the understanding that this product is now clearly a 505(b)(2) and that literature regarding somatropin and FDA's prior finding of safety and efficacy for Genotropin could be relied on to make the conclusion. Given that, OCPB finds, and I concur, that the minor differences in formulation would not lead to changes in the somatropin molecule that would affect bioavailability through the relevant route of administration.

Establishment Evaluation Request:

The overall Compliance recommendation was satisfactory on August 13, 2004, for the Omnitrope Lyophilized formulation product. This remains valid for 2 years (i.e., that is, the recommendation is still in place).

Conclusions:

I believe the data submitted within this NDA support approval of the 5.8-mg formulation of Omnitrope for the treatment of pediatric GH deficiency without the need to refer to the finding of safety and efficacy of Genotropin or to specific data in the literature. The sponsor has satisfactorily addressed the scientific questions outlined in the bullets above. Since Genotropin was used as the positive-control in the phase 3 pediatric study of Omnitrope with similar efficacy and safety with the original drug substance source, since there is bridging data for the subsequent revisions to the drug product, and since Genotropin has been approved as safe and effective in replacement therapy in GH-deficient adults, I believe we can reference that previous finding of safety and efficacy of Genotropin, supported by the cited literature, for this indication and approve Omnitrope for treatment of adult GH deficiency, as requested by the sponsor.

At this time, with final labeling agreed upon and the acceptability of the final safety update assured and further adding to the scientific basis for approval, I will take an approval action for Omnitrope.

[3] The composition of the 1.5-mg formulation is not proportional to the 5.8-mg formulation, and the 1.5-mg formulation does not contain benzyl alcohol.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 31, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-426
Omnitrope (somatropin [rhGH] for injection) 5.8 mg & 1.5 mg Lyophilized Powder
Biochemie U.S., Inc.
Proposed use: pediatric and adult growth hormone deficiency

SUBJECT: NDA review issues

I. Introduction

This memorandum constitutes a summary review of the information contained in NDA 21-426, providing for the use of Omnitrope for the treatment of pediatric and adult growth hormone deficiency. Conclusions and recommendations based on the scientific merits of the information presented represent the best current thinking of the Division but explicitly do not take into account the various scientific, legal, and regulatory challenges raised by third parties to Agency approval of protein products, including recombinant human growth hormone (rhGH), under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. For many of its regulatory actions, FDA engages in discussion and deliberation with outside parties, including advisors and consultants, in order to reach final decisions. Against the backdrop of the uncertainties around the best approach to regulatory oversight of potential follow-on proteins, FDA has begun a public process involving interested parties to aid in rendering a scientifically and legally tenable policy on this issue. Final regulatory action on this application therefore awaits development of such a policy as it applies to human growth hormone.

II. Executive summary

This application proposes approval under section 505(b)(2) of the Act of a new recombinant human growth hormone drug product for the treatment of pediatric and adult growth hormone deficiency (GHD), relying in part on previous findings of safety and effectiveness of Genotropin (Pfizer), an approved rhGH product.[4] The Omnitrope drug substance is made using recombinant DNA technology, specifically employing a bioengineered *E. coli* transformed with a plasmid containing a synthetic cDNA encoding hGH. The protein product of this expression system has an amino acid sequence identical to the sequence of human growth hormone (somatropin) that has been thoroughly documented in the application.

[4] As discussed herein, to rely on our previous findings with respect to Genotropin, the sponsor has "bridged" its product to Genotropin by demonstrating that the products are comparable in their active ingredients, bioavailability, chemical characterization, and efficacy and safety in one target population, among other things.

As above, the sponsor has established that the drug substance used in the Omnitrope formulation proposed for marketing (as well as another used in the early clinical trial formulation) is somatropin. They have also established through extensive chemical analyses that the drug product is comparable, or substantially similar, to Genotropin. The dissimilarities lie in the impurity profile of Omnitrope. Per the ONDC review, summarized below, the impurities have been adequately characterized, controlled, and acceptable product specifications established. The sponsor has characterized the rate and extent of absorption of Omnitrope based on its pharmacokinetic profile after subcutaneous administration in octreotide-suppressed healthy volunteers, and its clinical growth-promoting effects, immunogenicity, and overall safety profile in children with GHD. The biopharmaceutics and clinical trials program, with bridging across drug substance and formulation changes, further establishes that the rate and extent of absorption of Omnitrope are comparable to Genotropin, and, finally, that Omnitrope is clinically comparable to Genotropin.

In sum, the Division's current assessment is that the data contained in the NDA establish that Omnitrope is a safe, effective, and non-immunogenic rhGH product. In addition, the data establish that Omnitrope is comparable to Genotropin. As such, based on reports of clinical studies in pediatric GHD as well as relying in part on previous findings of safety and effectiveness of Genotropin, Omnitrope can be labeled for safe and effective use in the same patient populations as Genotropin, namely pediatric and adult GHD.

III. Background

Human Growth Hormone

Structural characteristics

[redacted]

Pharmacology

The clinical pharmacology of growth hormone is extremely well documented and understood and constitutes common medical scientific knowledge. Growth hormone action occurs via binding to a single, specific, cognate cell surface receptor which then mediates all of the well-described direct and indirect (via IGF-1) effects of growth hormone. To date, no alternative receptors mediating GH action have been identified. Likewise, there is no evidence for non-receptor-mediated actions of GH. Thus, as for other peptide and non-peptide hormones, the chemical structure of GH determines the specificity of its receptor binding and therefore of its biological actions. It is important to emphasize the universal dependence on this structure-function specificity for the therapeutic actions of hGH. Therefore, the conclusion of safety and effectiveness of a new native sequence rhGH product (whether by reference or based on full

reports of safety and effectiveness in the target population) would apply, logically and in fact, to any and all clinical uses for which GH has been shown to be safe and effective.

The biological effects of growth hormone have been demonstrated in isolated cells, tissues, or organs, in whole animals, and in humans from both clinical trials and from the "experiment of nature" associated with chronic growth hormone excess, acromegaly. Perhaps the best known therapeutic effect of GH in humans is its promotion of growth in children with growth hormone deficiency. With the replacement of missing GH, children with GHD will demonstrate accelerated ("catch-up") growth and in many instances ultimately achieve normal-range final adult heights.

Safety/Toxicology

The clinical effects (toxicities) of excess human growth hormone are known and have been thoroughly characterized based on the natural (untreated) history of acromegaly (endogenous growth hormone excess due to a pituitary somatotroph tumor). The clinical hallmarks of acromegaly are very well known and described extensively in standard textbooks of medicine and endocrinology. Furthermore, toxicities associated with the clinical use of human growth hormone are also well understood from published information, which documents, among other effects, abnormalities in glucose homeostasis, abnormalities of salt and water balance and of connective tissue leading to joint and tendon-sheath symptoms, and rare benign intracranial hypertension (in children treated with GH), all mechanism-of-action and dose- related. In light of the above, animal toxicologic assays of growth hormone *per se* are not necessary to understand the consequences of GH excess, either acute or chronic. Animal toxicity testing is not necessary for rhGH products unless, the products contain novel (not previously used) excipients and/or novel impurities.

Some GH NDAs have included data from 3-month "toxicity" studies in monkeys. These studies were not and are not needed to characterize the toxicity *per se* of GH (as noted above, the effects of GH excess are well known). Rather, such studies were undertaken as "screens" for potential immunogenicity in humans. This "screening" in monkeys arose from the finding that the well-recognized immunogenicity in humans of methionyl-GH (the first approved GH product—Genentech) carried over to rhesus monkeys, whereas the relatively non-immunogenic (in humans) native-sequence GH was similarly non-immunogenic in rhesus monkeys. Therefore, studies in monkeys were posited to have the capacity to distinguish more generally GH products with potential greater immunogenicity in humans from those expected to be less immunogenic in humans. Monkey immunogenicity data in no way obviate the need for immunogenicity assessments in humans. Human immunogenicity data have always been required and, for obvious reasons, always "trump" the monkey data. The Omnitrope NDA does not include monkey immunogenicity data (the sponsor did not develop these data, and the Omnitrope clinical program was complete at the time of the sponsor's initial interactions with FDA). However, such data are not necessary because, as discussed below, the NDA includes human data establishing that the drug product proposed for approval is not significantly immunogenic, and monkey data are not, as explained above, otherwise needed to assess the product's toxicity.

IV. Omnitrope NDA review
Clinical Efficacy

The phase 3 clinical program for Omnitrope involved different formulations (lyophilized powder and liquid) and a change in drug substance manufacturer to address high levels of host cell proteins and resultant immunogenicity of the first clinical trial formulation. Bridging across formulations is accomplished through data from extensive chemical characterization, bioassay, bioavailability studies, pharmocodynamic studies, and clinical trials.

The clinical program is diagrammed in figure 1 on page 28 of the medical officer review and discussed in detail in the medical and statistical reviews.

Prepubertal children (n=89) with growth hormone deficiency by standard diagnostic criteria were randomized to open-label treatment with either Omnitrope lyophilized powder using drug substance from Covance, U.S.A. (n=44) or Genotropin (n=45) at standard doses. After 9 months of follow-up on these therapies, all but 3 patients were enrolled, without interruption in therapy, into a 6-month open-label follow-up study whereby patients taking Covance Omnitrope were continued on Omnitrope lyophilized powder but with a formulation using drug substance from Biochemie, Austria (hereafter referred to as Biochemie Omnitrope), and those taking Genotropin were switched to Omnitrope liquid using the same drug substance. As above, the reason for the switch to a new manufacturer was the observation of the development of anti-GH antibodies in a high percentage of those treated with Omnitrope from Covance, U.S.A., attributed to high levels of host cell proteins in the Covance product. These impurities were addressed in the manufacture of the Biochemie, Austria drug substance, and as discussed further below, the Biochemie material was shown not to be significantly immunogenic. (Antibodies to GH do develop in some patients treated with GH, and this is well-described in published literature. Historically, this was most prevalent with the use of methionyl GH, however patients treated with native-sequence GH also, in rare instances, develop antibodies.)

At the end of 15 months of treatment, all 86 remaining patients were switched to Omnitrope Liquid using Biochemie drug substance, and treated and followed for an additional 15 months. These additional exposures will not be reviewed here except to say that the effects of continued treatment with Omnitrope liquid on height-related variables and on IGF-1 were consistent with the effects observed during the first 15 months of Omnitrope therapy.

The first 9 months of treatment clearly demonstrate the efficacy of Omnitrope in promoting growth in children with GHD. This was a period of continuous treatment with a single Omnitrope drug product and a direct comparison to the effect of Genotropin in this population. The primary endpoint measure of all the investigations was height by stadiometry, from which is calculated height standard deviation score (HSDS), height velocity, height velocity standard deviation score (HVSDS), and projected final height. The standard deviation scores are based on normative height data by age. Baseline characteristics by treatment groups at month 0 are summarized in Table 1 of the statistical review. Of note, mean and median ages across treatment groups was 7-8 years; mean height SDS was approximate -3.00, and mean height velocity was approximately 4 cm/year, consistent with GHD.

As summarized in the statistical review in tables 2-7 and accompanying figures, the effect of Omnitrope over 9 months was comparable to Genotropin with regard to change in height, change in height SDS, change in height velocity, and change in height velocity SDS. For example, the annualized height velocity increased in both treatment groups from a baseline of approximately 4 cm/year to approximately 12 cm/year by month 3 and was approximately 10.5 cm/year by month 9. The table that follows summarizes the statistical comparison of height-related efficacy variables between Omnitrope and Genotropin for the 9 months of the head-to-head trial. As is clear, the numerical differences in the effects of treatment are small, not statistically significant (do not exclude a difference of zero), and (as per the 95% confidence intervals for the treatment differences) leave open the possibility that Omnitrope is either slightly less effective or slightly more effective than Genotropin.

Month 9 growth effects of Omnitrope and Genotropin					
	Omnitrope LS mean	Genotropin LS mean	Tx diff	p-value	95% CI
Height (cm)	119.8	119.6	0.23	0.58	-0.59, 1.06
HSDS	-2.29	-2.41	0.13	0.15	-0.05, 0.30
Height velocity (cm/yr)	10.6	10.8	-0.23	0.69	-1.37, 0.91
HVSDS	6.03	5.38	0.64	0.39	-0.83, 2.12

The effect of Omnitrope was clearly comparable to that of Genotropin in this head-to-head comparison. In addition, the effects of both were consistent with those of other effective growth hormones based on information culled by the sponsor and submitted in the application (and summarized in table 11 of the statistical review) from the publicly available Genotropin, Nutropin, Nutropin AQ, and Humatrope NDA summaries, from the Nutropin Depot prescribing information, and from published literature. These data show mean height velocity after 12 months of GH treatment in children with GHD ranging from ~7.7 to ~13 cm/year. Figure 6 of the statistical review plots the means with 95% CI for height velocity from the Omnitrope 12-month time point and from the 12-month data from table 11, clearly showing the consistency of the Omnitrope effect with historical data. Additionally, the effects of Omnitrope on height, height velocity, and standardized scores were all highly statistically significantly greater than baseline.

It should be noted here that previous hGH clinical programs have not, as a rule, included concurrent controls in trials in pediatric GHD. Therefore, conclusion of efficacy of a GH product in GHD children relies on the observed change in rate of linear growth on treatment relative to baseline. In particular, in these circumstances trials with no-treatment or placebo controls would be likely to raise substantial ethical concerns. This is not only because the natural (untreated) history of pediatric GHD is well described, highly predictable with regard to growth consequences, and not spontaneously reversed, but also because the effect of adequate GH replacement in such children is known to be dramatic, as documented in multiple studies and reviews in the published literature. The well-described, published effects of hGH replacement therapy in these children routinely have served as benchmarks in considering the demonstrated effects of novel hGH products.

Although the drug substance in the proposed-for-market Omnitrope product (from Biochemie, Austria) was not formally studied in GH-naïve GHD children, it is important to note that the transition from the Covance drug substance at month 9 to the Biochemie drug substance resulted in continuation of constant growth out to month 15 along the curve for the ITT population established in months 0-9 (see figure 1 in the statistical review). Consistent with this observation, the effects on IGF-1 and IGFBP-3 serum concentrations (markers of GH pharmacodynamic action) observed over the first 9 months of treatment relative to baseline in response to Covance Omnitrope were maintained to month 15 after 6 months of treatment with Biochemie Omnitrope. Likewise, in the cohort treated with Genotropin for the first 9 months of the study, effects on growth and pharmacodynamic variables are similarly maintained by Biochemie Omnitrope from months 9 to 15 (see table 7 in the statistical review and table 6 in the medical officer review). These data, along with the extensive chemical characterization and biopharmaceutics data discussed below, adequately bridge the initial clinical trial drug substance and formulation to the product proposed for market.

Clinical Safety and Immunogenicity

With regard to the safety of Omnitrope, the Covance product demonstrated a profile similar to that of Genotropin. There were no deaths, drug-related serious adverse events, or withdrawals due to adverse events in the clinical trials. As mentioned elsewhere, the Covance material was immunogenic, and this was believed to be due to high levels of host cell proteins. Therefore, this

was a distinction in its overall clinical performance from Genotropin in the concurrent comparison 9-month study as initial hGH therapy in children with GHD. However, as is clear from the discussion of efficacy above, these antibodies did not neutralize the growth-promoting effects of Omnitrope. As is shown in figure 1 on page 65 of the medical officer review, the switch from Covance Omnitrope to Biochemie Omnitrope resulted in a progressive decline in the percentage of antibody-positive patients over 21 additional months of treatment. Furthermore, in the patients treated with Biochemie Omnitrope following 9 months of treatment with Genotropin, among whom there was a low incidence of antibody positivity (~ 5%), Omnitrope treatment was not associated with a meaningfully increased incidence of antibody positivity over the subsequent 21 months. Indeed, at any given time point between months 9 and 30, no more than 1-2 patients (3-5%) were antibody positive in the cohort initially treated with Genotropin and then subsequently with Biochemie Omnitrope. This rate is consistent with the published literature for hGH products. (Of note, methionyl GH, one of the initially approved and marketed GH products, was associated with a rate of GH antibody positivity as high as ~50%.)

In sum, the immunogenicity of Biochemie Omnitrope is low, not clinically significant, consistent with historical (published) data for native sequence rhGH products, comparable to Genotropin, and, overall, acceptable.

Labeling
Labeling discussions have not yet been undertaken.

Biopharmaceutics
The Biopharmaceutics package is adequate to label the proposed-for-market drug product, Omnitrope lyophilized powder. This is based on a double-blind, randomized, placebo-controlled, two-way crossover study of pharmacokinetics and pharmacodynamics of Omnitrope (Covance) (5 mg sc injection) in 12 healthy male and female subjects treated with continuous infusion of octreotide (somatostatin analogue) to suppress endogenous GH secretion. As pointed out by the reviewer, inability to detect GH in placebo samples (see figure 1 of the OCPB review) confirms the effect of octreotide. Robust effects on IGF-1 and IGFBP-3 were observed over 96 hours of sampling.

Extrapolation of the biopharmaceutics data from the study of Covance material to Biochemie material proposed for marketing is based, formally, on the results of a double-blind, randomized, 2-way crossover study to assess the comparative bioavailability and pharmacodynamic effects of 5 mg sc injection of Covance Omnitrope Powder and Biochemie Omnitrope Liquid. This study was conducted in 24 healthy volunteers treated with continuous octreotide infusion to suppress endogenous GH secretion. The data on Cmax and AUC (0-24), as shown in table 3 and figure 3 of the OCPB review, would meet bioequivalence criteria as applied to comparisons of rate and extent of absorption of small molecule drugs. The formulations were also pharmacodynamically comparable with regard to effects on IGF-1 and IGFBP-3. The pharmacodynamic comparability between products made using drug substances from different sources is certainly in keeping with the observation of consistent clinical efficacy in patients treated sequentially with Covance Omnitrope and Biochemie Omnitrope.

To create a biopharmaceutics-based "bridge" to the finding of safety and effectiveness for Genotropin, a double-blind, randomized, two-way crossover comparative bioavailability and pharmacodynamic study of Covance Omnitrope and Genotropin was conducted in 24 octreotide-suppressed healthy volunteers after sc injection of 5.8 mg of each product. As shown in Table 6 and Figure 6 of the OCPB review, the ratios of the means for Cmax and AUC for Omnitrope and Genotropin fall within the confidence interval of 80%-125%, and would therefore meet bioequivalence criteria that are applied to small molecule drugs. Likewise, pharmacodynamic comparability was also demonstrated, consistent with the data comparing effects on growth-related variables of Omnitrope and Genotropin.

These results, in conjunction with the chemical characterization data, and confirmed by the findings in the clinical trials, would also support a conclusion of bioequivalence of Biochemie Omnitrope proposed for market and Genotropin, were we to apply the same criteria we use in the evaluation of small molecule drugs. The extent to which bioequivalence criteria for small molecule drugs can support the "sameness" of follow-on protein products such as rhGH is likely to be further addressed through the public process the Agency is conducting.

No clinical studies or biopharmaceutics investigations have been conducted of the 1.5 mg product. Differences exist in the proportions of active and inactive ingredients between the 5.8 mg vial and 1.5 mg vial such that the biopharmaceutic data using the 5.8 mg product cannot be extrapolated to the 1.5 mg product. However, the OCPB review observes that the differences in the amounts of inactive ingredients between Omnitrope 1.5 mg and Genotropin 1.5 mg are smaller than the differences in the amounts of these same ingredients between Omnitrope 5.8 mg and Genotropin 5.8 mg. Insofar as the 5.8 mg strengths of Omnitrope and Genotropin have essentially identical rates and extents of absorption, it may be assumed that the 1.5 strengths would as well . Therefore, relying on the previous finding of safety and effectiveness of Genotropin, including of the 1.5 mg strength, the Omnitrope 1.5 mg strength is also safe and effective. Accordingly, this strength, like the 5.8 strength, may be approved. [redacted] Such information may be included in the label at a future time if a separate bioequivalence study is conducted postapproval.

Pharmacology/Toxicology

The applicant submitted the following preclinical pharmacology and toxicology studies with the NDA:

1. rat weight gain bioassays in hypophysectomized (thus GH deficient) rats to demonstrate biological activity
2. a subacute (14-day) toxicology study in rats
3. a local (skin) tolerance study in rabbits.

The results of these studies are discussed in the pharmacology/toxicology review and bear no further comment here.

Chemistry/ Microbiology

Chemistry

The drug substance used in the manufacture of Omnitrope is produced in an *E. coli* strain transformed with a plasmid containing a cDNA sequence encoding hGH. The drug substance used in the product studied in the initial studies, including the 9-month parallel group comparison study to Genotropin in children with GHD, was produced at Covance, USA, and the material used in the product proposed for market and used in the clinical exposures beyond the first 9 months is manufactured at Biochemie, Austria.

Chemical characterization was carried out of drug substance manufactured at both sites, including 4 full-scale batches from the Biochemie, Austria site. Among other procedures commonly used in characterizing peptides, complete peptide mapping of the molecules, partial amino acid sequencing, and sequence deduction based on the vector cDNA sequence, lead to a conclusion that both drug substances (Covance and Biochemie) have amino acid sequences identical to that of human GH. Furthermore, full chemical characterization studies indicate that the Covance and Biochemie drug substances are comparable overall. Covance material was shown to be comparable to Genotropin. Finally, Table 1 (p. 16) in the CMC review (#1) summarizes the results of the extensive characterization studies of the commercial scale batches made at Biochemie and demonstrates comparability to Genotropin as well as to two GH standards, including a WHO standard.

The Omnitrope drug substance from Biochemie does contain process-related impurities that do not appear in the tested Genotropin lots. Based on the batches used in the clinical studies, these are acceptable at documented levels and limits for these impurities are established for the drug product specifications.

Finally, as part of the Biochemie drug substance characterization, sequencing of vector DNA at the end of production establishes the stability of the hGH coding region.

Drug Product

Because inadequate U.S. Genotropin was available for the clinical studies conducted by the sponsor, and the need, therefore, for European marketed Genotropin, the sponsor conducted comparative characterization studies using multiple analytical tests (table 5, CMC review #1). The results demonstrate that the U.S. and European Genotropin products are comparable.

The impurity profiles of Omnitrope and Genotropin are similar but not identical. [redacted] impurities are detected in Omnitrope that are not present in Genotropin according to the sponsor's analyses (N.B., no information was reviewed on the impurity profile and specifications for Genotropin according to the approved NDA CMC section). The Omnitrope impurities are addressed in the in-process controls for the drug product.

The biological activity of different batches of Omnitrope made from drug substance manufactured at both Covance and Biochemie was compared to that of international reference standards and Genotropin, using the rat weight gain assay. The results showed activity similar to the reference standards and to Genotropin. If anything, the bioactivity (IU/mg) for Omnitrope was somewhat higher than for the comparators, suggesting perhaps a greater degree of purity.

In sum, adequate information is provided to establish comparability of Omnitrope drug substance used in the product intended for market to material used in the early portion of the phase 3 program in pediatric GHD. In addition, Omnitrope drug substance from both sources is comparable by physical chemical characterization to Genotropin and reference standards. Omnitrope drug product made using substance from both sites is chemically comparable to Genotropin and reference standards and has similar bioactivity to Genotropin and reference standards. Process-related impurities exist in Omnitrope that are not present in Genotropin and these are addressed in product specifications.

The CMC reviewer concludes that "the applicant has satisfactorily demonstrated by full physico-chemical and biological characterization that the active ingredient of Omnitrope is human growth hormone (somatropin). Additionally, the applicant has demonstrated that the somatropin in Omnitrope is comparable to the somatropin in Genotropin." I concur.

Beyond this extensive physical chemical characterization of the drug product, as would be required to establish the identify, purity, and potency of any recombinant protein product, the remaining CMC information, including stability of the drug product and in-use stability of the diluted material, as well as the establishment inspections, are satisfactory and ONDC recommends approval.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

Microbiology
The microbiology final review finds no deficiencies the would lead to concerns over sterility assurance and recommends approval.

Therapeutic Equivalence
The sponsor has not requested a determination of the therapeutic equivalence of Omnitrope to Genotropin. Accordingly, we are not rendering a determination in this regard.

DSI/Data Integrity
No DSI audits were conducted. Monitoring functions at the clinical sites were performed by [redacted] An EMEA audit conducted in February 2000 was reported by the sponsor in the NDA. Violations related to informed consent procedures were cited as was the use of GH in the comparator (Genotropin) group from a source other than the trial medication supply. The sponsor attests to the fact that the only approved GH product in Poland (where the trials were conducted) at the time of the trials was Genotropin, and a report from [redacted] ; included in the NDA confirms this claim. Neither of these findings appears to undermine the use of these data to support a regulatory decision on Omnitrope.

Financial disclosure
The financial disclosure information for all six studies in the NDA is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a

proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

ODS/nomenclature
No issues at the present time.

Summary and conclusions
The application contains reports of clinical studies of safety, efficacy, and immunogenicity in children with GHD. The clinical efficacy of Omnitrope is fully supported by these studies, based on changes in height-related variables comparable to those with Genotropin in head-to-head studies. Additionally, the efficacy of Omnitrope is comparable to historical responses to GH in children with GHD. The overall safety of Omnitrope is as expected for GH and not distinguishable from Genotropin in the 9-month trial in which they were compared. Adequate chemical characterization and biopharmaceutics investigations have been conducted to bridge different clinical trial formulations and drug substances and to establish chemical comparability to Genotropin. Finally, the immunogenicity of Omnitrope as proposed for marketing is low, not clinically significant, comparable to Genotropin and to other native sequence hGH products (in contrast to methionyl GH) based on published information.

In sum, Omnitrope has been shown to be safe and effective in trials in pediatric GHD. Additionally, based on the best current thinking of the Division, Omnitrope has been shown to be chemically comparable to Genotropin, similar in rate and extent of absorption to Genotropin such that a conclusion of bioequivalence would be supported were we to apply small molecule drug bioequivalence criteria, pharmacodynamically indistinguishable from Genotropin, and clinically comparable to Genotropin for the treatment of pediatric GHD. As such, relying in part on the FDA's previous findings of safety and effectiveness of Genotropin for pediatric and adult GHD, the Division considers Omnitrope safe and effective for these same indications.

Recommendation
The proposed indications for the treatment of pediatric and adult GHD may be approved based on the scientific merits of the data presented in the application reviewed based upon our current understanding of rhGH products. However, given the scientific, legal, and regulatory challenges that have been raised by outside parties and are under review by the Agency, the Agency is not prepared at this time to take final regulatory action on this application. A formal study would be useful for labeling to compare the bioavailability of Omnitrope 5.8 mg and Omnitrope 1.5 mg dosage strengths, though this may be conducted post approval.

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/s/

Robert Meyer
5/30/2006 05:48:25 PM
MEDICAL OFFICER

8.30.04

MEDICAL OFFICER REVIEW
Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	21-426	**APPLICATION TYPE:**	NDA
SPONSOR:	Biochemie U.S., Inc.	PROPRIETARY NAME:	Omnitrope
CATEGORY OF DRUG:	Recombinant human growth hormone	GENERIC NAME:	Somatropin
		ROUTE:	Injectable (subcutaneous)
MEDICAL REVIEWER:	Dragos Roman, MD	REVIEW DATE	08-27-2004
		PDUFA DATE:	08-31-2004

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
O7/30/2003	O7/31/2003	NDA, 505 (b)(2)	

RELATED APPLICATIONS

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: Omnitrope is somatropin (human recombinant growth hormone). The clinical data presented in this NDA supports the safe and effective use of a 5.8 mg Omnitrope Lyophilized powder formulation in children with growth hormone deficiency (GHD). This NDA is a 505 (b)(2) application, the first for a human growth hormone. The applicant provides ample evidence that Omnitrope can be expected to be clinically comparable to Genotropin (though the sponsor is not seeking AB rating). The evidence of similarity with Genotropin comes from several sources: 1) physical chemistry data, 2) clinical pharmacology data, and 3) clinical data from studies conducted in children with GHD. In addition to comparative data, this NDA provides ample stand-alone evidence (i.e. without relying on the comparison to Genotropin) that Omnitrope is safe and effective in pediatric GHD. This is based on clinical trial evidence of growth-promoting effects of Omnitrope in pediatric GHD (with each patient serving as his or her own control) as expected for a human growth hormone product based on historical (published) information.

The applicant seeks both the pediatric GHD indication (for which clinical data are presented) and the adult GHD indication (for which extensive published literature data obtained with Genotropin are submitted). In that Omnitrope Lyophilized Powder is (1) proven to be chemically growth hormone, (2) has demonstrable efficacy (and favorable safety profile) in one

patient population (children with GHD), (3) is clinically similar and pharmacokinetically bioequivalent to an approved GH product (Genotropin) that has been used safely and effectively in adults with GHD, and (4) has expected pharmacodynamic effects in healthy adults, it is reasonable to infer that it will be safe and effective in both children and adults with GHD.
Recommended Regulatory Action: Approval
Signed: Medical Reviewer: Dragos Roman M.D. **Date: 04/23/2004** **Medical Team Leader: _____ Date: _____**

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability from a Clinical Perspective

The clinical data presented in this NDA supports the safe and effective use of Omnitrope Lyophilized powder in children with growth hormone deficiency when used according to the proposed label. This reviewer agrees, overall, with the applicant's conclusions and recommends approval of Omnitrope for the proposed indication of replacement therapy for pediatric growth hormone deficiency (GHD).

It is reasonable to infer that Omnitrope will be safe and effective in adults with GHD as well, on the basis that (1) it is chemically proven to be growth hormone (GH), (2) it has demonstrable efficacy (and favorable safety profile) in children with GHD, (3) it has expected pharmacodynamic effects (on IGF-I[1] and IGFBP-3[2]) in healthy adults, and (4) is clinically similar and pharmacokinetically bioequivalent to an approved GH product (Genotropin) that has been shown in published clinical studies to be safe and effective in adult patients with GHD.

B. Recommendation on Phase 4 Studies and Risk Management Steps

None.

II. Summary of Clinical Findings

A. Background and Brief Overview of Clinical Program

Omnitrope is somatropin (human recombinant growth hormone). This NDA is a 505 (b)(2) application, the first for a human growth hormone. The applicant (Biochemie US., Inc.) references NDA 20-280, Genotropin, and proposes that FDA rely in part on previous findings with that GH product in support of the safety and efficacy of Omnitrope for the proposed uses. Specifically, the applicant has structured a "bridge" between the two products based on chemical analysis, bioavailability/bioequivalence, and clinical comparison to Genotropin in pediatric GHD to support the efficacy and safety of Omnitrope in both pediatric and adult GHD.

This NDA contains clinical data obtained with three Omnitrope drug products: the "Covance" lyophilized Omnitrope[3], the "Biochemie" lyophilized Omnitrope[4], and Omnitrope Liquid[5]. The applicant seeks market approval for only one of these three drug products: the "Biochemie"

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[1] Insulin-like Growth Factor-I
[2] Insulin Growth Factor Binding Protein-3
[3] Manufactured by Covance Biotechnologies, USA.
[4] Manufactured by Biochemie GmbH in Kundl, Austria.
[5] Manufactured by Biochemie GmbH in Kundl, Austria.

lyophilized Omnitrope, formally named Omnitrope Lyophilized powder[6]. The applicant is seeking market approval for Omnitrope Lyophilized powder in two strengths (1.5 mg and 5.8 mg). Omnitrope is to be administered subcutaneously as a daily injection.

The applicant conducted three clinical pharmacology studies in healthy adult volunteers and three consecutive (and continuous) clinical studies in children with growth hormone deficiency. The three clinical pharmacology studies are: 1) a pharmacokinetic/pharmacodynamic (PK/PD) study of "Covance" Omnitrope, 2) a comparative PK/PD study that shows bioequivalence between "Covance" Omnitrope and Genotropin, and 3) a comparative PK/PD study that shows bioequivalence between "Covance" Omnitrope and Omnitrope Liquid[7]. The three clinical studies are, in essence, one study in which two cohorts of patients with GHD (approximately 44 patients per cohort) have been exposed sequentially to different pairs of GH products: "Covance" Omnitrope vs. Genotropin for the initial 9 months, "Biochemie" Omnitrope vs. Omnitrope Liquid for the next 6 months, followed by Omnitrope Liquid alone in an open-label extension up to 30 months. There were no washout periods and no randomizations in-between these sequential studies.

In this NDA, the applicant provides ample evidence that Omnitrope can be expected to be clinically comparable to Genotropin (though the sponsor is not seeking AB rating). The evidence of similarity with Genotropin comes from several sources: (1) physical chemistry data (for details see the chemistry review), (2) clinical pharmacology data (for details see the biopharm. review), and (3) clinical data from studies conducted in children with GHD (see the efficacy and safety conclusions, next). In addition, this NDA provides ample stand-alone evidence (i.e. without relying on the comparison to Genotropin) that Omnitrope is safe and effective in pediatric GHD. This is based on clinical trial evidence of growth-promoting effects of Omnitrope in pediatric GHD (with each patient serving as his or her own control) as expected for a human growth hormone product based on historical (published) information.

Finally, as above, the applicant seeks both the pediatric GHD indication (for which clinical data are presented) and the adult GHD indication (for which extensive published literature data obtained with Genotropin are submitted)[8].

[6] [redacted]. The data obtained with Ommitrope Liquid is presented in this NDA only as "supportive evidence."

[7] All the PK/PD studies used a single dose of GH (5 mg). As described, the lyophilized Omnitrope product investigated in all the clinical pharmacology studies was "Covance" Omnitrope. The applicant later ceased production of the "Covance" product because it was found in clinical studies to be highly immunogenic.

[8] Currently, the Genotropin label includes four indications. In addition to pediatric and adult GHD indications, Genotropin is approved for treatment of short stature in children with Pradder-Willi syndrome and in children born small for gestational age without catch-up growth by two years of age.

B. Efficacy

"Covance" Omnitrope

The clinical trial data presented in this NDA support the conclusion that "Covance" Omnitrope and Genotropin have similar effects on short-term linear growth and standard pharmacodynamic measures of GH activity in children with GHD. Specifically, after 9 months of treatment, "Covance" Omnitrope and Genotropin were comparable with respect to mean height gain (cm)[9], mean height gain standard deviation score (SDS)[10], mean annualized height velocity (cm)[11], mean annualized height velocity SDS[12], mean predicted final height[13], mean IGF-I[14] and mean IGFBP-3[15] serum concentrations. Most importantly, the on-trial mean height velocity SDS change with Omnitrope was demonstrated to be statistically equivalent to that of Genotropin at the end of 9 months of treatment in children with GHD.

"Biochemie" Omnitrope

Although not compared directly to Genotropin, when evaluated over six months against Omnitrope Liquid, the to-be-marketed "Biochemie" Omnitrope maintained an accelerated mean height velocity relative to that recorded prior to GH treatment initiation[16]. In addition, "Biochemie" Omnitrope kept IGF-I serum concentrations at levels that were similar to those observed during treatment with "Covance" Omnitrope and Genotropin (and higher than those

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[9] Omnitrope treatment added on average 8.6 cm and Genotropin treatment added 8.4 cm to pretreatment growth.

[10] Omnitrope treatment added on average 0.7 of a standard deviation and Genotropin treatment added 0.6 of a SD to pretreatment growth.

[11] Annualized height velocity was on average 10.7 ± 2.57 cm/yr with Omnitrope treatment and 10.7 ± 2.90 cm/yr with Genotropin treatment.

[12] Annualized height velocity SDS was on average +6.1 ± 3.67 with Omnitrope treatment and +5.4 ± 3.16 with Genotropin treatment.

[13] Predicted adult height increased in the Omnitrope group by 4.9 ± 2.68 cm relative to baseline. In the Genotropin group predicted adult height increased by 4.3 ± 3.01 cm relative to baseline for the same time interval.

[14] Mean IGF-I serum levels increased to 291.1± 173.97 ng/ml in the Omnitrope group and 301.9± 182.94 ng/dl for the Genotropin group.

[15] Mean IGFBP-3 serum levels increased to 4.6 ± 2.97 µg/ml in the Omnitrope group and 4.0 ± 1.53 µg/dl for the Genotropin group.

[16] Height velocity SDS at Month 12 and 15 timepoints were 3.8 ± 3.73 and 3.4 ± 2.55, respectively for "Biochemie" Omnitrope. For Omnitrope Liquid the height velocity SDS at Month 12 and 15 timepoints were 3.1±2.66 and 3.2 ±2.89, respectively.

present before initiation of GH therapy)[17] and improved the mean predicted final height by 1.7 cm for this interval.

Omnitrope Liquid

Additional data collected during the open-label (and uncontrolled) use of Omnitrope Liquid further support sustained efficacy of Omnitrope. Specifically, over an additional 15-month period, Omnitrope Liquid maintained an accelerated mean height velocity SDS[18], higher IGF-I levels than those noted prior to GH therapy, and improved the mean predicted adult height by 2.7 cm.

Conclusions

The proof of comparable efficacy of the to-be-marketed "Biochemie" Omnitrope to Genotropin is based on the combined clinical data obtained with three Omnitrope investigational drug products. Bridging between these Omnitrope drug products (including bridging of the to-be-marketed Omnitrope product to the comparator Genotropin) was done via several PK/PD studies and a clinical study. To this end, the to-be-marketed "Biochemie" Omnitrope was clinically similar over 6 months to Omnitrope Liquid. In turn, Omnitrope Liquid was equivalent in a PK/PD single-dose study to "Covance" Omnitrope; the latter was shown to be clinically equivalent (over 9 months) and bioequivalent (in a PK/PD single dose study) to Genotropin. Irrespective of the above-listed bridging studies, it is important to recognize that, according to the chemistry reviewer, the to-be-marketed "Biochemie" Omnitrope and the "Covance" Omnitrope are physico-chemically identical and differ only in the amount of E.coli contaminants.

Finally (and importantly) the short-term efficacy data (annual height velocity) observed with Omnitrope in children with GHD was comparable to historical (published) efficacy data obtained with several approved GH products[19].

C. Safety

"Covance" Omnitrope

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[17] The IGF-I serum concentrations were in the range of 290 to 320 ng/ml on GH treatment for both "Biochemie" Omnitrope and Liquid Omnitrope at all tested timepoints between Month 9 and Month 15, almost twice the pre-treatment IGF-I levels.

[18] Between 3.3 and 2.5.

[19] The annual height velocity on Omnitrope (8.9 ± 2.9 cm) was comparable with data from published literature which range from 8.8 ± 1.8 cm to 13.3 ± 3.9 cm for other GH products (see statistical review). Different GH doses and drug regimens (three times per week vs. seven times per week) were used in the referenced studies.

In a side-by-side comparison to Genotropin over 9 months, "Covance" Omnitrope displayed a comparable safety profile, with no deaths, no drug-related serious adverse events, and no patient withdrawals due to adverse events.[20] "Covance" Omnitrope was found, however, to be highly immunogenic. Specifically, 57 % of patients treated with this product developed anti-GH antibodies after 9 months of continuos treatment; this finding compared unfavorably to Genotropin which was immunogenic in only 2% of patients. The applicant does not plan to market "Covance" Omnitrope.

"Biochemie" Omnitrope

The to-be-marketed "Biochemie" Omnitrope had a favorable safety profile during short-term (6 months) treatment: there were no deaths, no drug-related serious adverse events, no patient withdrawals due to adverse events and no unusual pattern of treatment-emergent adverse events. When used in patients previously exposed to "Covance" Omnitrope who had anti-GH antibodies, it was associated with a reduction in the percentage of antibody-positive patients from 57% to 36%. Although not compared side-by-side with Genotropin, "Biochemie" Omnitrope was associated with a similar adverse event profile as illustrated by a comparison across trials of the rates of adverse events normalized per patient-year.

Liquid Omnitrope

Omnitrope Liquid had an adverse event profile which was comparable to that of "Biochemie" Omnitrope, as seen in an analysis of adverse event rates normalized per patient-year. Additionally, and importantly, in a cohort of patients previously exposed to Genotropin who had a low percentage of anti-GH antibody-positive patients at baseline[21], treatment with Liquid Omnitrope maintained a low antibody positivity[22]. Furthermore, when the original "Covance" Omnitrope cohort with a high percentage of antibody-positive patients was changed to Omnitrope Liquid at Month 15, the decrease in the percentage of antibody-positive patients noted between Month 9 and Month 15 on "Biochemie" Omnitrope continued over the next 21 months (further reduction from 36% to 16 %).

Conclusions

In final analysis, the Omnitrope active pharmaceutical ingredient manufactured at the Biochemie GmbH site (and contained in the to-be-marketed "Biochemie" Omnitrope) appears to be safe and comparable to Genotropin in children with GHD. This conclusion is based on a combination of safety data obtained during both controlled and open-label studies conducted with three different Omnitrope drug products, of which, only one is proposed for approval ("Biochemie" Omnitrope).

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[20] A threefold increase in the incidence of hypothyroidism relative to Genotropin was observed in association with "Covance" Omnitrope but this observation was not replicated with the to-be-marketed "Biochemie" Omnitrope.
[21] One patient (or 2%).
[22] Three patients or approximately 5 % (95% CI: 0.6% - 16.9%).

D. Dosing

The GH dose administered in the Omnitrope clinical trials was well within the range of GH doses approved for the treatment of pediatric GHD[23].

E. Special Populations

The Phase III clinical trials presented in this NDA were conducted exclusively in children. The clinical studies enrolled approximately equal numbers of boys and girls[24]. The applicant conducted gender analyses for several efficacy endpoints; they did not demonstrate any gender-related differences. As the clinical studies were conducted in Europe (Poland and Hungary), all the patients enrolled were Caucasian and no race-specific analyses were done.

[23] The starting GH dose was 0.03 mg/kg/day given daily at bedtime as a subcutaneous injection; this corresponds to a weekly dose of approximately 0.2 mg/kg . The dose was adjusted periodically during the clinical trials.
[24] 55 % of patients were male and 45 % of patients were female.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Omnitrope is somatropin (human recombinant growth hormone). Somatropin is currently marketed under several commercial names by a variety of manufacturers for both adult and pediatric indications[25]. The applicant's proposed indications are: 1) pediatric growth hormone deficiency (GHD) and 2) adult GHD ("tentative indication"). The proposed pediatric doses are "0.16 to 0.24 mg/kg body weight/week." The adult dose is not specified in the proposed label.

B. State of Armamentarium for Indication

Human recombinant growth hormone has been approved since 1985 for the pediatric GHD indication. Several brands of somatropin are currently available for the treatment of pediatric GHD and for other approved indications.

C. Important Milestones in Product Development/Regulatory History

This application is a resubmission of the Omnitrope NDA. A brief chronology of the main regulatory events that occurred following the original NDA submission follows:

December 31, 2001: Biochemie submitted a New Drug Application in support of Omnitrope for the treatment of pediatric and adult GHD.

March 1, 2002: The Agency refused to file the Omnitrope application.[26]

August 5, 2002: A refuse-to-file-meeting took place within the Agency at which representatives from Geneva Pharmaceuticals (Biochemie's US representative) participated. Subsequently, the Division and representatives of Biochemie met and discussed ways to correct the deficiencies identified at the filing meeting.

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[25] Currently approved pediatric indications are: GH deficiency (1985), short stature in chronic renal insufficiency (1993), short stature in Turner syndrome (1996), short stature in Prader-Willi syndrome (2000), small for gestational age without catch up growth by age two years (2001), and idiopathic short stature (2003). Currently approved adult indications are: AIDS wasting or cachexia, adult growth hormone deficiency of either childhood- or adult-onset etiology.

[26] The main deficiency (chemistry) was related to the absence of a manufacturing facility ready for inspection.

July 31, 2003: Biochemie re-submits the Omnitrope NDA which is subsequently filed for review.

D. Other Relevant Information/Foreign Marketing History

Lyophilized Omnitrope is not currently marketed in any country. According to the applicant,

E. Important Issues with Pharmacologically Related Agents

Human growth hormone has been used in humans for over four decades. Recombinant human GH is currently available as somatropin (growth hormone) and somatrem (methionyl growth hormone). The efficacy and the safety profile of recombinant human GH in various patient populations is, generally, well understood.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A finalized chemistry review is pending at this time. Preliminary consultation with the chemistry reviewer (Dr. Janice Brown) indicates the following: 1) chemically, both "Covance" Omnitrope and "Biochemie" Omnitrope are comparable to Genotropin; 2) "Covance" Omnitrope and "Biochemie" Omnitrope are identical products except for the amount of E.coli host cell protein contaminants.

A finalized statistical review is also pending. Preliminary consultation with the statistical reviewer (Cynthia Liu) indicates that independent FDA analyses support applicant's efficacy conclusions.

III. Human Pharmacokinetics and Pharmacodynamics

The applicant presents three clinical pharmacology studies (EP2K-99-PhISUSA, EP2K-99-PhIUSA and EP2K-00-PhIAQ). They are briefly summarized next (for detailed analysis, see the biopharmaceutical review). All three clinical pharmacology studies were done in healthy volunteers and used the same GH dose of 5 mg, given subcutaneously.

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[27] The applicant states that a marketing authorization application for Omnitrope liquid 5 mg/1.5 mL (15 IU/1.5 mL), which is being submitted to this NDA as supportive information only,

Study EP2K-99-PhISUSA

Study EP2K-99-PhISUSA evaluated the pharmacokinetics (PK) and the pharmacodynamics (PD) of 5 mg of Omnitrope Lyophilized powder administered subcutaneously as a single bolus. The study used a double-blind, randomized, placebo controlled, two-way cross-over design. It was conducted in 12 healthy subjects (6 males and 6 females) who had their endogenous GH secretion suppressed by a continuous iv infusion of octreotide. The PK assessments were C_{max}, t_{max}, AUC_{inf}, $t_{1/2}$ calculated from somatropin serum concentrations up to 24 hours post-dose. The PD assessments were C_{max}, t_{max}, AUC_{last} calculated for IGF-1 and IGFBP-3 serum concentrations up to 96 hours post-dose and for NEFA (non-esterified fatty acids) serum concentrations up to 24 hours post-dose. The study used the bulk substance manufactured by Covance (a not-to-be-marketed product). All 12 randomized subjects were included in the pharmacokinetic and pharmacodynamic analyses.

Applicant's Figure 1 displays the GH serum concentration in the Omnitrope- and placebo-treated patients as a function of time (Omnitrope and EP2000 are interchangeable names). The constant iv infusion of octreotide appears effective in suppressing the endogenous secretion of GH in healthy volunteers, as illustrated by results in the placebo arm.

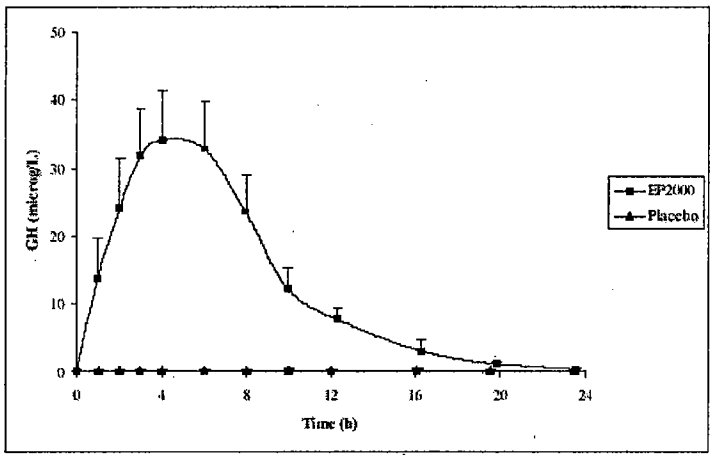

Figure 1: GH serum concentrations after subcutaneous injection of EP2000 and placebo (mean ± SD, n = 12)

The PK parameters are displayed in applicant's table below. A gender sub-group analysis does not report any statistical differences for PK parameters between males and females.

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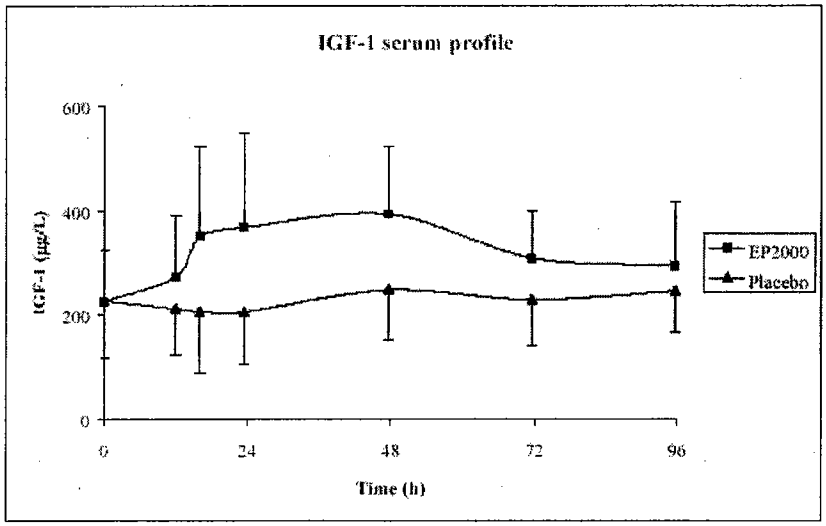
Table 3: Compartmental analysis of GH pharmacokinetics after sc injection of EP2000 5 mg

	t_{lag} (h)	C_{max} (µg/L)	t_{max} (h)	AUC_{inf} (h.µg/L)	k_a (h^{-1})	$t_{1/2}$ (h)	CL/F (L/h)
Mean	0.7	37	3.6	291	0.4	2.4	18
SD	0.5	9	0.5	42	0.2	0.4	3
Median	0.5	37	3.5	290	0.4	2.4	17
Min	0.4	21	2.9	206	0.3	1.6	14
Max	2.2	55	4.5	350	0.7	3.3	24

The PD responses (for IGF-I, IGFBP-3, and NEFA) following the administration of 5 mg of Omnitrope lyophilized powder are summarized below.

		IGF-1			IGFBP-3			NEFA		
		C_{max} (µg/L)	t_{max} (h)	AUC_{last} (µg/L*h)	C_{max} (mg/L)	t_{max} (h)	AUC_{last} (mg/L*h)	C_{max} (mg/dL)	t_{max} (h)	AUC_{last} (mg/dL*h)
EP2000	Mean	424	34	31890	5.0	43	399	39	5	409
	SD	163	15	11415	1.0	15	71	9	3	130
	Median	367	36	26912	5.0	48	386	37	4	386
	Min	256	16	20935	3.7	16	292	27	2	288
	Max	818	48	52946	6.6	71	498	58	12	789
Placebo	Mean	279	44	21674	4.2	39	344	18	2	114
	SD	107	40	8491	0.9	33	68	6	1	51
	Median	253	32	18506	3.9	24	316	15	2	106
	Min	144	0	11742	2.6	0	239	9	1	51
	Max	546	97	40945	5.5	96	457	33	4	218
Wilcoxon test (p value)		0.002	0.2	0.002	0.006	0.6	0.003	0.002	0.003	0.002

The mean concentration-time profile of IGF-I following a single subcutaneous injection with 5 mg of Omnitrope Lyophilized powder is displayed below:



taneous injection with

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Figure 3: IGF-1 serum concentrations after subcutaneous injection of EP2000 and placebo (mean ± SD, n = 12)

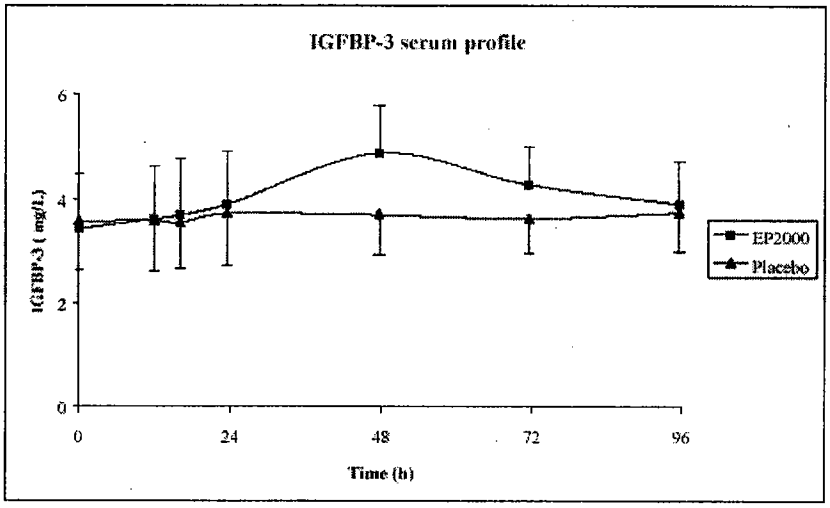


Figure 4: IGFBP-3 serum concentrations after subcutaneous injection of EP2000 and placebo (mean ± SD, n = 12)

The mean concentration-time profile of NEFA following a single subcutaneous injection with 5 mg of Omnitrope Lyophilized powder is displayed below:

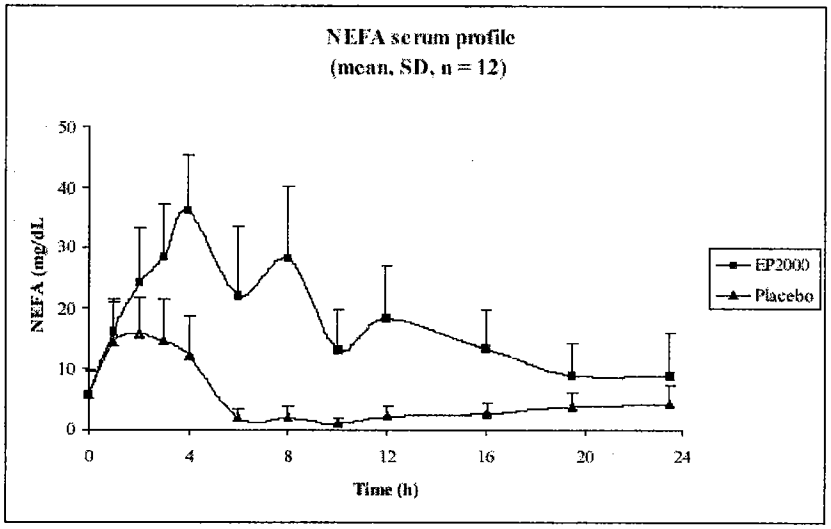


Figure 5: NEFA serum concentrations after subcutaneous injection of EP2000 and placebo (mean ± SD, n = 12)

The applicant concludes that the pharmacodynamic responses (IGF-1, IGFBP-3, NEFA) after administration of Omnitrope Lyophilozed powder (5 mg single dose) and of placebo are statistically different for C_{max} and AUC_{last}.

Study EP2K-99-PhIUSA

Study EP2K-99-PhIUSA compared the pharmacokinetics and the pharmacodynamics of Omnitrope Lyophilized powder to those of Genotropin, an approved GH product (Genotropin was used in the clinical trials as an active comparator to Omnitrope). It used a double-blind, randomized, two-way cross-over design in 25 healthy volunteers (12 males and 13 females) whose endogenous secretion of GH was suppressed by a continuous iv infusion of octreotide for 25 hours. The PK assessments were C_{max}, t_{max}, AUC_{inf} calculated for somatropin serum concentrations up to 24 hours post-dose. The PD assessments were C_{max}, t_{max}, AUC_{last}, C_{max}, AUC_{last} calculated for IGF-1 and IGFBP-3 serum concentrations up to 96 hours post-dose and from NEFA serum concentrations up to 24 hours post-dose. Omnitrope Lyophilized powder (manufactured by Covance) was administered as a 5 mg, subcutaneous bolus injection.

The objectives of the study were to compare the PK/PD and safety characteristics of Omnitrope Lyophilized powder to that of Genotropin.

The mean concentration-time profiles of GH after a 5 mg subcutaneous injection of Omnitrope Lyophilized powder (named EP2000 in this study) and Genotropin are

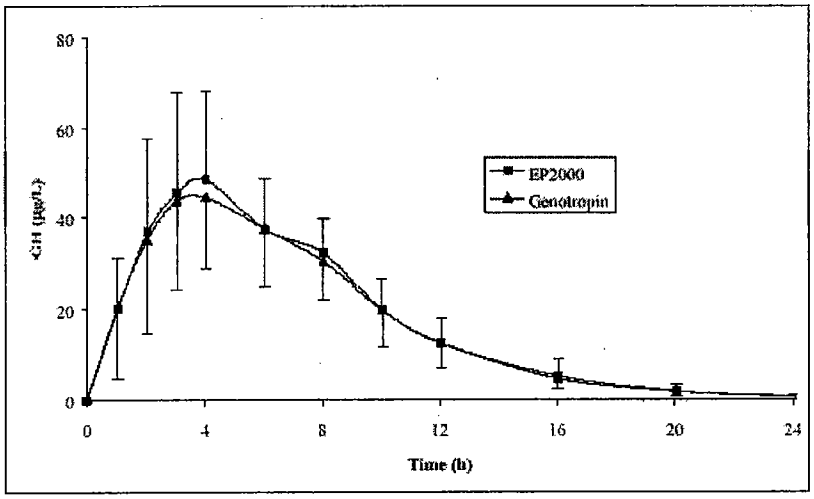


Figure 1: GH serum concentrations after subcutaneous injection of EP2000 and Genotropin® (mean ± SD, n = 24)

displayed below. The concentration-time profiles are very similar.

The PK characteristics for the two GH drug products are displayed in the next table, below:

Table 3: Non-compartmental analysis of GH pharmacokinetics after sc injection of EP2000 and Genotropin® (n = 24)

		C_{max} (µg/L)	t_{max} (h)	AUC_{last} (h*µg/L)	AUC_{inf} (h*µg/L)	$t_{1/2}$ (h)	Vz (L)	CL/F (L/h)	MRT_{last} (h)	MRT_{inf} (h)
EP2000	Mean	52	4.1	413	416	2.7	52	13	7.0	7.1
	SD	21	1.6	111	110	0.6	24	3	1.3	1.5
	Median	45	4.1	387	391	2.5	43	13	6.6	6.6
	Min	24	2.1	217	220	2.0	21	7	4.9	4.9
	Max	96	8.1	717	718	4.0	119	23	9.3	9.9
Genotropin®	Mean	48	4.9	396	400	2.9	57	13	7.0	7.2
	SD	20	1.8	106	105	0.6	27	4	1.2	1.3
	Median	44	4.1	391	393	2.7	50	13	7.0	7.1
	Min	21	2.0	208	211	2.1	24	7	3.9	4.0
	Max	108	10.1	696	697	4.6	142	24	9.2	10.2
Wilcoxon test	(p value)		0.052							

The mean concentration-time profiles of IGF-1 after a 5-mg sc injection of Omnitrope and Genotropin are displayed in the next figure, below. Comparable IGF-I profiles are

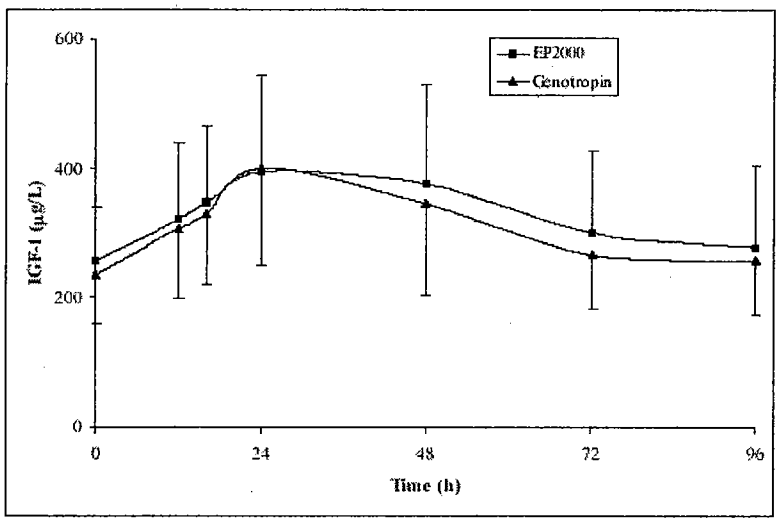


Figure 4: IGF-1 serum concentrations after subcutaneous injection of EP2000 and Genotropin® (mean ± SD, n = 24)

noted.

The IGF-I pharmacodynamic response to both GH products is presented in quantitative terms in the next table below.

Table 6: Pharmacodynamic response (IGF-1) after sc injection of 5 mg of EP2000 and Genotropin®

		C_{max} IGF-1 (µg/L)	t_{max} IGF-1 (h)	AUC_{last} IGF-1 (µg/L*h)	ΔC_{max} IGF-1 (µg/L)	ΔAUC_{last} IGF-1 (µg/L*h)
EP2000	Mean	458	34	31974	204	7761
	SD	159	24	10766	127	6279
	Median	425	24	29970	181	6343
	Min	197	12	15521	47	340
	Max	759	97	51684	562	24138
Genotropin®	Mean	428	32	29893	193	7384
	SD	152	22	9569	127	5187
	Median	385	24	28894	161	6124
	Min	219	12	16288	42	1447
	Max	750	96	52810	477	17235
Wilcoxon test (p value)			0.6			

The mean concentration-time profiles of IGFBP-3 after a 5-mg sc injection of Omnitrope

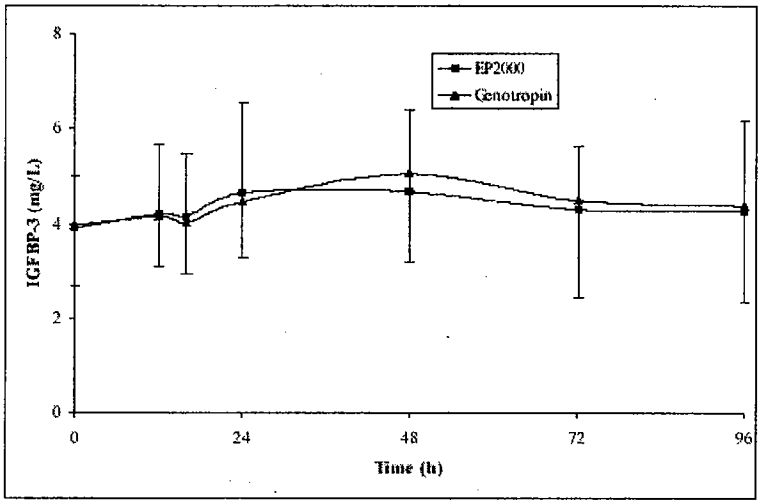


Figure 5: IGFBP-3 serum concentrations after subcutaneous injection of EP2000 and Genotropin® (mean ± SD, n = 24)

and Genotropin are displayed in the next figure, below. Comparable profiles are noted.

The mean concentration-time profiles of NEFA after a 5-mg sc injection of Omnitrope and Genotropin are displayed in the next figure, below. Comparable profiles are noted.

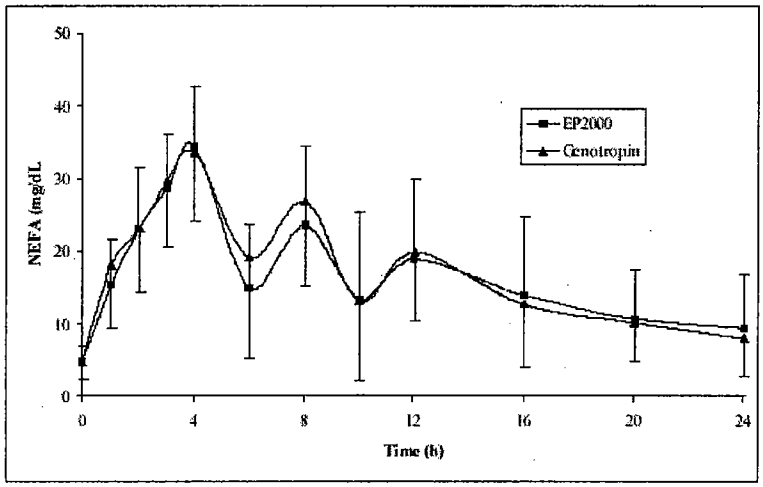


Figure 6: NEFA serum concentrations after subcutaneous injection of EP2000 and Genotropin® (mean ± SD, n = 24)

The applicant concludes that Omnitrope and Genotropin are pharmacodynamically bioequivalent in terms of IGF-1, IGFBP-3 and NEFA C_{max} and AUC_{last} with 90% confidence intervals entirely within the bioequivalence acceptance range of 80-125%.

Study EP2K-00-PhIAQ

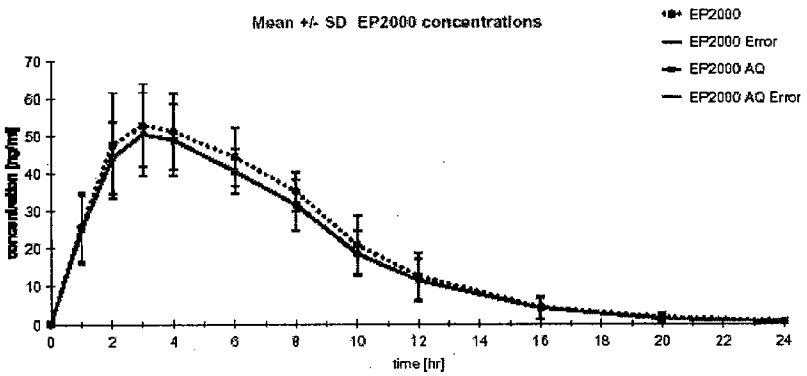
Study EP2K-00-PhIAQ investigated the bioequivalence between Omnitrope Lyophilized powder and a liquid formulation of Omnitrope[28]. The study was conducted in 24 healthy volunteers (12 males and 12 females) and used a double-blind, randomized, two-way, cross-over design. Subjects received a continuous iv infusion of octreotide for 25 hours to suppress endogenous secretion of GH. The PK assessments were C_{max}, t_{max}, AUC_{inf} determined from somatropin serum concentrations. The PD assessments were C_{max}, t_{max}, AUC_{last}, C_{max}, determined from IGF-1, IGFBP-3, and NEFA serum concentrations. Omnitrope Lyophilized powder (manufactured by Covance) and Omnitrope Liquid (manufactured by Biochemie GmbH) were administered as a 5 mg, subcutaneous bolus injections.

The mean concentration-time profiles of GH after a 5 mg subcutaneous injection of Omnitrope Lyophilized powder (named EP2000 in this study) and Omnitrope Liquid

[28] Liquid Omnitrope is not subject of this NDA but clinical data obtained with this drug product are presented as supportive evidence of efficacy and safety. Liquid Omnitrope contains the same drug substance as in the to-be-marketed Omnitrope Lyophilized powder.

(named EP2000 AQ in this study) are displayed below. The concentration-time profiles are very similar.

Figure 1: Mean Somatropin Plasma Concentrations



The pharmacokinetic parameters calculated on the basis of the individual somatropin plasma
concentrations are summarized in table format, below. The mean somatropin concentrations
following Omnitrope Liquid ($EP2000_{AQ}$) were slightly lower compared to those obtained after administration of Omnitrope lyophilized (EP2000). Consequently, mean C_{max}, C_{24h} and AUC values are slightly lower. T_{max} and half-life remained unchanged.

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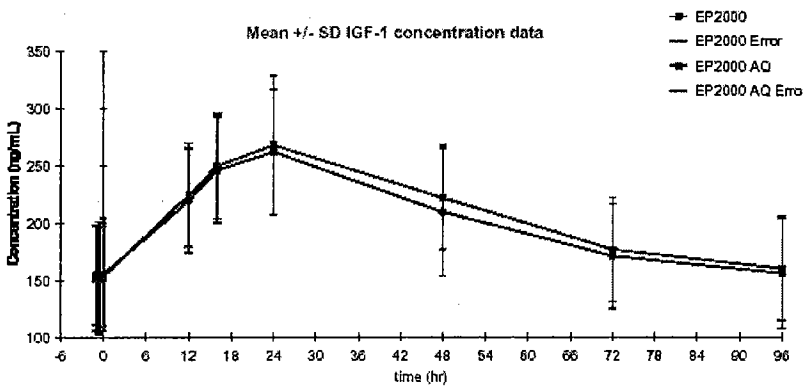
Table 4: Summary of Somatropin Pharmacokinetic Parameters

Summary of Somatropin Pharmacokinetic Parameters				
	EP2000 [AQ] (N=24)		EP2000 (N=24)	
Parameter	geo.Mean	SD	geo.Mean	SD
AUC(0-24) [ng*h/ml]	422	44.7	453	43.4
AUC(0-∞) [ng*h/ml]	426	44.9	456	44.1
C_{24h} [ng/ml]	0.436	0.372	0.512	0.304
Cmax [ng/ml]	51.7	9.90	54.6	12.9
	EP2000 [AQ] (N=24)		EP2000 (N=24)	
Parameter	Mean	SD	Mean	SD
λz [1/h]	0.314	0.072	0.307	0.078
t1/2 [h]	2.35	0.668	2.40	0.644
tmax [h]	3.54	1.28	3.92	1.79

values taken from Table 17 (Section 14)

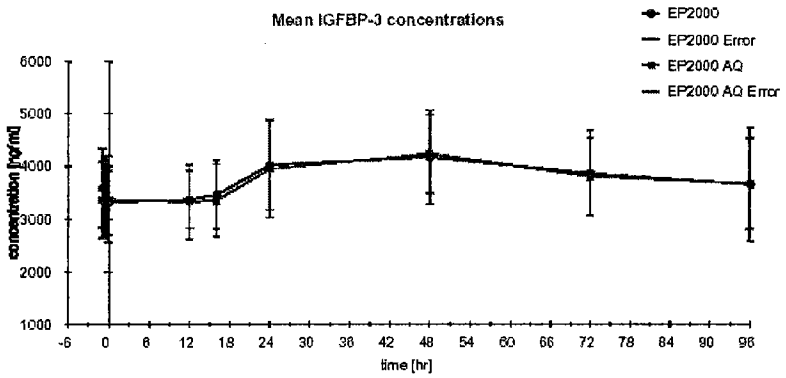
The mean concentration-time profiles of IGF-1 after a 5-mg sc injection of Omnitrope Lyophilized and Omnitrope Liquid are displayed below. Comparable IGF-I profiles are noted.

Figure 2: Mean IGF-1 Plasma Concentrations



The mean concentration-time profiles of IGFBP3 after a 5-mg sc injection of Omnitrope

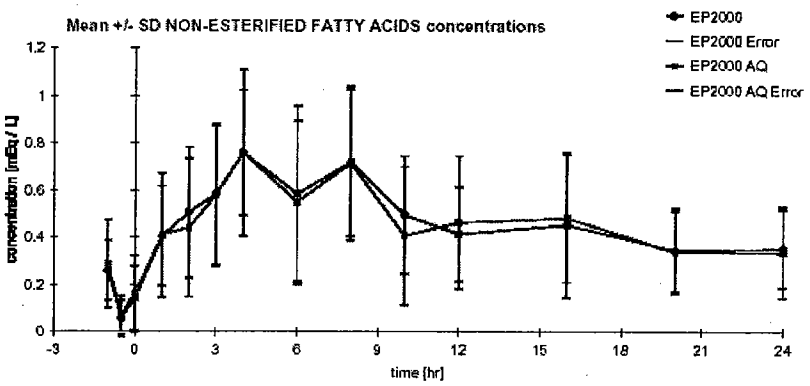
Figure 3: Mean IGFBP-3 Plasma Concentrations



Lyophilized and Omnitrope Liquid are displayed below. They are comparable.

Similarly, the mean concentration-time profiles of NEFA after a 5-mg sc injection of Omnitrope Lyophilized and Omnitrope Liquid are comparable (see figure, below).

Figure 4: Mean NEFA Plasma Concentrations



The applicant concludes that the lyophilized and the liquid Omnitrope formulations are bioequivalent based on somatropin plasma concentrations and equivalent pharmacodynamic responses.

IV. Description of Clinical Data and Sources

A. Overall Data

The clinical data reviewed in this NDA include the following:

- three clinical studies conducted sequentially in two cohorts of children with GHD (studies EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIII$_{AQ}$)
- three clinical pharmacology studies (EP2K-99-PhISUSA, EP2K-99-PhIUSA and EP2K-00-PhIAQ) conducted in healthy volunteers

B. Tables Listing the Clinical Trials

The three clinical trials and the three clinical pharmacology studies are listed in Table 1.

Table 1: Summary of Studies Reviewed/Summarized

Study number	Objective	Type of Study/Patient population
EP2K-99-PhIII	To compare the short-term efficacy and safety of Omnitrope Lyophilized Powder against Genotropin (an approved GH product) over a treatment period of 6 months.	Efficacy study in children with GHD.
EP2K-00 PhIIIFo	To compare the short-term efficacy and safety of Omnitrope Lyophilized Powder against Genotropin over an additional treatment period of 3 months following study EP2K-99-PhIII.	Efficacy study in children with GHD.
EP2K-00-PhIIIAQ	To compare the short-term efficacy and safety of Omnitrope Lyophilized Powder* against [redacted] (Omnitrope Liquid).	Efficacy study in children with GHD.
EP2K-99-PhISUSA	To evaluate the PK characteristics and the effects on IGF-I, IGFBP-3, and NEFA serum concentrations of Omnitrope Lyophilized powder.	PK/PD in healthy volunteers.
EP2K-99-PhIUSA	To compare the PK characteristics and the effects on IGF-I, IGFBP-3, and NEFA serum concentrations of Omnitrope Lyophilized powder against those of Genotropin.	PK/PD in healthy volunteers.
EP2K-00-PhIAQ	To show bioequivalence between Omnitrope Lyophilized powder and a liquid formulation of Omnitrope.	PK/PD in healthy volunteers.

*The Omnitrope Lyophilized product used in this study is similar to that used in the previous two clinical studies (EP2K-99-PhIII and EP2K-00 PhIIIFo) except that included a further purification step to reduce the product's immunogenecity.
Abbreviations: GHD = growth hormone deficiency; IGF-I = Insulin-like growth factor-I; IGFBP-3 = Insulin-like growth factor binding protein 3; NEFA = non-esterified fatty acids.

C. Postmarketing Experience

There is no postmarketing experience with Omnitrope. Other human growth hormone products have been used for over four decades[29]. The safety and the efficacy profile of GH is, in general, well understood and appropriately labeled.

D. Literature Review

There is no published literature with Omnitrope.

V. Clinical Review Methods

A. Overview of Materials Consulted in Review

This clinical review has been conducted from the electronic submission of this NDA.

B. Ethical Conduct of the Study

[29] Purified cadaveric pituitary GH has been used since the late 50's and early 60's (and discontinued in 1985 due to its association with Jacob Creutzfeld disease). Human recombinant GH has been used since 1985.

The applicant states that "the study was conducted in accordance with the World Medical Association Declaration of Helsinki," the "Note for Guidance on Good Clinical Practice (GCP)," as well as the "demands of national drug and data protection laws and other applicable regulatory requirements".

C. Financial Disclosure

Financial disclosure documents are provided for all six studies included in this NDA (three clinical pharmacology studies and three clinical trials). All the investigators and the subinvestigators listed in the financial disclosure documents signed documents stating that

- they did not own or enter into an agreement to own a proprietary interest in Biochemie GmbH
- they did not enter into any financial agreement with Biochemie GmbH that could influence the outcome of the clinical trial
- they did not receive payments, grants, and/or equipment form Biochemie GmbH having a monetary value exceeding $25,000
- did not own equity in Biochemie GmbH that exceeds $50,000.

D. Data Quality and Integrity

In conducting the clinical studies, the applicant, reportedly, followed the GCP Guidelines. The applicant engaged the services of [redacted] to perform all monitoring functions. [redacted] monitors worked in accordance with [redacted] monitoring SOPs. They, reportedly, established and maintained regular contact between the Investigator and the Sponsor; monitoring visits were made to each center on average every 4 weeks.

The applicant states that an EMEA audit was conducted in February 2000 and uncovered "several deficiencies and GCP violations" related to informed consent procedures[30] and to the use of GH in the comparator group from a source other than the trial medication supply[31]. The applicant has "recognized" and "accepted" these GCP violations. It is

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[30] They were described as follows: 1) absence of an "adequate quality control on the translation and backtranslation of the PICF [patient information and consent] form," 2) "the PICF that was signed by the patients was sometimes not the same as the PICF that was approved by the Ethics Committee, and 3) "the patients sometimes signed the PICF before the Ethics Committee had approved it."

[31] On three occasions during the EP2K-99-PhIII and EP2K-00-PhIIIFo studies, local hospital pharmacy stock was dispensed to study patients in order to ensure uninterrupted treatment with Genotropin due to the absence of clinical trial supplies from the dedicated Central Pharmacy. This was caused by an

important to note that a post-hoc report written by [redacted] and provided with this NDA is consistent with the applicant's claim that all out-of-trial GH used in the comparator arm was Genotropin, as Genotropin was the only approved GH product in Poland at the time of the clinical trials.

No DSI audit was conducted. The data submitted in the NDA appeared complete and no critical inconsistencies or errors were identified between tables and text in different sections of the submission.

VI. Integrated Review of Efficacy

A. Efficacy Conclusions

This NDA contains efficacy data obtained with three Omnitrope drug products: the "Covance" lyophilized Omnitrope[32], the "Biochemie" lyophilized Omnitrope[33], and Omnitrope Liquid[34]. The applicant seeks market approval for only one of these three drug products: the "Biochemie" Omnitrope[35].

The clinical trial data presented in this NDA support the conclusion that "Covance" Omnitrope and Genotropin have similar effects on short-term linear growth and standard pharmacodynamic measures of GH activity in children with GHD. Specifically, after 9 months of treatment, "Covance" Omnitrope and Genotropin were comparable with respect to mean height gain (cm)[36], mean height gain standard deviation score (SDS)[37], mean annualized height velocity (cm)[38],

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inadequate supply from the Central Pharmacy to the site. Since Genotropin was the only available GH in Poland, the applicant states that "no patients received any unapproved medication".

[32] Manufactured by Covance Biotechnologies, USA.
[33] Manufactured by Biochemie GmbH in Kundl, Austria.
[34] Manufactured by Biochemie GmbH in Kundl, Austria.
[35] The applicant does not plan to market the liquid Omnitrope drug product at this point in time [redacted]. The data obtained with Ommitrope Liquid is presented in this NDA only as "supportive evidence."
[36] Omnitrope treatment added on average 8.6 cm and Genotropin treatment added 8.4 cm to pretreatment growth.
[37] Omnitrope treatment added on average 0.7 of a standard deviation and Genotropin treatment added 0.6 of a SD to pretreatment growth.
[38] Annualized height velocity was on average 10.7 ± 2.57 cm/yr with Omnitrope treatment and 10.7 ± 2.90 cm/yr with Genotropin treatment.

mean annualized height velocity SDS[39], mean predicted final height[40], mean IGF-I[41] and mean IGFBP-3[42] serum concentrations. Most importantly, the on-trial mean height velocity SDS change with Omnitrope was demonstrated to be statistically equivalent to that of Genotropin at the end of 9 months of treatment in children with GHD.

Although not compared directly to Genotropin, when evaluated over six months against Omnitrope Liquid, the to-be-marketed "Biochemie" Omnitrope maintained an accelerated mean height velocity relative to that recorded prior to GH treatment initiation[43]. In addition, "Biochemie" Omnitrope kept IGF-I serum concentrations at levels that were similar to those observed during treatment with "Covance" Omnitrope and Genotropin (and higher than those present before initiation of GH therapy)[44] and improved the mean predicted final height by 1.7 cm for this interval.

Additional data collected during the open-label (and uncontrolled) use of Omnitrope Liquid further support sustained efficacy of Omnitrope. Specifically, over an additional 15-month period, Omnitrope Liquid maintained an accelerated mean height velocity SDS[45], higher IGF-I levels than those noted prior to GH therapy, and improved the mean predicted adult height by 2.7 cm.

The proof of comparable efficacy of the to-be-marketed "Biochemie" Omnitrope to Genotropin is based on the combined clinical data obtained with three Omnitrope investigational drug products. Bridging between these Omnitrope drug products (including bridging of the to-be-marketed Omnitrope product to the comparator Genotropin) was done via several PK/PD studies and a clinical study. To this end, the to-be-marketed "Biochemie" Omnitrope was clinically similar over 6 months to Omnitrope Liquid. In turn, Omnitrope Liquid was equivalent in a PK/PD single-dose study to "Covance" Omnitrope; the latter was shown to be clinically equivalent (over 9 months) and bioequivalent (in a PK/PD single dose study) to Genotropin. Irrespective of the above-listed bridging studies, it is important to recognize that, according to

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[39] Annualized height velocity SDS was on average +6.1 ± 3.67 with Omnitrope treatment and +5.4 ± 3.16 with Genotropin treatment.

[40] Predicted adult height increased in the Omnitrope group by 4.9 ± 2.68 cm relative to baseline. In the Genotropin group predicted adult height increased by 4.3 ± 3.01 cm relative to baseline for the same time interval.

[41] Mean IGF-I serum levels increased to 291.1± 173.97 ng/ml in the Omnitrope group and 301.9± 182.94 ng/dl for the Genotropin group.

[42] Mean IGFBP-3 serum levels increased to 4.6 ± 2.97 µg/ml in the Omnitrope group and 4.0 ± 1.53 µg/dl for the Genotropin group.

[43] Height velocity SDS at Month 12 and 15 timepoints were 3.8 ± 3.73 and 3.4 ± 2.55, respectively for "Biochemie" Omnitrope. For Omnitrope Liquid the height velocity SDS at Month 12 and 15 timepoints were 3.1±2.66 and 3.2 ±2.89, respectively.

[44] The IGF-I serum concentrations were in the range of 290 to 320 ng/ml on GH treatment for both "Biochemie" Omnitrope and Liquid Omnitrope at all tested timepoints between Month 9 and Month 15, almost twice the pre-treatment IGF-I levels.

[45] Between 3.3 and 2.5.

the chemistry reviewer, the to-be-marketed "Biochemie" Omnitrope and the "Covance" Omnitrope are physico-chemically identical and differ only in the amount of E.coli contaminants.

Finally (and importantly) the short-term efficacy data (annual height velocity) observed with Omnitrope in children with GHD was comparable to historical (published) efficacy data obtained with several approved GH products[46].

B. General Approach to Review of the Efficacy of the Drug

The three clinical efficacy studies submitted in this application are reviewed extensively in the next section. Original data and tables were re-formatted as needed in order to follow the structure of this clinical review (the NDA source for each re-formatted table is listed at the bottom of the table). Extensive data in table format are included in the clinical review to serve as references for future inquires by secondary, and tertiary reviewers.

C. Detailed Review of Trials by Indication

With this submission, the applicant is seeking two indications: 1) pediatric growth hormone deficiency and 2) adult growth hormone deficiency. The data submitted for each of the two indications are reviewed separately in the following sections.

C.1. Pediatric growth hormone deficiency indication

The applicant submitted three sequential Phase III clinical studies conducted in pediatric patients with GHD in support of this indication. They are (1) study EP2K-99-PhIII, (2) study EP2K-00-PhIIIFo, and (3) study EP2K-00-PhIIIAQ.

C.1.1 Study Design and Objectives

The design of the three Phase III studies is summarized in Figure 1. Study EP2K-99-PhIII was a Phase III, open-label, multicenter[47], active control, parallel group study in which patients were

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[46] The annual height velocity on Omnitrope (8.9 ± 2.9 cm) was comparable with data from published literature which range from 8.8 ± 1.8 cm to 13.3 ± 3.9 cm for other GH products (see statistical review). Different GH doses and drug regimens (three times per week vs. seven times per week) were used in the referenced studies.

[47] One center in Hungary and six centers in Poland.

randomized to receive either Omnitrope Lyophilized Powder[48] or Genotropin. Both drug products were given as a single daily subcutaneous dose of GH (0.03 mg/kg/day) at bedtime, over 6 months. Patients who completed study EP2K-99-PhIII could then enter the follow-up study EP2K-00-PhIIIFo. In this 3-month study the patients continued on the same treatment and the same dose regimen they had received for the first 6 months (the total daily dose was adjusted to the actual body weight at study entry). The combined objective of studies EP2K-99-PhIII and EP2K-00-PhIIIFo was to evaluate the short-term efficacy and safety of Omnitrope Lyophilized Powder relative to an approved growth hormone product (Genotropin) over a treatment period of 9 months.

Study EP2K-00-PhIIIAQ was an open-label, multicenter, active control, parallel group, Phase III study performed in the patients who completed studies EP2K-99-PhIII/EP2K-00-PhIIIFo. It included two periods: Part A (first 6 months) and Part B (15 subsequent months and currently ongoing). During Part A, patients who had received Omnitrope Lyophilized Powder during studies EP2K-99-PhIII/EP2K-00-PhIIIFo were continued on the same dose of an Omnitrope Lyophilized Powder product manufactured at a different site[49]; patients who had received Genotropin during studies EP2K-99-PhIII/EP2K-00-PhIIIFo were treated with the same dose of another Omnitrope product: Omnitrope Liquid[50]. In the Part B of EP2K-00-PhIIIAQ study, all patients were switched to Omnitrope Liquid. The total daily doses were adapted to body weight at inclusion, and thereafter at each scheduled visit. The objectives were different for the two periods of study EP2K-00-PhIIIAQ. The objective of Part A was to evaluate the short-term efficacy and safety of the two Omnitrope products tested (Omnitrope Lyophilized Powder and Omnitrope Liquid).

Figure1: Design of the OMNITROPE Phase III Clinical Trials

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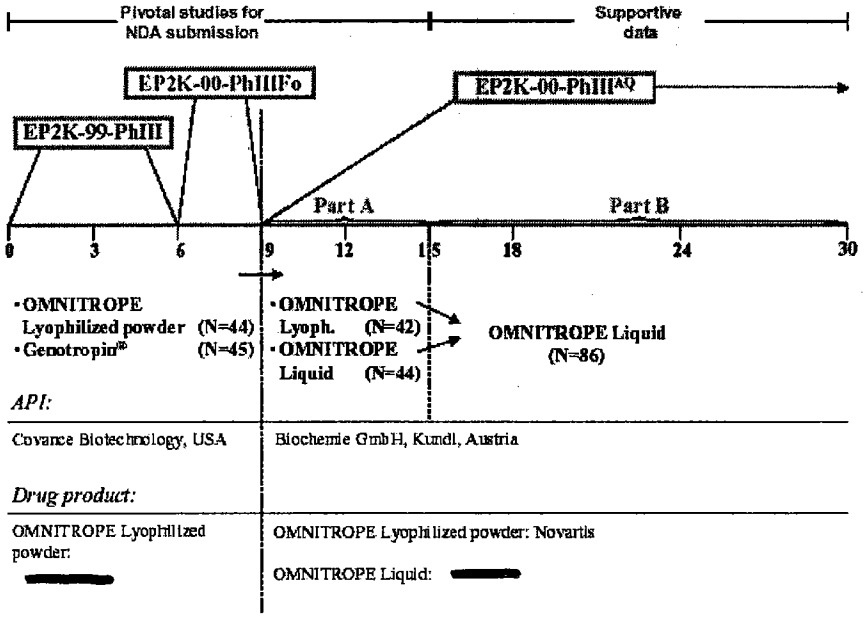
[48] The Omnitrope Lyophilized powder used an Active Pharmaceutical Ingredient (API) manufactured by Covance, USA).
[49] The API was manufactured by Biochemie, Austria.
[50] The API was also manufactured by Biochemie, Austria.
[51]



C.1.2 Main Inclusion and Exclusion Criteria

The main inclusion criteria for study EP2K-99-PhIII are displayed in Table 2:

Table 2: Inclusion criteria - study EP2K-99-PhIII

Age	prepubertal (boys and girls)
Height	below < 2 standard deviation score (SDS) for chronological age (using the appropriate national standard curves)
Height velocity	< -1 SDS at enrollment assessed over an interval of at least 6 months
GH insufficiency diagnostic criteria	2 standard pharmacological provocation tests (insulin, L-dopa, glucagon, arginine or clonidine) with growth hormone peak < 10 g/L
Thyroid status	euthyroid
Bone age	documented bone age radiography

Patients were excluded if they had evidence of intrauterine growth retardation[52], chronic systemic diseases, tumors, progression or recurrence of intracranial tumors,[53] idiopathic intracranial hypertension, chromosomal abnormalities and "medical

[52] Intrauterine growth retardation was defined as full term birth weight below 2500 g.

[53] by CT or MRI scan within 4 weeks prior to or at study entry.

"syndromes,"[54] use of other growth promoting medications such as anabolic steroids.[55] Although the protocol allowed to enroll both GH-treatment naïve and patients previously treated with GH, only treatment-naïve patients were actually enrolled.

At the end of study EP2K-99-PhIII patients could be enrolled in study EP2K-00-PhIIIFo (and subsequently in study EP2K-00-PhIIIAQ) if they showed a response to GH therapy during the previous Phase III study and if they were euthyroid.

C.1.3 Protocol amendments

The study EP2K-99-PhIII protocol was amended twice prior to study initiation[56]. "Amendment 1" incorporated a funduscopic evaluation at baseline, expanded the number of study centers from 5 to 7, and changed the formulation of the diluent for Omnitrope. "Amendment 2" added a funduscopic examination at Visit 3 (Month 3) and changed the randomization procedure.

Study EP2K-00-PhIIIAQ had three amendments:

- "Amendment 1"(30 November 2000) added one more visit and several assessments of anti-GH antibodies[57])
- "Amendment 2" (May 4, 2001) added an interim analysis of the anti-GH antibody incidence during the study, an efficacy analysis in anti-GH positive patients, and allowed patients to be switched from Omnitrope Lyophilized powder to Omnitrope Liquid formulation
- "Amendment 3" (March 8, 2002) added bone age to be assessed after 24 months of GH treatment and reassessed baseline bone age "to avoid potential inconsistencies in the earlier applied reading methodologies."

None of the above-mentioned amendments appear to have affected the results of the clinical trial.

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[54] with the exception of holoprosencephaly/septo-optic dysplasia.

[55] Pituitary hormone replacement therapy (thyroxin, hydrocortisone and vasopressin analogue) were allowed

[56] "Amendment 1" was on October 13, 1999 and "Amendment 2" was on December 6, 1999, both before patient enrollment began (the first patient was enrolled on February 15, 2000 and the last patient's last visit was March 26, 2001).

[57] This was due to the occurrence of anti-GH antibodies in the previous Phase III studies in 57% of patients who received Omnitrope Lyophilized powder.

C.1.4 Patient Disposition

Study EP2K-99-PhIII

Eighty nine patients were randomized to study EP2K-99-PhIII; 44 received Omnitrope Lyophilized powder and 45 received Genotropin (Table 3). Three subjects were prematurely withdrawn from the study: two patients in the Omnitrope group (Patients 05/18 and 07/26) were withdrawn after enrollment due to violation of protocol inclusion criteria[58] and one patient in the Genotropin group, (patient 02/79) was withdrawn due to non-compliance[59].

Table 3: Patient Disposition: Study EP2K-99-PhIII

	Omnitrope	Genotropin
Randomized	44 (100%)	45 (100%)
Completed	42 (95.5%)	44 (97.8%)
Withdrawn	2 (4.5%)	1 (2.2%)

Source: Text

Study EP2K-00-PhIIIFo

All 86 patients enrolled (42 patients in the Omnitrope group and 44 in the Genotropin group) completed this 3-month follow-up study.

Study EP2K-00-PhIIIAQ

[58] Between Visit 2 (Month 1) and Visit 3 (Month 3).

[59] Between Visit 2 (Month 1) and Visit 3 (Month 3), at 56 days.

Of the 86 patients who enrolled, all completed the Month 15 visit (Part A of the study); 78 (91%) completed the Month 30 visit (Part B of the study). Eight subjects were withdrawn during Part B of the study for the following reasons: non-compliance[60], withdrawal of consent[61], and "other reasons."[62] In addition, three patients (02/07, 07/75 and 07/76) were withdrawn from the study after Month 30 (the study is ongoing).

C.1.5. Protocol violations

During study EP2K-99-PhIII three patients had major protocol violations (this reviewer could not identify how protocol violations were defined in the protocol). There were two violations of the inclusion criteria (both in the Omnitrope arm[63]) and one due to noncompliance (in the Genotropin arm[64]).

The applicant reports that "a number of other protocol violations" occurred during the study that were considered to be "minor" and "did not result in withdrawal". In addition, some patients in the Genotropin arm received Genotropin from a source other than the trial medication supply (therefore, full drug accountability for the comparator product was not possible). The sponsor states, however, that "Genotropin was the only growth hormone available in Poland during the time of the EP2K-99-PhIII and EP2K-00-PhIIIFo studies" and "no patients received any marketed growth hormone preparation other than Genotropin."

No major protocol violations were reported during Part A of the EP2K-00-PhIIIAQ study. Four patients were judged as major protocol violators during the Month 15 to Month 30 period (Part B) of the study due to non-compliance. They were: patient 07/71 (a 7-year-old female was withdrawn from the study at Month 18), patient 07/28 (a 9-year-old female, was withdrawn

[60] Two patients in the original "Omnitrope" cohort (Patients 07/28 and 07/32) and two patients in the original "Genotropin" cohort (Patients 04/89 and 07/71).
[61] One patient in the original "Omnitrope" cohort (Patient 07/33) and two patients in the original "Genotropin" cohort (Patients 07/73 and 07/77).
[62] One patient in the original "Genotropin" cohort (Patient 07/72).
[63] Patient 05/18, a 6-year-old female, was withdrawn from the on February 28, 2000 because genetic screening indicated that she had minor chromosomal abnormalities (Turner's syndrome was excluded). Patient 07/26, a 6-year-old male, was withdrawn on March 10, 2000 as he did not meet the height velocity inclusion criterion: his growth velocity was +0.4 SDS (i.e. greater than -1 SDS).
[64] Patient 02/79, a 6-year-old male in the 'Genotropin' group, was withdrawn on May 12, 2000 due to non-compliance.

at Month 18), patient 04/89 (a 12-year-old male was withdrawn at Month 18), and patient 07/32, a 8-year old male was withdrawn at Month 24).

C.1.6 Treatment compliance

Patient compliance was evaluated during the clinical trials but the applicant does not define categorically patient compliance in the protocol[65].

According to the applicant, during study EP2K-99-PhIII, one patient in the Genotropin group (Patient 02/79) was judged to be significantly non-compliant during the Month 1 visit and was withdrawn from the study. Five patients were described as non-compliant at, and following, Month 18 during Part B of the EP2K-00-PhIIIAQ study[66] (of these, four were classified as "protocol violators" by the applicant).

C.1.7 Demographic and Baseline Patient Characteristics

Baseline age, weight, growth characteristics (height, height velocity, bone age, predicted adult height, IGF-I levels), and the results of the GH provocation tests at the beginning of the EP2K-99-PhIII study are presented in Table 4. Mean age, height and weight were similar between treatment groups. A higher proportion of patients in the Omnitrope group were male (28 or 64%), compared to the Genotropin group (21 or 47%). All 89 patients underwent two provocation tests (either clonidine, glucagon, insulin induced hypoglycemia, or L-dopa; the clonidine provocation tests was the most commonly used).

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[65] The clinical protocols state the following: "Patients will be required to record daily in a diary the time of the injection of the study treatment. The number of returned vials and the quantity of unused treatment remaining in the vials will also provide information on treatment compliance....Patients will be required to record daily in a diary the time of the injection of the study treatment. The number of returned vials and the quantity of unused treatment remaining in the vials will also provide information on treatment compliance". CRF forms included an evaluation of the number of vials dispensed. Patient compliance data were not collected at the Month 6 and Month 9 visits.

[66] Three patients (07/28, 07/71 and 04/89) were judged to be significantly non-compliant at Month 18, and they were withdrawn from the study. One patient (07/32) was withdrawn from the study due to non-compliance at Month 24. One patient (07/76) was declared non-compliant after the Month 30 visit.

Table 4: Baseline growth characteristics*

Variable	Omnitrope (N=44)	Genotropin (N=45)
Age (years)		
Mean (SD)	7.8 ± 2.56	7.4 ± 2.84
Range	3.0 to 13.0	2.0 to 14.0
Weight (kg)		
Mean (SD)	20.8 ± 6.04	20.1 ± 7.51
Range	11.7 to 37.2	8.8 to 46
Height (cm)		
Mean(SD)	113.3 ± 13.33	109.3 ± 15.68
Range	86.4 to 142.6	75.7 to 143.0
Height SDS		
Mean(SD)	-3.0 ± 0.72	-3.1 ± 0.89
Range	NA	NA
Height velocity (cm/yr)		
Mean(SD)	3.8 ± 1.23	4.0 ± 0.83
Range	1.0 to 6.1	1.8 to 5.6
Height velocity SDS		
Mean(SD)	-2.4 ± 1.30	-2.3 ± 1.12
Range	-6.0 to 0.4*	-5.5 to –1.0
Bone age (months)		
Mean(SD)	67.5±33.09	64.2±34.49
Range	12 to 144	12 to 150
Growth hormone stimulation (Mean of two tests)	4.17 g/l	4.12 g/l
IGF-I (ng/ml)		
Mean(SD)	159 ± 92.0	158 ± 43.0
Range	NA	NA
Projected Height (cm)		
Mean(SD)	154.5 ± 7.02	151.3 ± 7.87
Range	NA	NA

Source: Tables 3 and 4 and text. Combines baseline characteristics with "growth history" characteristics (growth history data are obtained before inclusion in the study and include annual height velocity in cm/yr and SDS).

* protocol inclusion criteria violation (in one patient who was withdrawn from the study)

SDS = standard deviation score. NA = not available

All 89 patients were prepubertal at baseline. The majority were still prepubertal at Months 6, 9 and 12[67]. The applicant states that "with the exception of short stature, which

[67] Thirty-nine patients (93%) in the Omnitrope group and 42 patients (95%) in the Genotropin group were still prepubertal at Month 6. Thirty-five patients (83%) in the Omnitrope group and 42 patients (95%) in the Genotropin group were prepubertal at Month 9. Thirty-five patients (83%) in the Omnitrope group and 39 patients (89%) in the Genotropin group were prepubertal at Month 12.

was noted for many patients, the majority of patients had no abnormalities, or only minor abnormalities noted during the baseline physical examination".

C.1.8. Data sets analyzed

The applicant conducted data analysis in three patient populations:

- intent-to-treat (ITT) population (included all patients randomized to study EP2K-99-PhIII)
- per-protocol (PP) population (included all patients without major protocol violations who were compliant with treatment)
- safety population (included all 89 randomized patients who received at least one dose of study medication)

C.1.9 Efficacy variables and statistical plan

Efficacy variables

The primary and secondary efficacy endpoints for studies EP2K-99-PhIII, EP2K-00-PhIIIFo, and EP2K-00-PhIIIAQ are presented in Table 5:

Table 5: Summary of Primary and Secondary Endpoints for the Pediatric Studies

Study	Primary endpoint(s)	Secondary endpoint(s)
EP2K-99-PhIII and EP2K-00-PhIIIFo	• Height, height SDS, height velocity, and height velocity SDS at Months 3, 6 and 9*.	• IGF-1 and IGFBP-3 serum levels at Months 6 and 9. • Safety evaluations
EP2K-00-PhIIIAQ	• Height, height SDS, height velocity, and height velocity SDS at Months 12, 15**, 24, and 30***. • Projected final height at Month 24.	• IGF-1 and IGFBP-3 serum levels at Months 12, 15, 24, and 30. • Safety evaluations

*Used the Month 0 assessment as reference value.
** Used Month 9 as reference value.
*** Used Month 15 as reference value.
Bone age was measured at Month 0 and Month 24.

For study EP2K-99-PhIII, the protocol-specified analyses of the primary endpoints were:

- a comparison of "the height [and height SDS] at month 6 while on treatment, with the height at inclusion in the study" by analysis of variance (ANOVA)
- a comparison of "annual height velocity, calculated from the annualized height velocity observed between Months 0 to 6 while under treatment, with the annual height velocity determined prior to inclusion in the study" by ANOVA
- a "time course of height and growth rate from baseline to Month 3 and 6" (assessed by ANOVA)

The "time course of the serum IGF-1 and IGFBP3 levels from baseline to Month 6" (secondary endpoints analysis) was to be compared between the treatment arms by ANOVA.

For study EP2K-00-PhIIIFo, the protocol-specified analyses of the primary endpoints were:

- a comparison of "height at Month 9 while under treatment, with the height at inclusion in the previous phase III study" by ANOVA
- a comparison of "annual height velocity, calculated from the annualized height velocity observed between Months 0 to 9 while under treatment, with the annual height velocity determined prior to inclusion in the previous phase III study" by ANOVA
- a "time course of height and growth rate from baseline of the previous phase III study to Month 9" (to be assessed by ANOVA)

The time course of the serum IGF-1 and IGFBP3 levels from Months 0 to 9 (a secondary endpoint analysis) was to be compared between the treatment arms by ANOVA.

For study EP2K-00-PhIIIAQ, the protocol-specified analyses of the primary endpoints were:

- A comparison of "height [and height SDS] at Month 12 in this study, with the height at inclusion in this study (corresponding to the visit at Month 9 in the initial phase III study)" by ANOVA . Then, the height measured every year since the inclusion in this study will be compared"
- A comparison of "annual height velocity [and height velocity SDS], calculated from the annualised height velocity observed between Months 0 and month 12 while under treatment, with the annual height velocity determined prior to inclusion in the previous phase III study" by ANOVA
- a "time course of height and growth rate from baseline to Month 12 (of this present study) and to every year" by ANOVA

The "time course of the serum IGF-1 and IGFBP3 levels from baseline to Month 6 of this present study" (a secondary endpoint analysis) were to be compared between the treatment arms by ANOVA.

The following changes in planned analyses were made to the statistical analysis plan on July 21, 2000:

- The protocol stated that the primary and secondary endpoints were to be compared by ANOVA; this was amended to ANCOVA.
- "The protocol stated that the time course of treatment on biological parameters would be evaluated using ANOVA. However, the results of the biological evaluations were not data based and so these evaluations were not done".

C.1.10. Efficacy Results

The applicant presents the clinical information from Month 0 to Month 15[68] obtained with Omnitrope Lyophilized powder as "pivotal data" and the information from Months 15 to Month 30[69] obtained with Omnitrope Liquid as "supportive data" [redacted]). It should be noted that the "pivotal" and "supportive" clinical trials are in essence a continuous study in which two cohorts of GH-treatment naïve patients have been exposed sequentially to different pairs of GH products (Omnitrope Lyophilized[70] vs. Genotropin for the initial 9 months, Omnitrope Lyophilized[71] vs. Omnitrope Liquid for the next 6 months, and Omnitrope Liquid alone in open-label extension up to 30 months). For the sake of consistency, this efficacy review follows the sponsor's presentation of efficacy data. In addition, whenever available, analyses that present data comparing Omnitrope Lyophilized powder to Genotropin at the Month 9 timepoint are highlighted. The Month 9 timepoint is the longest duration of side-by-side comparison between Omnitrope and Genotropin.

C.1.10.1 Pivotal study data

Main efficacy analyses

Table 6 presents descriptively the efficacy results for the primary endpoints (height, height SDS, height velocity, HVSDS) and for the secondary endpoints (IGF-I and IGFBP-3 serum levels) during the first 15 months of treatment. Table 6 also includes information on changes in predicted adult height ("projected height"). The "Omnitrope group" represents a cohort of patients who received sequentially the "Covance" Omnitrope and the "Biochemie" Omnitrope for 15 months. The "Genotropin group" is the cohort of patients who received Genotropin for the first 9 months and Omnitrope Liquid between Months 9 to 15. The measurements at Months 3, 6, and 9 are of particular importance since they reflect direct Omnitrope to Genotropin comparisons. This descriptive presentation of the data suggests that the results presented for all clinical parameters are comparable between Omnitrope and Genotropin over 9 months of treatment (and between the two cohorts for the sequence of GH administered over 15 months). The pharmacodynamic endpoints measured during the trial (IGF-I and IGFBP-3) were also comparable between Omnitrope Lyophilized and Genotropin (for Month 0 to Month 9) and Omnitrope Lyophilized powder and Omnitrope Liquid (for Month 9 to Month 15). Both Omnitrope and Genotropin improved predicted adult height (PAH) at Month 9. Further improvement in PAH occurred at Month 15 with "Biochemie" and Liquid Omnitrope, respectively[72].

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[68] Studies EP2K-99-PhIII, EP2K-00-PhIIIFo, and EP2K-00-PhIIIAQ Part A.
[69] Study EP2K-00-PhIIIAQ Part B.
[70] Manufactured by Covance, USA.
[71] Manufactured by Biochemie in Kundl, Austria.
[72] Although the applicant does not always indicate the patient population analyzed (e.g. ITT vs. per-protocol), for practical purposes the ITT and PP patient populations are virtually the same since there were only three patient discontinuations during 15 months of treatment and all three took place early in the clinical trials, before a true on-trial assessment of efficacy could be collected (i.e. less than 3 months).

Table 6: Efficacy Results for Studies EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIIIAQ-Part A*

Treatment group	Month	Height (cm)	HSDS	Height velocity (cm/yr)	HVSDS	IGF-1 (ng/ml)	IGFBP-3 (µg/ml)	Projected height (cm)
"Omnitrope"*	0	113.3±13.33	-3.0±0.72	3.8±1.23	-2.4±1.30	159±92.0	3.5±1.31	154.5 ± 7.02
(N=44)	3	116.7±13.30	-2.7±0.69	12.0±3.94	7.5±5.00	200±97.9	4.1±1.31	n.a.
	6	119.5±13.07	-2.4±0.67	11.7±3.03	7.3±4.21	257±127.8	3.8±1.29	n.a.
	9	121.9±13.06	-2.3±0.68	10.7±2.57	6.1±3.67	291±174.0	4.6±2.97	159.0 ± 7.08
	12	124.0±12.89	-2.1±0.70	8.9±2.89	3.8±3.73	304±150.4	4.2±1.08	n.a.
	15	126.1±12.95	-2.0±0.72	8.5±1.80	3.4±2.55	300±225.2	4.6±1.29	160.7 ± 7.06
"Genotropin"+	0	109.3±15.68	-3.1±0.89	4.0±0.83	-2.3±1.12	158±43.0	3.5±1.01	151.3 ± 7.87
(N=45)	3	112.5±15.47	-2.9±0.90	12.0±4.13	6.8±4.93	193±78.3	4.1±1.26	n.a.
	6	115.3±15.06	-2.6±0.78	11.6±3.13	6.3±3.45	248±131.2	3.7±1.25	n.a.
	9	117.7±14.71	-2.5±0.73	10.7±2.90	5.4±3.16	302±182.9	4.0±1.53	155.1 ± 7.33
	12	119.9±14.70	-2.3±0.73	8.7±2.25	3.1±2.66	318±166.7	4.5±1.49	n.a.
	15	122.0±14.68	-2.2±0.73	8.6±2.04	3.2±2.89	323±189.1	4.9±1.41	156.9 ± 7.54

* "Omnitrope" patients received: - OMNITROPE™ Lyophilized powder (using the API manufactured by Covance, USA) from Month 0 to 9;
- OMNITROPE™ Lyophilized powder (using the API manufactured by Biochemie, Austria) from Month 9 to 15.

+ "Genotropin" patients received: - Genotropin® from Month 0 to 9;
- OMNITROPE™ Liquid (using the API manufactured by Biochemie, Austria) from Month 9 to 15.

Source: Table 1(ISE).

The applicant concludes that Omnitrope Lyophilized powder and Genotropin have equivalent effects on growth rate after 9 months of therapy. This conclusion is based on the statistical observation that the 95% confidence interval of the difference of height velocity SDS between the two treatments rests entirely within a predefined equivalence interval of ± 2.8 cm (see figure, below)[73]. It is important to mention that the statistical reviewer (Cynthia Liu) "could not find any background rationale regarding the choice of 2.8 [cm]." Therefore a methodologically independent analysis was conducted (see the statistical review for details); it confirmed the applicant's conclusion of equivalence.

[73] This "equivalence interval" is defined by the applicant as the 95% confidence interval for 1 standard deviation of the HVSDS at one year of Genotropin treatment that was recorded, reportedly, in the clinical study TRN 86-073 of NDA 20-280.

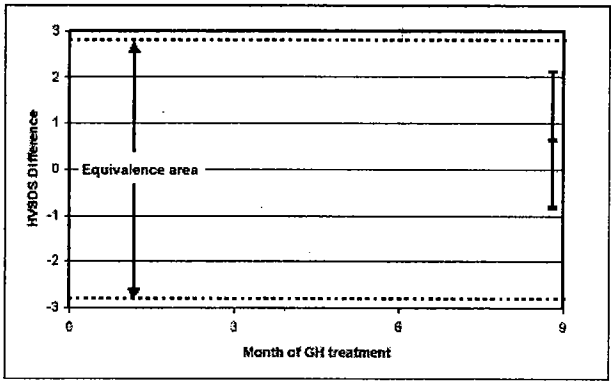

Figure 5: 95% confidence interval of the difference in HVSDS determined after 9 months of treatment.
Source: Section 14, Table 8.1.2.

The applicant presents a non-parametric (Mann-Whitney) statistical comparison performed between the Omnitrope and the Genotropin cohorts for all efficacy endpoints at Months 0, 3, 6 and 9 (see applicant's Table 20, below). This analysis does not detect any between-group statistical differences at any of the timepoints analyzed.

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Table 20: P-values of Mann-Whitney test between the 'Omnitrope' and 'Genotropin' groups (95% confidence interval)

	Height			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	44	42	42	42
N in 'Genotropin' group	45	44	44	44
p value	0.36	0.31	0.28	0.22
	HSDS			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	43	41	42	42
N in 'Genotropin' group	43	43	43	43
p value	0.45	0.49	0.24	0.12
	Height Velocity			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	44	42	42	42
N in 'Genotropin' group	45	44	44	44
p value	0.69	0.83	0.72	0.93
	HVSDS			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	44	41	41	41
N in 'Genotropin' group	45	44	44	44
p value	0.68	0.56	0.25	0.34
	IGF-1 serum levels			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	20	34	38	35
N in 'Genotropin' group	20	33	40	38
p value	0.29	0.98	0.59	0.92
	IGFBP-3 serum levels			
	Month 0	Month 3	Month 6	Month 9
N in 'Omnitrope' group	40	42	42	40
N in 'Genotropin' group	36	44	44	43
p value	0.35	0.99	0.80	0.54

Source: Appendix 16.2, Listings 7 and 8. Values for some patients are missing because standard values were not available for the HSDS/HVSDS calculation.
N = number of patients.
Statistical test performed using Systat® 7.0, Mann-Whitney non-parametric test, confidence interval 95%.

Predicted adult height

GH therapy with Omnitrope Lyophilized powder and Genotropin resulted in a mean predicted adult height increases of +4.9 cm and +4.3 cm, respectively at 9 months ($p < 0.0001$, within group analysis). No significant differences were found between boys and girls regarding the change of predicted final height between Month 0 and Month 9 ($p = 0.91$ for the Omnitrope cohort and $p = 0.60$ for the Genotropin cohort). No significant difference was found between groups (Omnitrope vs. Genotropin) regarding the change of predicted final height between Month 0 and Month 9 (for all patients, irrespective of the gender: $p = 0.17$; for girls: $p = 0.33$; for boys: $p = 0.46$).

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Secondary efficacy endpoints: IGF-I and IGFBP-3

IGF-I serum levels

A time course of the mean serum levels of IGF-I (from Month 0 to Month 9) is presented graphically in applicant's Figure 6, below. A similar timecourse for this pharmacodynamic endpoint are noted in both treatment arms (Omnitrope Lyophilized

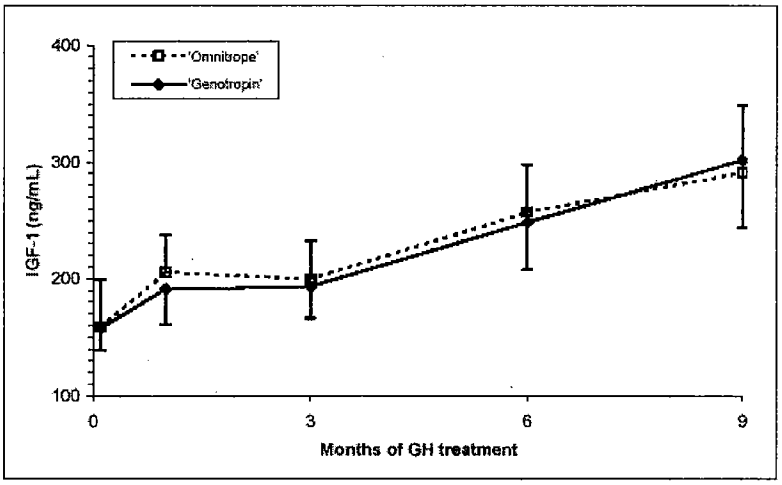

Figure 6: Mean IGF-1 serum levels over time by treatment group (ITT population) (Means and 95% Confidence Limits).

powder and Genotropin).

IGFBP-3 serum levels

A timecourse of the mean serum levels of IGFBP-3 (from Month 0 to Month 9) is presented graphically in applicant's Figure 7, below. As noted with IGF-I serum concentrations, a similar timecourse for the IGFBP-3 pharmacodynamic endpoint is

noted in both treatment arms (Omnitrope Lyophilized powder and Genotropin). The IGFBP-3 serum levels at Month 9, although divergent graphically, were not statistically

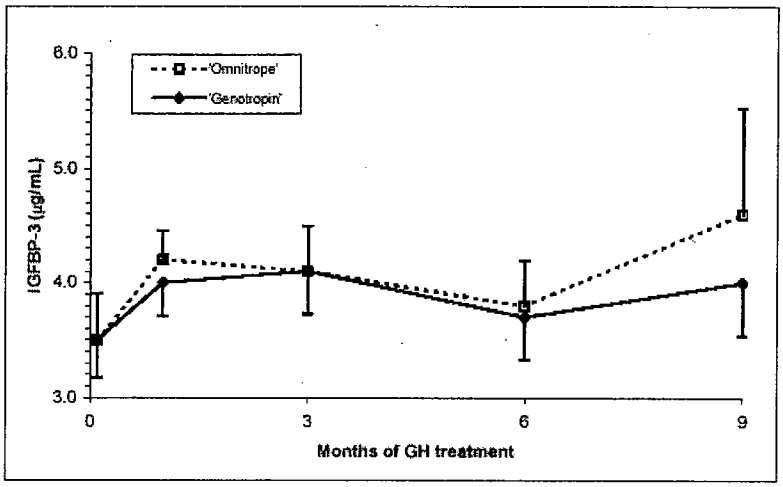

Figure 7: Mean IGFBP-3 serum levels over time by treatment group (ITT population) (Means and 95% Confidence Limits).

different.

Efficacy data obtained with the to-be-marketed Omnitrope Lyophilized powder

The to-be-marketed "Biochemie"-manufactured Omnitrope Lyophilized powder was used clinically between Months 9 and Month 15 (or "Part A" of clinical trial EP2K-00-PhIIIAQ). For this interval, "Biochemie" Omnitrope was compared with Omnitrope Liquid (an Omnitrope drug product which contains the same drug substance as the to-be-marketed product).

Applicant's Table 16 presents a statistical comparison between "Biochemie" Omnitrope and Omnitrope Liquid at Months 9 through 15 for the primary and secondary efficacy variables: height (cm), height SDS, height velocity (cm), height velocity SDS, IGF-I and IGFBP-3 serum levels. No statistical differences could be detected at any time between groups regarding any of these efficacy endpoints. "Omnitrope" group is the cohort that received "Covance" Omnitrope for the first 9 months and "Biochemie" Omnitrope between Months 9 and 15. "Genotropin" group is the cohort that received Genotropin for the first 9 months and Omnitrope Liquid between Months 9 and 15.

Table 16: P-values of Mann-Whitney test between the 'Omnitrope' and 'Genotropin' groups (95% confidence interval)

	Height		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	42	42	42
N in 'Genotropin' group	44	44	44
p value	0.22	0.23	0.21
	HSDS		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	42	42	42
N in 'Genotropin' group	43	43	43
p value	0.12	0.08	0.14
	Height Velocity		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	42	42	42
N in 'Genotropin' group	44	44	44
p value	0.93	0.74	0.93
	HVSDS		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	41	41	41
N in 'Genotropin' group	44	44	44
p value	0.34	0.38	0.54
	IGF-1 serum levels		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	35	41	39
N in 'Genotropin' group	38	43	42
p value	0.92	0.80	0.58
	IGFBP-3 serum levels		
	Month 9	**Month 12**	**Month 15**
N in 'Omnitrope' group	40	42	42
N in 'Genotropin' group	43	44	44
p value	0.54	0.47	0.40

Source: Appendix 16.2, Listings 7 and 8. Values for some patients are missing because standard values were not available for the HSDS/HVSDS calculation.
N = number of patients.
Statistical test performed using Systat® 7.0, Mann-Whitney non-parametric test, confidence interval 95%.

Applicant's Figure 5 presents an analysis of equivalence between Omnitrope Lyophilized powder and Omnitrope Liquid. It depicts the 95% confidence interval of the difference in HVSDS determined after 15 months of treatment, which lies entirely within the equivalence interval (-2.8, +2.8)[74]. A major limitation of this comparison is that patients were not re-randomized at the beginning of trial EP2K-00-PhIIIAQ; rather, they entered directly from study EP2K-00-PhIIIFo. In addition, the clinical protocol does not mention a washout period between studies and therefore, a carryover effect from the previous study cannot be formally excluded. The statistical reviewer (Cynthia Liu) compared the height velocity of "Biochemie" Omnitrope between Months 9 and 15 with that of "Covance" Omnitrope between Months 6 and 9 and found them to be similar (see

[74] The equivalence interval (± 2.8) was defined as the standard deviation of the HVSDS in the Genotropin study TRN 86-073 (NDA 20-280). As previously mentioned, the statistical reviewer "could not find any background rationale regarding the choice of 2.8 [cm]".

statistical review). This indicates that the two Omnitrope drug products have comparable efficacy.

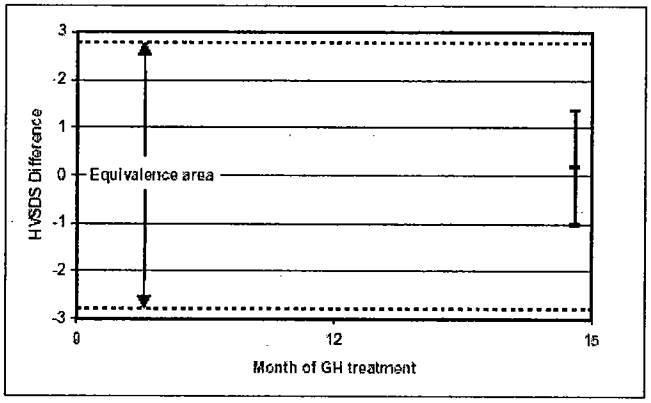

Figure 5: 95% confidence intervals of the difference in HVSDS determined after 15 months of treatment. Source: Section 14, Table 4.1.2.

C.1.10.2 Supportive efficacy data

The "supportive"data consists in information collected between Month 15 and Month 30 (Part B of study EP2K-00-PhIIIAQ). All patients enrolled in this study received open-label Omnitrope Liquid that contained the same drug substance as the to-be-marketed Omnitrope Lyophilized Powder.

The efficacy results for the primary endpoints (height, height SDS, height velocity, HVSDS) and for the secondary endpoints (IGF-I and IGFBP-3 serum levels) are presented descriptively in applicant's Table 9. These data indicate a sustained effect of Omnitrope Liquid over an additional 15-month period. Omnitrope Liquid maintained an accelerated mean height velocity SDS between 3.3 and 2.5, higher IGF-I levels than those noted prior to GH therapy, and improved the mean predicted adult height by 2.7 cm for this 15 month interval.

Table 9: Primary (height, HSDS, height velocity, HVSDS) and secondary (IGF-1 and IGFBP-3 serum levels) endpoints, as well as projected final height, from Month 15 to Month 30 for all patients. (Mean ± SD).

Month	Height (cm)	HSDS	Height velocity (cm/yr)	HVSDS	IGF-1 (ng/ml)	IGFBP-3 (µg/ml)	Projected height (cm)
15	124.0 ± 13.93	-2.1 ± 0.73	8.5 ± 1.92	3.3 ± 2.72	312 ± 206.3	4.8 ± 1.35	158.8 ± 7.51
18	125.8 ± 13.88	-2.0 ± 0.74	7.7 ± 2.49	2.3 ± 3.42	388 ± 179.7	4.9 ± 1.45	n.a.
24	129.3 ± 14.35	-1.9 ± 0.81	7.4 ± 1.66	2.5 ± 5.16	342 ± 161.7	6.1 ± 1.62	160.5 ± 7.94
30	132.6 ± 14.01	-1.7 ± 0.87	7.4 ± 1.60	2.5 ± 3.25	489 ± 248.0	4.5 ± 1.23	161.4 ± 8.17

C.1.10.3 Efficacy data in anti-GH antibody-positive patients

An important event during the Omnitrope clinical development has been the observation that "Covance" Omnitrope was immunogenic. To this end, it was noted that 57% of the patients treated with this drug substance developed anti-GH antibodies after 9 months of treatment. This issue is addressed in detail in the safety section. The applicant provides several efficacy sub-group analyses that compare height and height velocity between antibody-positive and antibody-negative patients. No statistical differences were noted at any time during the trial between patients with and without anti-GH antibodies regarding these efficacy variables, suggesting that the presence of anti-GH antibodies had no detectable effect on any of the growth efficacy parameters.

C.1.10.4 Comparison of the efficacy data obtained with Omnitrope against historical (published) efficacy data of other GH products in GH deficient children

The statistical reviewer (Cynthia Liu) conducted a comparison of efficacy data obtained with Omnitrope and that derived from several published clinical trials of GH in children with GHD (see statistical review for details); she concludes that "the mean height velocities of Omnitrope-treated children" were "within the historical range".

C.2. Adult growth hormone deficiency indication

The applicant did not conduct any clinical studies with Omnitrope in adult patients with GHD. Instead, the applicant submitted, among others, several publications from peer-reviewed scientific journals which I summarized in the Appendix. These published clinical trials were conducted in adult patients with GHD and used several dose regimens of GH (Genotropin). They confirm the known benefits of GH in this patient population including the normalization of serum IGF-I concentrations and improvements in body composition (increase in lean body mass, decrease in fat mass) and bone mineral density.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

This NDA contains clinical safety data obtained with three Omnitrope drug products: the "Covance" lyophilized Omnitrope[75], the "Biochemie" lyophilized Omnitrope[76], and Omnitrope Liquid[77]. The applicant seeks market approval for only one of these three drug products: the "Biochemie" Omnitrope[78]. In final analysis, the Omnitrope active pharmaceutical ingredient manufactured at the Biochemie GmbH site (and contained in the to-be-marketed "Biochemie" Omnitrope) appears to be safe and comparable to Genotropin when used in children with GHD. This conclusion is based on a combination of safety data obtained during both the controlled and the open-label studies conducted with all three Omnitrope drug products.

In a side-by-side comparison to Genotropin over 9 months, "Covance" Omnitrope displayed a comparable safety profile, with no deaths, no drug-related serious adverse events, and no patient withdrawals due to adverse events[79]. "Covance" Omnitrope was found, however, to be highly immunogenic. Specifically, 57 % of patients treated with this product developed anti-GH antibodies after 9 months of continuos treatment; this finding compared unfavorably to Genotropin which was immunogenic in only 2% of patients. The applicant does not plan to market "Covance" Omnitrope.

The to-be-marketed "Biochemie" Omnitrope had a favorable safety profile during short-term (6 months) treatment: there were no deaths, no drug-related serious adverse events, no patient withdrawals due to adverse events and no unusual pattern of treatment-emergent adverse events. When used in patients previously exposed to "Covance" Omnitrope who had anti-GH antibodies, it was associated with a reduction in the percentage of antibody-positive patients from 57% to 36%. Although not compared side-by-side with Genotropin, "Biochemie" Omnitrope was associated with a similar adverse event profile as illustrated by a comparison across trials of the rates of adverse events normalized per patient-year.

Omnitrope Liquid had an adverse event profile which was comparable to that of "Biochemie" Omnitrope, as seen in an analysis of adverse event rates normalized per patient-year. Additionally, and importantly, in a cohort of patients previously exposed to Genotropin who had a low percentage of anti-GH antibody-positive patients at baseline[80], treatment with Liquid

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[75] Manufactured by Covance Biotechnologies, USA.
[76] Manufactured by Biochemie GmbH in Kundl, Austria.
[77] Manufactured by Biochemie GmbH in Kundl, Austria.
[78] [redacted] The data obtained with Ommitrope Liquid is presented in this NDA only as "supportive evidence."
[79] A threefold increase in the incidence of hypothyroidism relative to Genotropin was observed in association with "Covance" Omnitrope but this observation was not replicated with the to-be-marketed "Biochemie" Omnitrope.
[80] One patient (or 2%).

Omnitrope maintained a low antibody positivity[81]. Furthermore, when the original "Covance" Omnitrope cohort with a high percentage of antibody-positive patients was changed to Omnitrope Liquid at Month 15, the decrease in the percentage of antibody-positive patients noted between Month 9 and Month 15 on "Biochemie" Omnitrope continued over the next 21 months (further reduction from 36% to 16 %).

B. Description of Patient Exposure

The total patient exposure to Omnitrope Lyophilized powder was 53 patient-years (42 patients treated for 15 months). It included 32 patient-years for Omnitrope Lyophilized powder manufactured by Covance and 21 patient-years for the to-be-marketed Omnitrope Lyophilized powder manufactured by Biochemie[82]. Additional patient exposure with the to-be-marketed drug substance manufactured by Biochemie was obtained with Omnitrope Liquid (123 patient-years)[83].

C. Specific Findings of the safety review

C.1. Pediatric growth hormone deficiency indication

C.1.1. Safety data from pivotal clinical trials

The "pivotal" trials (as described by the applicant) are the first 15 months of Omnitrope treatment[84]. For this 15-month interval clinical safety data were collected with three Omnitrope drug products:

- the "Covance" Lyophilized Omnitrope
- the to-be-marketed "Biochemie" Lyophilized Omnitrope
- Omnitrope Liquid

This section of the safety review will focus on the safety data obtained with "Covance" Omnitrope and the to-be-marketed "Biochemie" Omnitrope. Safety data with Omnitrope Liquid (not subject for market approval) will be reviewed separately in the "supportive data" section. Emphasis will be placed on the comparison between "Covance" Omnitrope and Genotropin because it represents the only clinical trial dataset that compares directly Omnitrope with an approved GH drug product[85].

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[81] Three patients or approximately 5 % (95% CI: 0.6% - 16.9%).

[82] For comparison, 44 patients received Genotropin for 9 months and one patient (02/79) for 56 days (in total, 33 patient-years).

[83] [redacted]

[84] They include clinical trials EP2K-99-PhIII, EP2K-00-PhIIIFo, and Part A of EPK-00PhIIIAQ.

[85] This comparison includes an almost identical duration of exposure to each of the two GH products: 32 patient-years for "Covance" Omnitrope vs. 33-patient years Genotropin, respectively, accumulated for a trial duration of 9 months.

C.1.1.1 Deaths

No deaths were reported during the study period.

C.1.1.2 Serious Adverse Events

Serious adverse events by drug product (Omnitrope vs. Genotropin) and by drug product manufacturing site (Covance vs. Biochemie) are presented in Table 8. None of these serious adverse events was considered to be related to study medication by the investigators.

Table 8: Serious Adverse Events

Patient Identifier	Drug Product	Serious Adverse Event	Related to Study Medication*
01/01	Omnitrope Lyophilized powder (Covance)	Parasitic infection (Toxocara canis) **	No
02/38	Omnitrope Lyophilized powder (Covance)	"Slight mental impairment" **	No
06/24	Omnitrope Lyophilized powder (Covance)	Acute gastritis	No
06/25	Omnitrope Lyophilized powder (Biochemie)	Acute gastritis**	No
04/89	Genotropin	Inflicted injury to one eye	No
04/56	Genotropin	Nose trauma	No

*By applicant's report.
** Hospitalization

C.1.1.3 Patient Discontinuations Due to Adverse Events

The applicant does not report any patient discontinuations from the study due to adverse events (most patient discontinuations were, reportedly, for non-compliance or protocol violations; see "Patient disposition" section for details).

C.1.1.4 Treatment-Emergent Adverse Events

C.1.1.4.1 Incidence of treatment-emergent adverse events

Overall, the number and percentage of patients who developed treatment-emergent adverse events (TEAEs) were comparable between the "Covance" Omnitrope and Genotropin (applicant's Table 3). To this end, 36 (82%) patients reported 172 adverse events under treatment with Omnitrope and a slightly higher number of patients reported adverse events with Genotropin: 43 (96%) patients reported 201 adverse events. For a shorter duration and patient exposure, 28 (67%) patients reported 67 adverse events under treatment with the to-be-marketed "Biochemie"Omnitrope.

The majority of the TEAEs reported with these three drug products were mild in severity. Nine (20%) patients treated with "Covance" Omnitrope, 14 (31%) patients treated with Genotropin, and 3 (7%) patients treated with "Biochemie" had events that were of moderate intensity. Only two (5%) patients treated with "Covance" Omnitrope and 1 (2%) patient treated with Genotropin

had events that were judged to be of severe intensity. None of these severe adverse events were reported to be drug-related.

Overall, the most common TEAEs (by body system) were those associated with the respiratory system, the body as a whole, and the gastrointestinal system.[86] TEAEs (by body system) which were more frequent with "Covance" Omnitrope relative to Genotropin for the first 9 months of treatment were in the cardiovascular system[87], endocrine system[88], gastrointestinal system[89], metabolic and nutritional system[90], psychiatric system[91], and skin and appendages system[92]. A visual inspection of the individual "preferred terms" within the above-mentioned categories does not identify any specific TEAE that can be clearly attributed to Omnitrope; the small number of patients in each "preferred term" category limits the ability to draw further conclusions.

Table 3: Overall summary of adverse events (Safety population)

	Number (%) of patients with adverse events			Total number of adverse events		
	OMNITROPE™ Lyophilized powder (API Covance) N=44	OMNITROPE™ Lyophilized powder (API Biochemie) N=42	Genotropin® N=45	OMNITROPE™ Lyophilized powder (API Covance) N=44	OMNITROPE™ Lyophilized powder (API Biochemie) N=42	Genotropin® N=45
Treatment-emergent adverse events:						
Mild	25 (57%)	25 (60%)	28 (62%)	147	64	177
Moderate	9 (20%)	3 (7%)	14 (31%)	23	3	23
Severe	2 (5%)	0	1 (2%)	2	0	1
Total	**36 (82%)**	**28 (67%)**	**43 (96%)**	**172**	**67**	**201**
Drug-related adverse events:						
Mild	13 (30%)	6 (14%)	18 (40%)	40	9	35
Moderate	3 (7%)	0	1 (2%)	3	0	1
Severe	0	0	0	0	0	0
Total	**16 (36%)**	**6 (14%)**	**19 (42%)**	**43**	**9**	**36**

Individual TEAEs reported in more than 5% (i.e. more than 3 patients) of the safety population are displayed in applicant's Table 4, below. Adverse events that occurred more frequently with "Covance" Omnitrope relative to Genotropin were: hypothyroidism,[93] abdominal pain,[94]

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[86] In total, 21 (48%) patients treated with "Covance" Omnitrope, 26 (58%) patients treated with Genotropin, and 16 (38%) patients treated with Omnitrope "Biochemie" reported respiratory system adverse events. General disorders (body as a whole) were reported in 12 (27%) patients treated with "Covance" Omnitrope, 16 (36%) patients treated with Genotropin, and 6 (14%) patients treated with "Biochemie" Omnitrope. Gastrointestinal adverse events were reported in 16 (36%) patients, 9 (20%) patients, and 8 (19%) and, respectively.

[87] 1 (2%) Omnitrope (heart murmur) vs. none with Genotropin.

[88] 7 (16%) Omnitrope (6 out of 7 patients with hypothyroidism) vs. 5 (11%) Genotropin (most also thyroid related).

[89] 16 (36%) Omnitrope (accounted mostly by abdominal pain and vomiting) vs. 9 (20%) Genotropin.

[90] 10 (23%) Omnitrope vs. 6 (13%) Genotropin.

[91] 3 (7%) Omnitrope vs. 1 (2%) Genotropin.

[92] 6 (14%) Omnitrope vs. 1 (2%) Genotropin.

[93] 6 (14%) patients on Omnitrope vs. 3 (7%) patients on Genotropin.

[94] 7 (16%) patients on Omnitrope vs. 1(2%) patients on Genotropin.

vomiting[95], hypercholesterolemia[96], hypertriglyceridemia[97], coughing[98], upper respiratory tract infection[99], varicella[100], elevated HbA1c[101], and eosinophilia[102].

Individual TEAEs that occurred more frequently with the to-be-marketed "Biochemie" Omnitrope relative to "Covance" Omnitrope Lyophilized were: fever[103], infection viral[104], bronchitis[105], and lymphadenopathy[106].

The only individual TEAEs that occurred more frequently with the to-be-marketed "Biochemie" Omnitrope relative to Genotropin were: abdominal pain[107] and hypertriglyceridemia[108].

Finally, the individual TEAEs that occurred more frequently with Genotropin relative to "Covance" Omnitrope were: ESR increased[109], fever[110], diarrhea[111], SGOT increased[112], SGPT increased[113], hematoma[114], purpura[115], viral infection[116], bronchitis[117], pharyngitis[118], rhinitis[119], inflicted injury[120], urinary tract infection[121], and lymphadenopathy[122].

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[95] 5 (11%) patients on Omnitrope vs. 2 (4%) patients on Genotropin.
[96] 6 (14%) patients on Omnitrope vs. 4 (9%) patients on Genotropin.
[97] 3 (7%) patients on Omnitrope vs. 2 (4%) patients on Genotropin.
[98] 4 (9 %) patients on Omnitrope vs. 3 (7%) patients on Genotropin.
[99] 13 (30%) patients on Omnitrope vs. 1 (24%) patients on Genotropin.
[100] 3 (7%) patients on Omnitrope vs. 2 (4%)patients on Genotropin.
[101] 4 (9%) patients on Omnitrope vs. 3 (7%) patients on Genotropin.
[102] 9 (20%) patients on Omnitrope vs. 8 (18%) patients on Genotropin.
[103] 3 (7%) patients on Omnitrope (Biochemie) vs. 2 (5%) patients on Omnitrope (Covance)
[104] 2 (5%) patients on Omnitrope (Biochemie) vs. 1 (2%) patients on Omnitrope (Covance)
[105] 3 (7%) patients on Omnitrope (Biochemie) vs. 2 (5%) patients on Omnitrope (Covance).
[106] 2 (5%) patients on Omnitrope (Biochemie) vs. 1 (2%) patients on Omnitrope (Covance).
[107] 2 (5%) patients on Omnitrope (Biochemie) vs. 1(2%) patients on Genotropin.
[108] 3 (7%) patients on Omnitrope (Biochemie) vs. 2 (4%) patients on Genotropin.
[109] 8 (18%) patients on Genotropin vs. 5 (11%) patients on Omnitrope.
[110] 6 (13%) patients on Genotropin vs. 2 (5%) patients on Omnitrope.
[111] 3 (7%) patients on Genotropin vs. 1 (2%) patients on Omnitrope.
[112] 4 (9%) patients on Genotropin vs. 2 (2%) patients on Omnitrope.
[113] 3 (7%) patients on Genotropin vs. none on Omnitrope.
[114] 5 (11%) patients on Genotropin vs. 4 (9 %) patients on Omnitrope.
[115] 3 (7%) patients on Genotropin vs. none on Omnitrope.
[116] 7 (16%) patients on Genotropin vs. 1 (2 %) patients on Omnitrope.
[117] 5 (11%) patients on Genotropin vs. 2 (5 %) patients on Omnitrope.
[118] 14 (31%) patients on Genotropin vs. 9 (20%) patients on Omnitrope.
[119] 7 (16 %) patients on Genotropin vs. 5 (11%) patients on Omnitrope.
[120] 3 (7%) patients on Genotropin vs. none on Omnitrope.
[121] 5 (11%) patients on Genotropin vs. 1 (2%) patients on Omnitrope.
[122] 4 (9%) patients on Genotropin vs. 1 (2%) patients on Omnitrope.

Table 4: Incidence of treatment-emergent adverse events experienced by > 5% of patients (Safety population).

Preferred Term	Incidence (%) of treatment-emergent adverse events[a,c]								
	OMNITROPE™ Lyophilized powder (API Covance) N=44			OMNITROPE™ Lyophilized powder (API Biochemie) N=42			Genotropin[b] N=45		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ESR increased	5 (11%)			2 (5%)			8 (18%)		
Fever	2 (5%)			3 (7%)			4 (9%)	2 (4%)	
Headache	6 (14%)	1 (2%)		3 (7%)			5 (11%)	2 (4%)	
Hypothyroidism	6 (14%)						3 (7%)		
Abdominal pain	6 (14%)	1 (2%)		2 (5%)			1 (2%)		
Diarrhea	1 (2%)			1 (2%)			3 (7%)		
Vomiting	4 (9%)	1 (2%)		1 (2%)			1 (2%)	1 (2%)	
SGOT increased	1 (2%)						4 (9%)		
SGPT increased							3 (7%)		
Hypercholesterolemia	6 (14%)			2 (5%)			4 (9%)		
Hypertriglyceridemia	3 (7%)			3 (7%)			2 (4%)		
Hematoma	4 (9%)			2 (5%)			5 (11%)		
Purpura							3 (7%)		
Infection viral	1 (2%)			2 (5%)			6 (13%)	1 (2%)	
Bronchitis	2 (5%)			2 (5%)	1 (2%)		5 (11%)		
Coughing	2 (5%)	2 (5%)					2 (4%)	1 (2%)	
Pharyngitis	5 (11%)	4 (9%)		7 (17%)			10 (22%)	4 (9%)	
Rhinitis	5 (11%)			2 (5%)			6 (13%)	1 (2%)	
Upper resp. tract infection	11 (25%)	2 (5%)		6 (14%)			6 (13%)	5 (11%)	
Inflicted injury							2 (4%)		1 (2%)
Varicella	2 (5%)	1 (2%)		1 (2%)			2 (4%)		
Elevated HbA1c	4 (9%)						3 (7%)		
Urinary tract infection	1 (2%)						5 (11%)		
Eosinophilia	9 (20%)			3 (7%)			8 (18%)		
Lymphadenopathy	1 (2%)			1 (2%)	1 (2%)		4 (9%)		

Individual TEAEs that were reported in two (or less < 5%) patients treated with "Covance" Omnitrope were: allergic reaction, allergy, influenza-like symptoms, leg pain, pain, heart murmur, coma, vertigo, puberty precocious, gastritis, mucositis NOS, nausea, esophagitis, stomatitis, tooth caries, respiratory acidosis, hyperglycemia, hyperuricemia, arthralgia, anorexia, mental deficiency, thinking abnormal, anemia, infection parasitic, otitis media, pneumonia, alopecia, eczema, pruritus, rash, urticaria, face edema and leukocytosis.

Individual TEAEs that were reported in two (or less < 5%) patients treated with Genotropin were: injection site pain, allergic reaction, allergy, hypothermia, influenza-like symptoms, leg pain, vertigo, T4 decreased, TSH decreased, vascular malformation peripheral, cheilitis, constipation, tooth ache, tooth caries, arthralgia, bone disorder, myalgia, sting, anorexia, anemia,

infection, infection bacterial, infection parasitic, otitis media, laryngitis, sinusitis, scoliosis, rash maculo-papular, planned hospitalization – test with D-xylose, polyuria, urine abnormal, conjunctivitis, eye infection, vision abnormal and leukocytosis.

Individual TEAEs that were reported in two (or less < 5%) patients treated with the to-be-marketed "Biochemie" Omnitrope were: allergy, influenza-like symptoms, leg pain, heart murmur, convulsions grand mal, vertigo, constipation, gastritis, gastroenteritis, irritable bowel syndrome, stomatitis, tooth caries, hyperlipemia, hypocalcemia, infection parasitic, laryngitis, haematuria, renal calculus and leukocytosis.

A search of preferred terms that may be associated with a potential allergic reaction to the drug product did not identify any imbalance between "Covance" Omnitrope and Genotropin[123].

Incidence of "drug-related" adverse events

Hypothyroidism was the only "drug-related" TEAE which occurred in a predominant fashion in association with "Covance" Omnitrope relative to Genotropin (3X more frequently); however, no cases of hypothyroidism were reported in association with the to-be-marketed "Biochemie" Omnitrope. Eosinophilia and "elevated HbA1c" were more frequent in the "Covance" group relative to Genotropin but the differences were minor. Most of the "drug-related" TEAEs were mild to moderate in intensity and none were severe[124]. The most common drug-related adverse events are displayed in Table 9. TEAEs that occurred in more than one patient that are not listed in Table 9, above, are TSH decreased[125], and hypertriglyceridemia[126], both with higher incidence in the Genotropin group.

Table 9: Incidence of most frequent "drug-related" adverse events

Adverse Event	Omnitrope Lyophilized (Covance)	Omnitrope Lyophilized (Biochemie)	Genotropin
Hematoma*	4 (9%)	2 (5%)	5 (11%)
Eosinophilia**	5 (11%)	2 (5%)	3 (7%)
Hypothyroidism	6 (14%)	0	2 (4%)
Headache	3 (7%)	2 (5%)	3 (7%)
Elevated HbA1c	4 (9%)	0	3 (7%)

* All were located at the injection site.
** All cases of drug-related eosinophilia were reported in one site (07).

[123] "Allergic reaction": 2 (5%) Omnitrope and 1 (2%) Genotropin. "Allergy": 1 (2%) Omnitrope and 2 (4%) Genotropin. "Pruritus": 1(2%) Omnitrope and none in Genotropin. "Rash": 2 (5%) Omnitrope and none Genotropin. "Urticaria": 1 (2%) Omnitrope and none Genotropin.
[124] Only 4 "moderate" drug-related TEAEs were reported, all for the first 9 months of the trial: three were in the "Covance"Omnitrope group and one in the Genotropin group. Patient 01/02 (Omnitrope) lost consciousness ("coma") at the moment of blood sampling. Patient 04/11 (Omnitrope) had a worsening of an existing systolic heart murmur during the study but resolved at the end of 9 months. Patient 07/28 (Omnitrope) reported moderate persistent pruritus 51 days from the start of treatment. Patient 02/81 (Genotropin) had moderate scoliosis.
[125] None with either "Covance" or "Biochemie" Omnitrope and 2 (4%) patients on Genotropin.
[126] 2 (5%) patients on "Covance" Omnitrope , 1 (2%) patients on "Biochemie" Omnitrope, and 2 (4%) patients on Genotropin.

C.1.1.4.2 Treatment-emergent adverse event rates

An analysis of event rates for TEAEs that occurred in >5% of patients (i.e. in more than 3 patients) are presented in applicant's Table 12. Overall, the event rates in this category were comparable between the three drug products[127]. The data provided by this analysis are consistent with the analysis of the adverse event incidence. Most of the adverse events occurring with higher rates represent symptoms or signs of common childhood illnesses (e.g. pharyngitis, upper respiratory tract infection, etc). A higher event rate for eosinophilia was noted for "Covance" Omnitrope (0.35) relative to Genotropin (0.27) but not with "Biochemie" Omnitrope (0.14)[128]. Similarly, hypothyroidism had higher event rates in association with "Covance" Omnitrope but no such events were reported in association with the to-be-marketed Biochemie Omnitrope[129]. Overall, "drug-related" adverse event rates were comparable among the three drug products[130].

[127] 4.3 for "Covance" Omnitrope, 2.5 for "Biochemie" Omnitrope, and 4.9 for Genotropin.
[128] The "drug-related" eosinophilia event rate showed similar trends for all three drug products (0.22 for "Covance" Omnitrope, 0.10 for "Biochemie" Omnitrope, and 0.09 for Genotropin).
[129] Events rates of 0.19 for "Covance" Omnitrope and 0.09 for Genotropin. "Drug-related" events rates of 0.19 for "Covance" Omnitrope and 0.06 for Genotropin. Hypothyroidism was not reported with the to-be-marketed "Biochemie" Omnitrope.
[130] 1.37 for "Covance" Omnitrope, 0.43 for "Biochemie" Omnitrope, and 1.09 for Genotropin.

Table 12: Rate of AEs experienced by > 5% of patients treated with OMNITROPE™ Lyophilized powder (using API manufactured by Covance, USA). OMNITROPE™ Lyophilized powder (using API manufactured by Biochemie, Austria) and Genotropin*

Preferred Term	Rate of events per patient-year		
	OMNITROPE™ Lyophilized powder (API Covance)	OMNITROPE™ Lyophilized powder (API Biochemie)	Genotropin*
ESR increased	0.19	0.30	0.30
Fever	0.10	0.34	0.24
Influenza-like symptom	0.16	0.30	0.06
Leg pain	0.03	0.05	0.03
Headache	0.32	0.44	0.33
Hypothyroidism	0.19	*not experienced*	0.09
Abdominal pain	0.25	0.30	0.03
Diarrhea	0.03	0.05	0.12
Tooth caries	0.06	0.30	0.03
Vomiting	0.22	0.05	0.06
SGOT increased	0.03	*not experienced*	0.12
SGPT increased	*not experienced*	*not experienced*	0.09
Hypercholesterolemia	0.19	0.30	0.12
Hypertriglyceridemia	0.10	0.44	0.09
Phosphatase alkaline increased	*not experienced*	*not experienced*	*not experienced*
Hematoma	0.16	0.30	0.21
Purpura	*not experienced*	*not experienced*	0.09
Infection viral	0.10	0.30	0.24
Bronchitis	0.10	0.39	0.21
Coughing	0.16	*not experienced*	0.09
Pharyngitis	0.44	0.33	0.75
Rhinitis	0.19	0.30	0.27
Upper resp. tract infection	0.48	0.29	0.36
Inflicted injury	*not experienced*	*not experienced*	0.09
Varicella	0.10	0.05	0.06
Elevated HbA1c	0.19	*not experienced*	0.15
Urine abnormal	*not experienced*	*not experienced*	0.03
Urinary tract infection	0.03	*not experienced*	0.15
Eosinophilia	0.35	0.34	0.27
Leukocytosis	0.06	0.05	0.03
Lymphadenopathy	0.03	0.30	0.12
Total	4.3	2.5	4.9

n = number of events

*The rate of events per patient-year was calculated as: 12 x [(number of events) ÷ (months of exposure)]

Funduscopic evaluation

Results of funduscopic evaluations that resulted in a diagnosis of idiopathic intracranial hypertension (IIH) are presented in applicant's Table 16, below. The numbers of patients with IIH are low and comparable between the "Covance" Omnitrope and Genotropin treatment arms (one patient in each treatment group for timepoints up to Month 9). No additional patients with IIH were diagnosed after 12 months (and up to Month 30). The funduscopy assessment was not performed on all patients at all times, however.[131].

[131] Funduscopy was performed on all 86 patients at Month 3, on 1 patient in each group at Month 6 and on 4 patients in the 'Omnitrope' group and 3 patients in the 'Genotropin' group at Month 9.

Table 16
Summary of Funduscopy Examinations by Time Point (Safety)
Signs of Idiopathic Intracranial Hypertension

	Omnitrop (N=44)		Genotropin (N=45)		All Patients (N=89)	
	No	Yes	No	Yes	No	Yes
Time of GH Treatment						
Month 1	43 (100%)	0	45 (100%)	0	88 (100%)	0
Month 3	42 (100%)	0	44 (100%)	0	86 (100%)	0
Month 6	41 (98%)	1 (2%)	43 (96%)	1 (2%)	84 (98%)	2 (2%)
Month 9	41 (98%)	1 (2%)	43 (96%)	1 (2%)	84 (98%)	2 (2%)
Month 12	40 (95%)	2 (5%)	43 (96%)	1 (2%)	83 (97%)	3 (3%)

C.1.1.5. Clinical Laboratory

Most of the laboratory testing was performed at local laboratories[132]. In contrast, IGF-1, IGFBP-3, (both efficacy variables) and anti-GH antibodies were measured in a centralized fashion. The applicant presents abnormal analytes as "shift values" (i.e. below or above the normal reference range). During the clinical studies, most patients had normal laboratory values. Minor differences between treatment groups were occasionally recorded. There was no clear pattern of abnormal "shift values" for any of the drug products analyzed.

Clinically significant laboratory abnormalities recorded as adverse events

Abnormal laboratory results that were recorded as adverse events during the first 9 months ("Covance" Omnitrope vs. Genotropin) are summarized in applicant's Table 31, below. Hypothyroidism, hypercholesterolemia, hypertrygliceridemia, elevated HbA1c, eosinophilia, and leukocytosis had slightly higher incidence rates in the Omnitrope group. The numerical differences were, however, small[133].

[132] Such testing includes hematology, biochemistry, urinalysis, fasting glucose, HbA1c, free thyroxine (T4), and thyroid stimulating hormone (TSH).

[133] Among these, the most common adverse events considered to be "drug-related" were hypothyroidism (reported in 6 or 14% patients in the Omnitrope group and 2 or 4% patients in the Genotropin group), eosinophilia (reported in 5 or 11% patients in the Omnitrope group and 3 or 7% patients in the Genotropin group), elevated HbA1c (reported in 4 or 9% patients in the Omnitrope group and 3 or 7% patients in the Genotropin group).

Table 31: Incidence of treatment-emergent laboratory adverse events from Month 0 to Month 9 of overall GH therapy (Safety population)

Preferred Term	Incidence (%) of treatment-emergent laboratory adverse events^					
	'Omnitrope' N=44			'Genotropin' N=45		
	Mild	Moderate	Severe	Mild	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ESR increased	5 (11%)			8 (18%)		
Hypothyroidism	6 (14%)			3 (7%)		
T4 decreased				1 (2%)		
TSH decreased				2 (4%)		
SGOT increased	1 (2%)			4 (9%)		
SGPT increased				3 (7%)		
Hypercholesterolemia	6 (14%)			4 (9%)		
Hyperglycemia	1 (2%)					
Hypertriglyceridemia	3 (7%)			2 (4%)		
Hyperuricemia	1 (2%)					
Anemia	1 (2%)			2 (4%)		
Elevated HbA1c	4 (9%)			3 (7%)		
Eosinophilia	9 (20%)			8 (18%)		
Leukocytosis	2 (5%)			1 (2%)		

Source: Section 14, Table 11.1; Appendix 16.2, Listing 15
N = number of patients.
^ Some patients had more than one adverse event.

Abnormal laboratory results that were recorded as adverse events between months 9 and 15 of treatment ("Biochemie" Omnitrope vs. Liquid Omnitrope) are summarized in applicant's Table 28. In this table "Omnitrope" is the cohort of patients treated with "Covance" Omnitrope for the first 9 months and switched to "Biochemie" Omnitrope for months 9 through 15 of treatment. "Genotropin" is the cohort of patients treated with Genotropin for the first 9 months and switched to Liquid Omnitrope for months 9 through 15 of treatment. Only small numerical differences are noted. It is important to keep in mind that both "Biochemie" Omnitrope and Liquid Omnitrope contain the same active pharmaceutical ingredient.

Table 28: Incidence of treatment-emergent laboratory adverse events from Month 9 to Month 15 of overall GH therapy (Safety population)

Preferred Term	Incidence (%) of treatment-emergent laboratory adverse events^					
	'Omnitrope' N=42			'Genotropin' N=44		
	Mild	Moderate	Severe	Mild	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ESR increased	2 (5%)			7 (16%)		
Hypothyroidism				1 (2%)		
SGOT increased				1 (2%)		
SGPT increased				1 (2%)		
Hypercholesterolemia	2 (5%)			3 (7%)		
Hyperlipemia	1 (2%)					
Hypertriglyceridemia	3 (7%)			2 (5%)		
Hypocalcemia	1 (2%)					
Anemia				1 (2%)		
Elevated HbA1c				4 (9%)		
Haematuria	1 (2%)					
Eosinophilia	3 (7%)			6 (14%)		
Leucopoenia				1 (2%)		
Leukocytosis	1 (2%)			2 (5%)		
Monocytosis				1 (2%)		

Source: Section 14, Table 7.1; Appendix 16.2, Listing 9
^ Some patients had more than one adverse event.
N = number of patients.

C.1.1.6. Anti-Growth Hormone Antibodies

An important event during the Omnitrope clinical development has been the observation that "Covance" Omnitrope was immunogenic. Applicant's Table 5, below, displays the incidence of anti-GH antibodies observed during the first 9 months of Omnitrope therapy (clinical trials EP2K-99-PhIII and EP2K-00-PhIIIFo). Exposure to "Covance" Omnitrope resulted in a progressive increase in incidence of antibody-positive patients; at the end of 9 months of treatment 24 (57%) patients were anti-GH antibody positive. In contrast, among patients who received Genotropin, only one patient (2.3%; 95% confidence limits 0.06-12.02%) was antibody-positive at Month 9[134].

Table 5: Presence of anti-GH antibodies in studies EP2K-99-PhIII and EP2K-00-PhIIIFo (Month 0 to Month 9 of overall GH therapy)

	Anti-GH antibodies (OMNITROPE™ Lyophilized powder, API Covance)	Anti-GH antibodies (Genotropin®)
Month 0	0/44	0/45
Month 3	11/42 (26%)	0/44
Month 6	14/42 (33%)	0/44
Month 9	24/42 (57%)	1/44 (2%)

[134] The results noted in the Genotropin group are comparable to published data on Genotropin immunogenicity. In one study, the incidence of anti-GH antibodies (with a mean binding capacity of around 0.07 mg/l) was reported in 4 out of 229 GHD children (1.7%; 95% confidence limits 0.5-4.4%) after 12 months of treatment with Genotropin (Lundin K et al. Development of anti-human GH antibodies during therapy with authentic human growth hormone. Acta Pediatr Scand [Suppl] 372: 167-168, 1991).

The applicant states that the drug substance manufactured by Covance, USA was subsequently found to have a high content of Host Cell Proteins (HCP)[135]. Following this observation, production of Omnitrope drug substance was changed to a different site (Biochemie in Kundl, Austria) using a modified manufacturing process which decreased the HCP content of the product[136]. The drug substance manufactured at Biochemie was used in all subsequent Omnitrope drug products (to-be-marketed "Biochemie" Omnitrope and Omnitrope Liquid) in clinical trials[137]. Applicant's Table 6 presents the incidence of anti-GH antibodies observed during the first 6 months ("Part A" or months 9 through 15) of clinical trial EP2K-00-PhIIIAQ. The percentage of patients who were antibody-positive was reduced from 57% to 36% after 6 months of treatment. Among the 18 patients who were antibody-negative at Month 9 on the "Covance-manufactured" Omnitrope, 2 (11%) became positive within the next 6 months. In addition, and importantly, among the patients who were previously treated with Genotropin and were switched to Omnitrope Liquid, only one (2%) developed anti-GH antibodies.

Table 6: Presence of anti-GH antibodies in study EP2K-00-PhIII^{AQ}, Part A (from Month 9 to Month 15 of overall GH therapy)

	Anti-GH antibodies (OMNITROPE™ Lyophilized powder, API Biochemie)			Anti-GH antibodies (OMNITROPE™ Liquid, API Biochemie)
EP2K-00-PhIII^{AQ}, Part A	Total	Covance pos[a]	Covance neg[b]	Total
Month 9	24/42 (57%)	24/24 (100%)	0/18	1/44 (2%)[c]
Month 10	19/42 (45%)	18/24 (75%)	1/18 (5%)	1/44 (2%)
Month 12	16/42 (38%)	15/24 (62%)	1/18 (5%)	0/44
Month 15	15/42 (36%)	13/24 (54%)	2/18 (11%)	1/44 (2%)

[a] Patients who developed anti-GH antibodies with OMNITROPE™ Lyophilized powder (using API manufactured by Covance, USA)
[b] Patients who did not develop anti-GH antibodies with OMNITROPE™ Lyophilized powder (using API manufactured by Covance, USA)
[c] Anti-GH antibodies developed during the previous 9 months of treatment with Genotropin®

Applicant's figure (displayed below) presents a visual comparison of the efficacy data obtained from antibody-positive and antibody-negative patients for the treatment period up to Month 15, irrespective of the treatment arm. No differences in mean values for height SDS and HV SDS are noted[138]. An analysis of the immunoglobulin content of the anti-GH antibodies in six patients with "high binding capacities" indicated that they were predominantly, but not exclusively, of IgG type. The applicant does not provide an efficacy comparison of antibody-positive patients vs. antibody-negative within the Omnitrope treatment arm[139].

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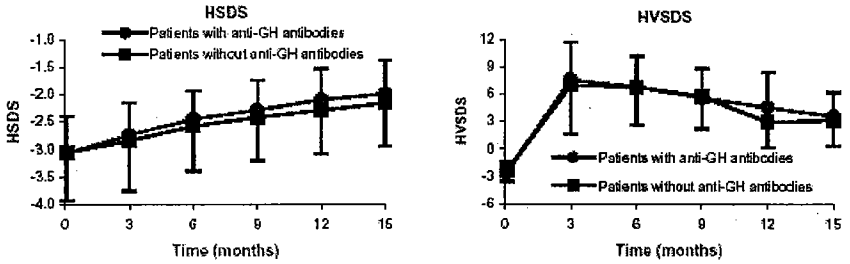
[135] At Month 9, 42/42 of patients on "Covance" Omnitrope developed anti-HCP antibodies. In contrast, none of the patients in the Genotropin group had anti-HCP antibodies at 9 months.
[136] Reportedly "by 2 orders of magnitude".
[137] The cohort of patients previously treated with "Covance" Omnitrope was switched at Month 9 to "Biochemie" Omnitrope; the cohort of patients treated with Genotropin were switched at Month 9 to Omnitrope Liquid.
[138] The antibody-positive group had a baseline (mean ±SD) height SDS of -3.1 ± 0.7 and a baseline mean HVSDS of -2.5 ± 1.2; at the end of 15 months of treatment the height SDS was -2.0 ± 0.6 and the HVSDS was 3.6 ± 2.7. The antibody-negative group had a baseline (mean ±SD) height SDS of -3.1 ± 0.9 and a baseline mean HVSDS of -2.3 ± 1.2; at the end of 15 months of treatment the height SDS was -2.2 ± 0.8 and the HVSDS was 3.1 ± 2.8.
[139] The statistical reviewer's analysis reveals no efficacy differences between the antibody-positive and the antibody-negative patients within the Omnitrope treatment arm at Month 9. The least-squares mean of HVSDS in

Height SDS and HVSDS for Anti-GH positive and anti-GH negative patients



This reviewer agrees with the main conclusions of the applicant:

- The "Covance" Omnitrope (which will not be marketed) is highly immunogenic; importantly, this GH product was not associated with an increase in incidence of allergic adverse events.
- The "Biochemie" Omnitrope (the to-be-marketed Omnitrope product), when used for 6-months, was associated with a reduction in the percentage of antibody-positive patients, implying that it is less immunogenic than "Covance" Omnitrope.
- The Liquid Omnitrope (which contains the same active pharmaceutical ingredient as the to-be-marketed Omnitrope Lyophilized powder) is markedly less immunogenic over 6 months of treatment; its level of immunogenicity is comparable to that of other currently marketed GH drug products.

C.1.1.7 Vital signs

Mean vitals sign measurements (systolic and diastolic blood pressure and heart rate) were similar across visits within each treatment group and similar between treatment groups within each clinical trial for all GH products: "Covance" Omnitrope, Genotropin, "Biochemie" Omnitrope, and Omnitrope Liquid.

C.1.2. Supportive safety information (safety results obtained with Omnitrope Liquid)

[redacted]; safety clinical data obtained with this drug

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the Omnitrope antibody-positive group is 5.6430 (N=23); for the Omnitrope antibody-negative group it is 6.4346 (N=17). They are not different from each other statistically (p = 0.4765).

product are provided as supportive evidence since the drug substance in Omnitrope Liquid is the same as in the to-be-marketed "Biochemie" Omnitrope.

Extent of exposure

Forty-four patients received Omnitrope Liquid for 6 months during Part A of study EP2K-00-PhIIIAQ for a total of 21 patient-years. During Part B of the study, 86 patients were treated with Omnitrope Liquid[140] (101 patient-years). The total exposure to Omnitrope Liquid was 123 patient-years. The treatment duration with Omnitrope Liquid ranged from 15 to 21 months. The dose of Omnitrope Liquid was the same as for all previously tested Omnitrope drug products (0.03 mg/kg/day).

C.1.2.1 Adverse events

There were no patient deaths during the study. During Part A of the study, four patients experienced a serious adverse event[141]. During Part B of the study, eight patients experienced ten serious adverse events[142]. The applicant does not report any patient withdrawals due to adverse events.

Seventy-nine (92%) patients reported 458 adverse events during treatment with Omnitrope Liquid. Of these, 33 (38%) patients reported 80 "drug-related" adverse events. The majority of these events were, reportedly, mild or moderate in severity. Four patients reported six events that were judged to be of severe intensity, three of which were considered to be drug-related[143].

The most common treatment-emergent adverse events were in the respiratory system (55 or 64 % patients), "body as a whole" (38 or 44% patients), "white cells and RES" (36 or 42 % patients), resistance mechanisms (24 or 28 % patients) and metabolism (23 or 27 % patients). Individual TEAEs which occurred in >5% of patients during treatment with Omnitrope Liquid are presented in applicant's Table 26, below. The most TEAEs were adverse events of the respiratory system (pharyngitis, reported by 27 or 31% patients and upper respiratory tract infection, reported by 25 or 29% patients) as well as eosinophilia (reported by 24 or 28% patients) and ESR increased (reported by 23 or 27% patients).

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[140] 42 patients who previously received "Biochemie" Omnitrope and 44 patients who previously received Omnitrope Liquid.

[141] Lymphadenopathy, adenoidectomy, acute tonsillitis, and chronic tonsillitis.

[142] Syncope, two episodes of scoliosis, two cerebral concussions, chronic rhinosinusitis, pharyngotonsillitis, headache, planned tonsillectomy, epileptic crisis. None of the events were considered drug-related with the exception of the two cases of scoliosis which was corrected surgically..

[143] The severe adverse events reported in four patients were in the following body system categories:central and peripheral nervous system, respiratory system, secondary terms, and white cell and RES. Three episodes of worsening of scoliosis occurred in one patient (02/81).

Table 26: Incidence of treatment-emergent adverse events occurring under treatment with OMNITROPE™ Liquid, experienced by > 5% of patients

Preferred Term	Incidence (%) of treatment-emergent adverse events*^			
	Mild	Moderate	Severe	Total
	N (%)	N (%)	N (%)	N (%)
Abdominal pain	6 (7%)			6 (7%)
Bronchitis	13 (15%)			13 (15%)
Elevated HbA1c	13 (15%)			13 (15%)
Eosinophilia	24 (28%)			24 (28%)
ESR increased	22 (26%)	1 (1%)		23 (27%)
Fever	8 (9%)			8 (9%)
Headache	8 (9%)	2 (2%)		10 (12%)
Hematoma	8 (9%)			8 (9%)
Hypercholesterolemia	11 (13%)	1 (1%)		12 (14%)
Hypertriglyceridemia	5 (6%)			5 (6%)
Infection viral	15 (17%)	2 (2%)		17 (20%)
Leukocytosis	7 (8%)			7 (8%)
Lymphadenopathy	9 (10%)	2 (2%)	1 (1%)	12 (14%)
Pharyngitis	19 (22%)	7 (8%)	1 (1%)	27 (31%)
Phosphatase alkaline increased	5 (6%)			5 (6%)
Rhinitis	6 (7%)	1 (1%)		7 (8%)
Tooth caries	4 (4%)	1 (1%)		5 (6%)
Upper resp. tract infection	22 (26%)	3 (3%)		25 (29%)
Urine abnormal	8 (9%)			8 (9%)
Varicella	6 (7%)	1 (1%)		7 (8%)

N = number of patients.
^ Some patients had more than one adverse event.
* Not all adverse events are presented in this table

The incidence of "drug-related" TEAEs are presented in applicant's Table 27, below. The most common drug-related adverse events reported were: elevated glycosylated hemoglobin (12 or 14% patients), eosinophilia (reported by 10 or 12% patients), and hematoma (reported by 8 or 9% patients). They all represent adverse events known to be associated with GH treatment. All drug-related adverse events were mild in severity with the exception of a case of worsening of scoliosis, which was reported as severe, and a case of headache, which was reported as moderate.

Table 27: Incidence of drug-related adverse events occurring under treatment with OMNITROPE™ Liquid

Preferred Term	Incidence (%) of drug-related* adverse events^			
	Mild	Moderate	Severe	Total
	N (%)	N (%)	N (%)	N (%)
Arthralgia	1 (1%)			1 (1%)
Bilirubinemia	1 (1%)			1 (1%)
Bronchitis	1 (1%)			1 (1%)
Convulsions	1 (1%)			1 (1%)
Elevated HbA1c	12 (14%)			12 (14%)
Endocrine disorder NOS	1 (1%)			1 (1%)
Eosinophilia	10 (12%)			10 (12%)
Headache	3 (3%)	1 (1%)		4 (4%)
Hematoma	8 (9%)			8 (9%)
Hypercholesterolemia	1 (1%)			1 (1%)
Hyperglycemia	2 (2%)			2 (2%)
Hypertriglyceridemia	1 (1%)			1 (1%)
Hypocholesterolemia	1 (1%)			1 (1%)
Hypothyroidism	2 (2%)			2 (2%)
Leg pain	2 (2%)			2 (2%)
Leucopenia	2 (2%)			2 (2%)
Leukocytosis	1 (1%)			1 (1%)
Pain	1 (1%)			1 (1%)
Phosphatase alkaline increased	4 (5%)			4 (4%)
Scoliosis			1 (1%)	1 (1%)
TSH decreased	2 (2%)			2 (2%)

*Drug-related = possible, probable or unclassified relationship to study drug.
^ Some patients had more than one adverse event.
N = number of patients.

Table 10 is a descriptive comparison of event rates for several adverse events known to be associated with GH therapy (e.g. headache, hypothyroidism, hypercholesterolemia, hypertriglyceridemia, elevated HbA1c); eosinophilia (an adverse event of potential concern in the context of immunogenicity of "Covance" Omnitrope) is also included. The rates of TEAEs are presented for all three Omnitrope drug products tested during the Omnitrope development program and for the comparator Genotropin. Although some adverse events (in particular hypothyroidism) have slightly higher rates in the "Covance" Omnitrope group, the event rates for the to-be-marketed "Biochemie" Omnitrope and for Omnitrope Liquid (which contains the same drug substance as the to-be-marketed "Biochemie" Omnitrope) were comparable to Genotropin in exposures of 6 months and 15 months, respectively.

Table 10: **Selected treatment-emergent adverse events* in the Omnitrope development program***

Event	Genotropin	"Covance" Lyophilized Omnitrope	"Biochemie" Lyophilized Omnitrope	"Biochemie" Liquid Omnitrope
Headache	0.33	0.32	0.14	0.14

Hypothyroidism	0.09	0.19	Not reported**	Not reported
Hypercholesterolemia	0.12	0.19	0.10	0.11
Hypertriglyceridemia	0.09	0.10	0.14	0.05
Hematoma	0.21	0.16	0.10	0.08
Elevated HbA1c	0.15	0.19	Not reported	0.15
Eosinophilia	0.27	0.35	0.14	0.22

* expressed as rate of events per patient-year. Event rates are included only if they occurred in > 5% of patients treated with the respective product. Not reported = not reported in > 5% of patients.

Similar to previous observations, when only the "drug-related" TEAEs are analyzed, hypothyroidism and eosinophilia were more commonly seen in association with "Covance" Omnitrope relative to Genotropin (Table 11). This imbalance relative to Genotropin was not seen when the same event rates were compared for the to-be-marketed "Biochemie" Omnitrope and Omnitrope Liquid (which contains the same drug substance as the to-be-marketed Omnitrope).

Table 11: **Selected treatment-emergent adverse events* in the Omnitrope development program* considered "drug-related"**

Event	Genotropin	"Covance" Lyophilized Omnitrope	"Biochemie" Lyophilized Omnitrope	"Biochemie" Liquid Omnitrope
Headache	0.09	0.10	0.10	0.07
Hypothyroidism	0.06	0.19	None	0.02
Hypercholesterolemia	None	0.03	0.05	0.02
Hypertriglyceridemia	0.09	0.06	0.05	0.02
Hematoma	0.18	0.16	0.10	0.08
Elevated HbA1c	0.15	0.19	None	0.13
Eosinophilia	0.09	0.22	0.10	0.09

* expressed as rate of events per patient-year. Event rates are included only if TEAEs occurred in > 5% of patients treated with the respective product. None = not reported in > 5% of patients.

C.1.2.2 Clinical laboratory evaluation

The applicant presents information on the "clinically significant changes" in laboratory values. Data are presented descriptively for hematology, biochemistry, urinalysis, thyroid function and glucose metabolism. In general, laboratory values remained within normal range for all or most patients. In the absence of a comparator, no further conclusions can be drawn.

C.1.2.3 Anti-GH antibodies

In the cohort who was treated with "Covance" Omnitrope in the initial 9 months and with "Biochemie" Omnitrope from Month 9 to Month 15, the percentage of antibody-positive patients diminished further upon treatment with Omnitrope Liquid from 36% (15 patients out of 42) at Month 15 to 16% (6 patients out of 38) at Month 36 (see applicant's Table 30, below). Only three of the 44 patients treated with Genotropin for the initial 9 months and who were treated for 27 subsequent months with Omnitrope Liquid (from Month 9 to Month 36) developed anti-GH antibodies.[144] At any given time, no more than 1-2 patients (3-5%) were antibody positive in this last cohort. The incidence rate of antibody positivity of 5% (95% CI of 0.6%-16.9%) observed with Omnitrope Liquid is comparable to that published in the medical literature.[145]

Table 30: Presence of anti-GH antibodies in study EP2K-00-PhIIIAQ, for patients treated with OMNITROPE™ Liquid (from Month 9/15 to Month 36 of overall GH therapy)

	Anti-GH antibodies (OMNITROPE™ Lyophilized powder, API Biochemie)			Anti-GH antibodies (OMNITROPE™ Liquid, API Biochemie)
EP2K-00-PhIIIAQ, Part A	**Total**	**Covance pos**	**Covance neg**	**Total**
Month 9 (= Month 0 of the EP2K-00-PhIIIAQ study)	*24/42 (57%)*[a]	*24/24 (100%)*	*0/18*	1/44 (2%)[b]
Month 10	*19/42 (45%)*	*18/24 (75%)*	*1/18 (5%)*	1/44 (2%)
Month 12	*16/42 (38%)*	*15/24 (62%)*	*1/18 (5%)*	0/44
Month 15	*15/42 (36%)*	*13/24 (54%)*	*2/18 (11%)*	1/44 (2%)
	Anti-GH antibodies (OMNITROPE™ Liquid, API Biochemie)			**Anti-GH antibodies (OMNITROPE™ Liquid, API Biochemie)**
EP2K-00-PhIIIAQ, Part B[c] Month 15	15/42 (36%)	13/24 (54%)	2/18 (11%)	1/44 (2%)
Month 18	10/42 (24%)	10/24 (41%)	0/18 (0%)	2/44 (5%)
Month 24	8/40 (20%)	8/24 (33%)	0/16 (0%)	2/40 (5%)
Month 30	7/39 (18%)	7/23 (30%)[d]	0/16 (0%)	1/39 (3%)[e]
Month 36	6/38 (16%)	6/22 (27%)	0/16 (0%)	2/37 (5%)[f]

a Anti-GH antibodies developed during the previous 9 months of treatment with OMNITROPE™ Lyophilized powder (API Covance)
b Anti-GH antibodies developed during the previous 9 months of treatment with Genotropin®
c After Month 15 of total GH treatment, all patients previously treated with OMNITROPE™ Lyophilized powder (API Biochemie) were switched to OMNITROPE™ Liquid (API Biochemie) (EP2K-00-PhIIIAQ study, part B)
d The patient who was withdrawn (Patient 07/32) had anti-GH (API Covance) antibodies at Month 9
e The patient who was withdrawn (Patient 07/72) had no anti-GH antibodies
f The patients who were withdrawn (Patients 07/75 and 07/46) had no anti-GH antibodies

[144] Patient 04/58 was positive for anti-GH antibodies at Month 10; patient 01/97 developed antibodies from Month 15 to Month 24 and again at Month 36; patient 04/82 developed antibodies from Month 18 of total GH treatment.
[145] Rougeot et al.: Comparative study of biosynthetic human growth hormone immunogenicity in growth hormone deficient children (Horm Res 1991; 35: 76-81).

C.1.3 Overall conclusions on the immunogenicity of Omnitrope

The combined data on the immunogenicity of the to-be-marketed Omnitrope drug substance supports the conclusion that the to-be-marketed "Biochemie" Omnitrope drug product has a low and acceptable level of immunogenicity. Applicant's Figure 1, below, visually integrates the information on immunogenicity generated in the Omnitrope clinical program. The left panel illustrates the development of anti-GH antibodies in patients treated with "Covance" Omnitrope in the first 9 months, followed by a continuous reduction of the percentage of antibody-positive patients on sequential treatment with the to-be-marketed "Biochemie" Omnitrope (Month 9 to Month 15) and Omnitrope Liquid (Months 15 to Month 36). The right panel illustrates the low immunogenicity of the treatment sequence: Genotropin (first 9 months) followed by Omnitrope Liquid (Months 9 to 36).

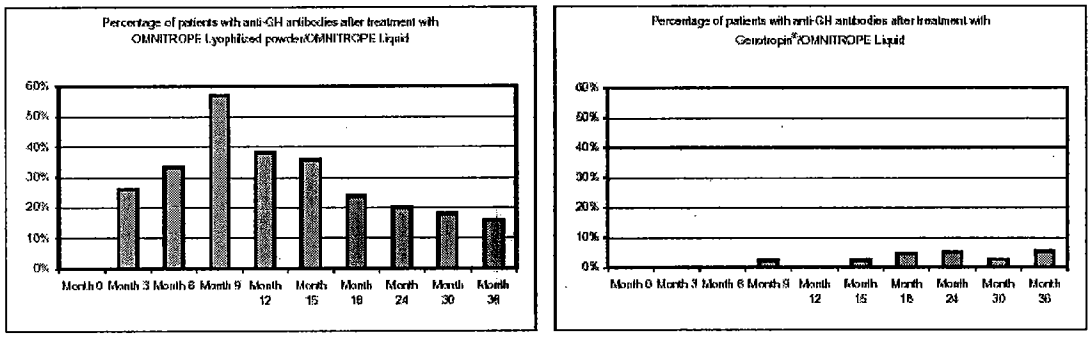

Figure 1: Percentage of patients with anti-GH antibodies during the Phase III studies

C.2. Adult growth hormone deficiency indication

The applicant submitted several publications from peer-reviewed scientific journals; they are summarized in the Appendix. The safety information collected in these published

clinical trials is consisted with the known safety profile of growth hormone in adults with GHD.

D. Adequacy of Safety Testing

The safety information presented in this NDA is adequate to allow a regulatory action. The extent of the collection of safety data in clinical trials was extensive and included physical exams, adverse events, vital signs, and a full set of analytes. Additionally, extensive data were collected for the evaluation of immunogenicity. Although the datasets are relatively small (approximately 44 patients per arm) they are comparable to the size of other datasets in similar applications for the pediatric GHD indication.

D. Summary of Critical Safety Findings and Limitations of Data

In final analysis, the safety of Omnitrope Lyophilized powder appears to be comparable to that of Genotropin in children with GH deficiency, when used short term. This conclusion is based on the combined clinical safety data obtained with three investigational Omnitrope drug products, of which, only one is subject for market approval in this NDA[146]. In general, there are no disagreements over the interpretation of the safety data by this reviewer and the applicant.

VIII. Dosing, Regimen, and Administration Issues

The GH dose administered in the Omnitrope clinical trials was well within the range of GH doses approved for the treatment of pediatric GHD[147].

IX. Use in Special Populations

A. Gender Effects Analyses

The applicant conducted several gender-related efficacy analyses including a statistical comparison between males and females for all the primary efficacy endpoints (height, height SDS, HV and HVSDS) at Months 0, 3, 6, 9 and 12. The results are shown in applicant's Table 21, below. No statistical differences could be detected at any time between male and female patients regarding these efficacy endpoints.

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[146] The "Biochemie-manufactured" Omnitrope Lyophilized powder.

[147] The starting GH dose was 0.03 mg/kg/day given daily at bedtime as a subcutaneous injection at rotating sites (this corresponds to a weekly dose of approximately 0.2 mg/kg) . The dose was adjusted periodically during the clinical trials.

In addition, no significant differences were found between the Omnitrope and the Genotropin cohorts regarding the changes in predicted final height from Month 0 to Month 9 of treatment (for girls: p = 0.33; for boys: p = 0.46).

Table 21: P-values of Mann-Whitney test between males and females

	Height				
	Month 0	**Month 3**	**Month 6**	**Month 9**	**Month 12**
N female patients	40	39	39	39	39
N male patients	49	47	47	47	47
p value	0.09	0.10	0.11	0.11	0.12
	HSDS				
	Month 0	**Month 3**	**Month 6**	**Month 9**	**Month 12**
N female patients	38	38	39	39	39
N male patients	48	46	46	46	46
p value	0.79	0.98	0.90	0.85	0.94
	Height Velocity				
	Month 0	**Month 3**	**Month 6**	**Month 9**	**Month 12**
N female patients	40	39	39	39	39
N male patients	49	47	47	47	47
p value	0.48	0.18	0.11	0.10	0.40
	HVSDS				
	Month 0	**Month 3**	**Month 6**	**Month 9**	**Month 12**
N female patients	40	38	38	38	38
N male patients	49	47	47	47	47
p value	0.47	0.46	0.56	0.61	0.95

N = number of patients. Values for some patients are missing because standard values were not available for the HSDS/HVSDS calculation.
Statistical test performed using Systat® 7.0, Mann-Whitney non-parametric test, confidence interval 95%.

B. Age, Race, or Ethnicity Effects on Safety or Efficacy

The clinical studies were conducted in Europe (six centers in Poland and one center in Hungary). The patients enrolled were exclusively Caucasian; therefore, no race-specific analyses of safety and efficacy were conducted.

The mean age at enrollment was approximately 7.6 years (range: 3 to 14 years). The efficacy and safety profile for GH is well characterized across the spectrum of pediatric ages. No age-specific efficacy and safety analyses were provided.

C. Pediatric Program

This NDA included exclusively pediatric patients.

D. Special Populations

No patients with chronic renal or hepatic conditions were enrolled in the clinical trials (in fact, patients with chronic conditions were appropriately excluded because of the confounding effect of such illnesses on linear growth).

X. Risk-Benefit Analysis, Recommendations, and Labeling

A. Risk Benefit Analysis

"Covance" Omnitrope has growth-promoting activity, as expected for a human GH product. In an active-controlled trial, it has a comparable efficacy and safety profile (with the exception of its immunogenicity) to that of Genotropin over 9 months of use in patients with GHD. The to-be-marketed "Biochemie" Lyophilized Omnitrope is (1) less immunogenic, (2) effective in maintaining an accelerated linear growth, and (3) identical physico-chemically to "Covance" Omnitrope. The risk/benefit of Omnitrope Lyophilized powder is clearly favorable and not different (based on published literature) to that associated with any other GH product in pediatric GHD.

B. Recommendations

The clinical data presented in this NDA supports the safe and effective use of Omnitrope Lyophilized powder ("Biochemie" Omnitrope) in children with growth hormone deficiency when used according to the proposed label. This reviewer agrees, overall, with the applicant's conclusions and recommends approval of Omnitrope for the proposed indication of replacement therapy for pediatric GHD.

It is reasonable to infer that Omnitrope will be safe and effective in adults with GHD as well, on the basis that (1) it is chemically proven to be growth hormone, (2) it has demonstrable efficacy (and favorable safety profile) in children with GHD, (3) it has expected pharmacodynamic effects (on IGF-I and IGFBP-3) in healthy adults, and (4) is clinically similar and pharmacokinetically bioequivalent to an approved GH product (Genotropin) that has been shown in published clinical studies to be safe and effective in adult patients with GHD.

C. Labeling

The applicant's proposed label appears to be modeled closely after the Genotropin label. Although the label is acceptable, in general terms, several revisions should be made to the "Clinical Studies" section and "Adverse Reactions" section:

___/___ Page(s) Withheld

_____ Trade Secret / Confidential

___✓___ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*___/___

XI. Appendix

1) Salomon et al.: The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency (*N Engl J Med 1089; 321: 1797-803*)

This study was a randomized, double-blind, placebo-controlled clinical trial conducted in 24 adults with GHD (mean age 39 years, range 21-51 years). Most patients acquired GHD during adulthood due to pituitary tumors and were on stable thyroid, adrenal, and gonadal hormone replacement for one year prior to GH treatment. The diagnosis of GHD was based on a peak plasma GH concentration < 3 mU/L (severe GHD) during an insulin stimulation test. The study duration was 6 months. The GH replacement dose was 0.07 U/kg given subcutaneously at bedtime; this dose was associated with peak plasma levels of GH that were similar to peak nocturnal values in normal subjects.

Efficacy

Figure 1 illustrates the changes in the mean fasting plasma concentrations of GH and IGF-I in the placebo and the GH-receiving patients. The increases in mean GH and IGF-I levels on treatment were statistically significant relative to placebo ($p<0.001$). GH-receiving patients had a mean (± SE) plasma IGF-I concentration increase from 0.41 ± 0.05 to 1.53 ± 0.16 U/L.

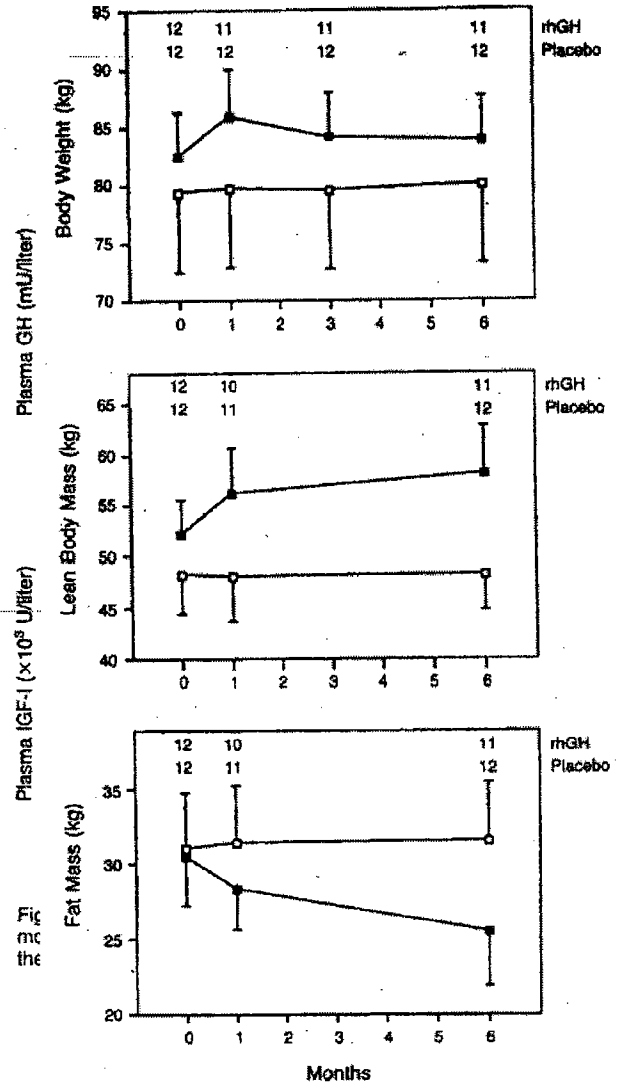

Figure 2. Mean Body Weight, Lean Body Mass, and Fat Mass during the Administration of rhGH (■—■) or Placebo (□—□) in Adults with Growth Hormone Deficiency.

The number of patients studied at each time in each group appears at the top of each panel. The horizontal bars indicate the SE for the mean values shown.

While GH treatment had no effect on body weight, the mean lean body mass increased by 5.5 ± 1.1 kg ($P<0.0001$), and the fat mass decreased by 5.7 ± 0.9 kg ($P<0.0001$) at the end of 6 months of treatment (neither changed significantly in the placebo group). These findings are illustrated in Figure 2.

The basal metabolic rate, measured at baseline and after 1 and 6 months of GH treatment administration, increased significantly (the respective values were 32.4 ± 1.4, 37.2 ± 2.2, and 34.4 ± 1.6 kcal per kilogram of lean body mass per day; p value was <0.001 for both comparisons).

Fasting total plasma cholesterol levels were lowered by GH treatment ($p<0.05$ relative to placebo) while plasma triglyceride concentrations did not change in either group. Plasma free fatty acids levels increased slightly (<2X, not statistically significant) with GH treatment after one month and remained at the same level for all subsequent measurements. Other minor

changes in analytes included: increases in plasma phosphate, calcium, creatinine clearance, along with decreases in plasma potassium and albumin. Triiodothyronine levels almost doubled after one month of treatment but returned to near pre-treatment levels by 6-months of GH administration; mean free thyroxine levels did not change significantly.

Safety:

One patient withdrew in the GH group 3 days after the beginning of treatment, because of "generalized misery and depression." Several adverse events occurred , all in the GH-treatment arm); they were adverse events already known to occur in association with GH administration. Specifically, six patients experienced fluid retention during the first month of treatment manifested as an increase in body weight, swollen ankles, and a sensation of tightness in the hands. In most patients these symptoms disappeared spontaneously in the next 1-2 months but in two of them the GH dose had to be reduced because of edema; one patient required diuretic therapy, the other had symptoms of carpal tunnel compression which persisted in a mild form. One patient had hypertension (blood pressure of 141/105 mm Hg)., which resolved with GH dose reduction. Five patients reported arthralgia without effusion. Three patients had mild discomfort in large proximal muscle group, which disappeared within the first three months. One patient developed an encephalocele at the site of previous trans-sphenoidal surgery in association with peripheral edema (both resolved concomitantly without alteration of the GH dose). The authors comment that the dose in the study was calculated to produce mean plasma GH levels in the upper-normal range (this was reflected in the plasma IGF-I levels) and it "may have been slightly excessive."

Conclusions:

- Six months of GH treatment in adults with GHD resulted in a clear change in body composition (an increase in lean body mass and a decrease in fat mass).
- The increase in energy expenditure (as measured by the basal metabolic rate) is consistent with the known anabolic effects of GH and likely is due to increased fat oxidation following the lypolitic effect of GH.
- The described changes in several analytes are well recognized to occur in association with GH.
- The described adverse events were expected during GH treatment; maintenance of IGF-I levels in the high range may account for a somewhat high incidence for such AEs.

2) Rosen et al.: Beneficial effects of 12 months replacement therapy with recombinant human growth hormone to growth hormone deficient adults (*Endocrinology and Metabolism, 1994, 1, 55-66*)

This study was a randomized, double-blind, placebo-controlled clinical trial for 6 months followed by an open treatment phase, which ended when all patients had received GH for 12 months. The clinical trial enrolled 25 patients (mean age 49 years; range 25-61 years). Patients had to have adult GHD for at least 12 months and a peak serum GH response less than 5 mU/L during insulin-induced hypoglycemia. The dose of GH was 0.125 IU/kg/week during the first 4

weeks of active treatment followed by 0.250 IU/kg/week for the rest of the treatment period. The weekly dose was divided into seven daily subcutaneous injections at bedtime.

Efficacy:

Body composition was determined from total body potassium, total body water, total body nitrogen, bioelectrical impedance analysis, and dual-energy X-ray absorptiometry.

Body fat was estimated by a four-compartment model, BIA, and DEXA. It decreased in the GH group relative to placebo according to the four-compartment model (-21.5% vs. +3.0%, $p<0.05$), according to BIA (-17.6% vs. –0.5%, $p<0.01$), and according to the DEXA scan (-14.2 % vs. -1.8%, $p<0.06$). These observations were made in the context of a decrease in mean body weight for the GH group at 6-months of 3.9% relative to an increase in placebo of 0.8% ($p<0.05$). There was a tendency for an increase in extracellular water (14.9 % vs. 1.9%; $p=0.065$) and an increase in lean body mass 2.1% vs. 0.4%; $p<0.05$) in association with GH treatment.

The mean concentrations of serum GH (1.91± 0.73 vs. 0.16±0.12 mIU/L; $p<0.05$), IGF-I (258±27 vs. 79±8 μg/L; $p<0.01$), and IGFBP-3 (2.99±0.22 vs. 1.56±0.15 mg/L; $p<0.01$) were all higher in the GH-treated group relative to placebo.

The following observations were recorded with respect to several biochemical analytes when the GH-treated group was compared to the placebo group at 6 months:

- there were no statistical differences in the blood glucose concentration and HbA1c
- the serum insulin concentration was higher in the GH group (15.7±2.9 vs. 8.1±mIU/L; $p<0.05$)
- there were no statistical differences in the total serum cholesterol (although the HDL was higher in GH-treated patients; $p<0.05$), triglycerides , sodium, potasium, and vitamin D
- serum concentrations of calcium, osteocalcin, and amino-terminal peptide of procollagen-III were higher, while intact PT was lower, in association with GH (all findings were statistically significant)

After 6 months of treatment the GH dose was reduced from 2.5 IU/day to 2.2 IU/day "because of side effects." The following observations were made after 12 months of treatment:

- body weight was similar to baseline (despite a decrease at 6 months)
- the body fat reduction was maintained; it was 15.5% ($p<0.001$) at 12 months and 23.1 % ($p<0.001$) at 6 months by four-compartment model; by DEXA the body fat decreased by 7.6% ($p<0.001$)
- lean body mass increased by 2.7% ($p<0.01$)
- extracellular water did not change significantly
- total body mineral density decreased at 12 months (but was higher in a subgroup followed to 18 months)
- serum IGF-I increased further to 337±μg at 12 months despite the GH dose reduction
- IGFBP-3 and GH serum levels were, as expected, higher relative to baseline
- the mean serum glucose and HbA1c increased slightly, while insulin levels remained in excess relative to baseline (all changes statistically significant)

- the total cholesterol and triglycerides concentrations were unchanged, while the HDL increase was still statistically significant
- the changes in serum calcium, osteocalcin, P-III-NP, PTH, and vitamin D showed the same trends at month 12 relative to those observed at 6 months of GH treatment

Safety:

No serious adverse events were reported. During the first 6 months of treatment 16/25 patients had swelling of the hands and/or feet and 11/25 patients had paresthesias/numbness in hands (likely carpal tunnel syndrome); all adverse events were resolved with dose reduction. No patients withdrew from the clinical trial.

Conclusions:

- changes in body composition (decrease in body fat, increase lean body mass, and increase in total body water) persisted after 12 months of treatment
- the observations made on carbohydrate metabolism were those expected with GH treatment based on its known physiologic anti-insulinemic effect
- similarly, the changes in lipids were those expected based on the lypolitic effect of GH
- the changes in bone metabolism were consistent with those observed in other GH studies and indicate an increase in bone turnover; GH treatment for 18 months may be associated with an increase in bone mineral density
- most adverse events occurred at higher GH dose during the first 6 months were due to water retention and resolved with GH dose reduction
- the GH dose of 0.25 U/kg/week may be too high in some patients (as evidenced by IGF-I levels in the upper normal range) and treatment needs to be individualized

3) Johansson et al.: Two years of growth hormone (GH) treatment increases bone mineral content and density in hypopituitary patients with adult-onset GH deficiency (*J Clin Endocrinol Metab 1996, 81: 2865-2873*)

This was a 2-year open-label study conducted in 44 patients (24 men and 20 women) with adult growth hormone deficiency (ages 23-66 years). The study evaluated the effect of GH on bone mineral density (BMD). GH was administered at a daily dose of 4.8 μg/kg (0.1 IU/kg/week) for 4 weeks and subsequently increased to a target dose of 12 μg/kg/day (0.25 IU/kg/week); dose adjustments were made on the basis of IGF-I serum levels, which were measured periodically. The mean GH dose at 2 years was 7.8±0.5 μg/kg/day (higher in women than in men). BMD was assessed with dual energy x- ray absorptiometry (DEXA). Additional measurements included serum concentrations of osteocalcin, carboxy-terminal propeptide of type I procollagen (PICP), and carboxy-terminal cross-linked telopeptide of type I collagen (ICTP).

Efficacy:

At the end of 2 years of treatment the BMD increased in the lumbar spine L2-L4 by 3.8% [95% confidence interval (CI), 2.1-5.5], in the femoral neck by 4.1% (CI, 2.1-6.1) in the femoral

trochanter by 5.6% (CI, 3.8-7.4) and in Ward's triangle by 4.9% (CI, 2.2-7.6) compared with baseline. An increase in BMD was noted after 18 months of GH treatment.

The mean z-scores change from baseline at the following anatomical sites were: lumbar spine L2-L4 (0.55±1.0), femoral neck (0.35±0.08), femoral trochanter (0.40±0.06), and Ward's triangle (0.34±0.08). Clearly, patients with low z-scores at baseline (below 1 SD) had a better

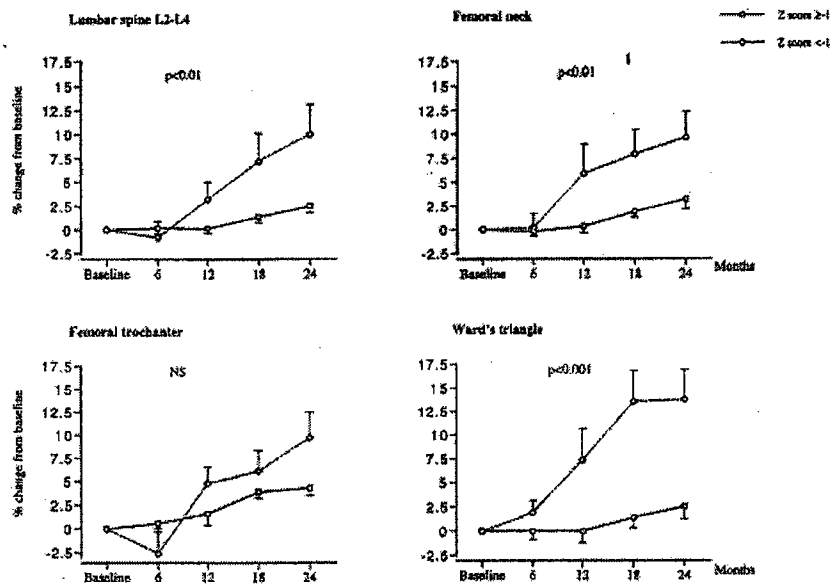

FIG. 1. BMD in response to 2 yr of GH treatment in two subgroups of patients with adult-onset GH deficiency. One group is comprised of 13 patients with a baseline z-score of less than −1 SD (*broken line*), and the second group is comprised of 31 patients with a baseline z-score of −1 SD or more (*solid line*). The *horizontal bars* indicate ±SE for the mean values shown, and *P* values denote the differences between the percent changes from baseline in the two groups of patients by two-way ANOVA.

response when compared to patients with z-scores greater than –1 (Figure 1, bellow).

Biochemical measurements indicated the following:

- the mean IGF-I plasma concentrations increased after 6 months of treatment (mean SD score of 2.3±0.3 vs. -2.2±0.1 at baseline) with no change thereafter, despite a mean reduction in the GH dose of 20% between months 6 and 24
- the mean serum calcium concentrations increased slightly and the mean serum PTH levels decreased
- the mean serum concentrations of osteocalcin, PICP, and ICTP increased after 6 months of treatment; although they decreased somewhat on subsequent measurements, they remained higher than baseline values throughout the 2 years of treatment.
- women demonstrated a more marked increase in total BMD than men

Safety:

Safety data are not reported in this study.

Conclusions:

- 2 years of GH treatment resulted in an increase in the overall remodeling activity along with an increase in bone mineral density
- the effects on BMD were noticeable after 18 months of GH treatment
- patients with the lowest z-scores demonstrated the most pronounced increase in BMD.

4) Janssen et al: A low starting dose of Genotropin in growth hormone-deficient adults (*J Clin Endocrinol Metab 82: 129-135, 1997*)

This study was a randomized, double-blind, dose-response clinical study in patients with adult GHD. It investigated the effect of 12 weeks of GH therapy in three different doses on serum IGF-I and IGFBP-3 (no placebo arm was included). Patients were randomized to one of three dose groups: Group 1 received a dose of 0.6 IU/day (i.e. 0.02 mg/kg/week) GH for 12 weeks; Group 2 was given a dose of 0.6 IU for 4 weeks followed by 1.2 IU/day (0.04 mg/kg/week) for 8 weeks; Group 3 used 0.6 IU for 4 weeks, followed by 1.2 IU/day for 4 weeks and 1.8 IU/day (0.06 mg/kg/week) thereafter. The three treatment groups were comparable with regard to age, sex, BMI, and severity of GHD at baseline. Injections were administered subcutaneously, in the evening. Sixty adult patients with GHD (30 males and 30 females, mean age 47 years, range 23.70 years) were enrolled; 51 patients had adult-onset GHD; the rest had childhood-onset GHD. The diagnosis of GHD during adulthood was made on a peak serum GH response < 7 mU/L during insulin-induced hypoglycemia.

Efficacy:

After 12 weeks of GH treatment IGF-I levels were low normal in the Group 1 (low dose group) and normal in Groups 2 and 3 (in both of them the GH dose has been escalated above that maintained in Group, 1albeit by different degrees). IGFBP-3 levels increased from low normal to high normal levels in adult-onset GHD patients and changed from below normal to low normal in childhood-onset GHD patients. The effect of GH on serum IGF-I concentrations in the three dose groups is illustrated in Figure 2, below.

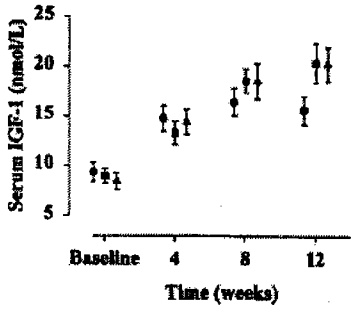

FIG. 2. Serum IGF-I concentrations (±SEM) during rhGH therapy in the three dose groups. The patients indicated with a *circle* used 0.6 IU rhGH/day for 12 weeks. Patients indicated with a *rectangle* started with 0.6 IU/day for 4 weeks followed by 1.2 IU rhGH/day. Patients indicated with a *triangle* used 0.6 IU/day for 4 weeks followed by 1.2 IU/day for 4 weeks and 1.8 IU/day thereafter.

Safety:

All subjects completed the study. Two patients in Group 3 could not have their doses escalated to the maximum dose of 1.8 IU/day. One developed carpal tunnel syndrome after 5 weeks while another had "fluid retention problems" at the about he same time. Both had IGF-I serum concentrations close to, or above the upper limit of normal.

Conclusions:

In addition to demonstrating several baseline differences in the biochemical characteristics of childhood-onset and adult-onset GHD, the study establishes that GH therapy at doses of 0.6 and 1.2 IU/day in male and female patients, respectively, is, in general, able to increase serum IGF-I into the normal range after 12 weeks of treatment, without reaching supraphysiological levels of IGF-I (higher doses were required in female patients because they had lower IGF-I levels at baseline). The authors suggest that the above-mentioned doses should be starting doses in GH-deficient adults.

5) Cuneo et al.: The Australian Multicenter Trial of Growth Hormone (GH) Treatment in GH-Deficient Adults (*J ClinEndocrinol Metab* 83: 107–116, 1998)

This was a, randomized double-blind, placebo-controlled clinical trial that studied the effects of GH in adults with GH deficiency. A 6-month placebo-controlled phase was followed by a 6-month open-label GH treatment phase. The study enrolled 163 patients (72 females and 91 males) with a mean age of 40 ± 1 yr (range 17–67 yr). Patients were randomly assigned to receive either GH (0.125 U/kg per week for 1 month and 0.25 U/kg per week for 5 months) or placebo. The primary end points were biochemical responses (IGF-1, IGFBP-3, serum lipids), body composition (anthropological measurements, bioelectrical impedance), quality of life (assessed by the Nottingham Health Profile), and safety (complete physical examination, routine

biochemistry evaluations, free T4, HbA1c, full blood examination, supine blood pressure, urinalysis and adverse events).

Efficacy:

Serum IGF-1 increased from a standard deviation score of -2.64 ± 0.27 (range -8.8 to +3.82; n=78) to +1.08 ± 2.87 (range -7.21 to +6.42) at 6 months in the GH group; 38% of the whole group were above the age-specific reference range (i.e.>2SD) following treatment; 17.6% had subnormal (i.e.< 2 SD) and 68.9% had normal (± 2 SD) IGF-I levels. Serum IGFBP-3 concentrations showed similar changes.

Fasting total cholesterol and LDL cholesterol decreased over the first 6 months (p= 0.042 and p= 0.006, respectively). The reductions in LDL cholesterol were still statistically significant at 12 months (p= 0.019) while the total cholesterol changes were not (p=0.103). For serum HDL cholesterol and triglyceride concentrations the differences were not significant.

Fat-free mass increased in the first 6 months, whether measured by bioelectrical impedance ($p < 0.001$) or by dual energy x-ray absorptiometry (DEXA $p<0.001$). Total-body water increased in the first 6 months, whether measured by bioelectrical impedance ($p <0.001$) or by deuterium dilution ($p = 0.002$). Fat mass measured by DEXA ($P<0.001$), skinfold thickness ($p<0.001$), and waist/hip ratio ($p < 0.001$) decreased in the first 6 months. Most changes in body composition were complete by 3 months of treatment and maintained to 12 months. Whole-body bone mineral density (BMD) (by DEXA) was unaffected by GH treatment.

Self-reported quality of life was considered good before treatment, and beneficial treatment effects were observed for energy, pain, and emotional reaction as assessed by the Nottingham Health Profile.

Safety:

During the first six months 290 events were reported by 70 of the 83 GH patients (84%); for the same duration 219 events were reported in 60 of the 80 placebo patients (75%). During the open-label phase of GH treatment, 411 new events were reported in 99 patients over 6 months. The authors present the adverse events as either expected or unexpected in relationship to GH. Such expected (or "predictable") AEs for the controlled phase of the clinical trial were:

- edema (which included generalized, peripheral, or facial edema, carpal tunnel symptoms, and peripheral swelling or tightness; it was reported in 48% of GH patients vs. 30% placebo; p = 0.016
- arthralgias, and myalgias (which included arthritis, arthrosis, myalgia, muscle stiffness, tendonitis, and muscle weakness; they were reported in 30% GH vs. 13% placebo; p = 0.007)
- paresthesia and anesthesia (12% GH vs. 4% placebo; p = 0.056),
- increased sweating (3.6% GH vs. 0% placebo; p = 0.078).

Adverse events that were not predicted to be associated with GH treatment included the following:

- "reduced frequency of reported pain" (0% GH vs. 6.3% placebo; p = 0.02)
- aggressive reactions (0% GH vs. 3.8% placebo; p = 0.075), and

- moniliasis (0% GH vs. 3.8% placebo; p = 0.075)

Other events not predicted to occur in association with GH were:
- five cases of adrenal insufficiency (all on GH)
- two cases of operation for pituitary tumors (one each on placebo and GH)
- two episodes of collapse in a patient with similar past history (on GH)
- one episode each of amaurosis fugax and chest pain in one patient (on GH)
- three abdominal surgical procedures
- one patient with pulmonary fibrosis and chronic graft vs. host disease following childhood acute lymphatic leukemia died of respiratory failure (this was not considered to be related to GH treatment)

The authors also provide data which indicate that there were no significant changes in mean fasting serum glucose levels, mean systolic, and mean diastolic blood pressure on-trial.

Overall, 19 patients from the GH group and 11 from the placebo group withdrew from the trial. The authors report that "the primary reason for withdrawal was a GH-related adverse event in 40% of these patients".

Conclusions:

GH treatment in adult patients with GHD at a dose of 0.25 IU/kg per week for 6–12 months was associated with the following:
- a marked increases (doubling) in serum IGF-I concentrations; 38% of all treated patients reached supraphysiological concentrations
- increases in serum IGFBP-3 concentrations
- a modest decrease in total and LDL cholesterol
- reductions in total-body and truncal fat mass
- an increases in fat-free mass
- modest improvements in perceived quality of life
- most adverse events were those predicted for GH therapy
- some unexpected adverse occurred but they were infrequent and causality was difficult to ascertain

6) Bengtsson et al.: The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults (*J Clin Endocrinol Metab* 84: 3929-3935, 1999)

This study is an efficacy analysis of GH use conducted in a large cohort of patients enrolled in KIMS (the Pharmacia & Upjohn International Metabolic Safety Database), a long-term, open-label research program of GH replacement therapy in hypopituitary patients with adult GHD who are treated in a conventional clinical setting. Of the 1572 patients enrolled into the KIMS database, only those who were naïve to GH treatment were analyzed. This cohort included 665 GHD adults (332 women; 169 with childhood-onset GHD; mean age, 44 yr).

GH treatment was initiated at a dose of ≤ 0.125 IU/kg/week (0.042 mg/kg/week). This dose was subsequently increased to a maximum of 0.25 IU/kg/week (0.083 mg/kg/week) "according to individual patient requirements". GH doses could be titrated on the basis of serum IGF-I measurements. Maintenance GH replacement doses were achieved within 6 months of therapy. Mean maintenance doses of GH were 0.43 and 0.53 mg/day for men and women, respectively.

Efficacy:

On GH treatment, the serum IGF-I SD scores increased from –2.2 at baseline to 1.8 and 0.6 at 6 and 12 months, respectively, in men and from –4.2 at baseline to –0.9 and –0.7 at 6 and 12 months, respectively, in women. For similar maintenance GH doses, female patients had a significantly lower increase in serum IGF-I levels than men ($p<0.0001$ at 6 and 12 months, respectively). The maintenance GH dose was higher in patients with childhood-onset GHD; these patients had lower baseline serum levels of IGF-I.

Lean body mass changed by 2.3 ($p=0.002$) and 1.1 ($p=0.005$) kg after 6 months and by 1.8 ($p=0.02$) and -0.2 (P=NS) kg after 12 months in men and women, respectively. There was no relationship between changes in lean body mass and age, dose of GH or baseline serum IGF-1 levels.

Body fat changed by -2.9 ($p=0.0004$) and -0.6 (p=NS) kg after 6 months and by -1.7 (p=NS) and 1.0 (p=NS) kg after 12 months in men and women, respectively. The waist/hip ratio decreased by 0.023 ($p<0.001$) and 0.023 ($p<0.001$) in men, and by 0.011 ($p=0.03$) and 0.012 (p=NS) in women after 6 and 12 months of treatment, respectively. This decrease in waist/hip ratio was significantly greater in men than in women ($p=0.04$), and was similar in patients with childhood-onset and adult- onset GHD. The decrease was more pronounced in patients with a high waist/hip ratio at baseline.

Total cholesterol serum concentrations decreased significantly in men, and HDL cholesterol increased in women. Systolic blood pressure was unchanged during GH therapy, while diastolic blood pressure decreased slightly in women. Quality of life score (measured by a disease-specific questionnaire) improved after 6 and 12 months of GH therapy.

Safety:

Safety data are not presented in this study.

Conclusions:

This uncontrolled study indicated that open-label GH therapy for one year in a large cohort of adult GHD patients in which GH dose is adjusted based on serum IGF-I concentrations, results in an increase in lean body mass, a decrease in body fat mass (primarily due to a reduction of

adipose tissue as indicated by a lower waist/hip ratio), and an improvement in QOL scores. Several gender-specific observations are made (e.g. greater responsiveness to GH therapy in male patients, gender-specific differences in cholesterol reduction); as this study lacked a control group, these need to be validated in a controlled study.

7) Verhelst at al.: Two years of replacement therapy in adults with growth hormone deficiency (*Clinical Endocrinology, 1997, 47, 485-494)*

This was a multicenter, double-blind, randomized, placebo-controlled study for 6 months followed by an open-label 18-month period. The trial enrolled 148 patients with adult GHD (89 males and 59 females); 134 patients had adult-onset GHD and 14 patients had childhood-onset GHD. GH was given for the first month in a dose of 0.125 IU/kg/week followed by a dose of 0.25 IU/kg/week for the rest of the trial, with a maximum dose of 4 IU/day. The weekly dose was divided into daily subcutaneous injections. Dose adjustments were made in case of adverse events. Body composition (measured using body impedance analysis) and well being (assessed using the Nottingham Health Profile) were evaluated every 3 months for the first year and every 6 months thereafter. Safety evaluations included full clinical examinations, serum glucose, HbA1c, IGF-I, creatinine, full blood count, thyroid hormones and liver function tests.

Efficacy:

No significant changes in IGF-I levels were reported during placebo administration. With GH therapy IGF-I levels increased from -2.00 ± 2.60 SDS to 1.47 ± 2.6 SDS after six months ($p<0.001$) and continued to rise despite no change in dose to 1.84 ± 2.8 SDS after one year; they remained constant thereafter (1.98 ± 2.4 after 2 years). After one year of GH treatment (when maximum IGF-I levels were attained), levels were < -2 SD in 9% of patients, between –2SD and O in 13%, between 0 and +2SD in 22% and >+2SD in 56% of patients (median 2.56).

Within 3 months of GH treatment lean body mass (LBM) increased by +5.09% ($p<0.001$), total body water (TBW) by +5.40% ($p<0.001$), while body fat (BF) dropped by -10.89% ($p<0.001$) and waist circumference by -1.42% ($p<0.004$). These effects were maintained during the first year of therapy, but the effect was attenuated after 24 months: LBM, +3.91% ($p<0.001$); TBW, +3.28% ($p<0.001$); BF, -6.42% (<0.001) and waist -2.22% ($p<0.009$). Individual differences in response were reported to be large and could not be predicted by any of the baseline parameters. Males appeared to have better responses. The mean changes in body composition for the pooled data (evaluable patients on GH for whole trial) are presented in Figure 1, below.

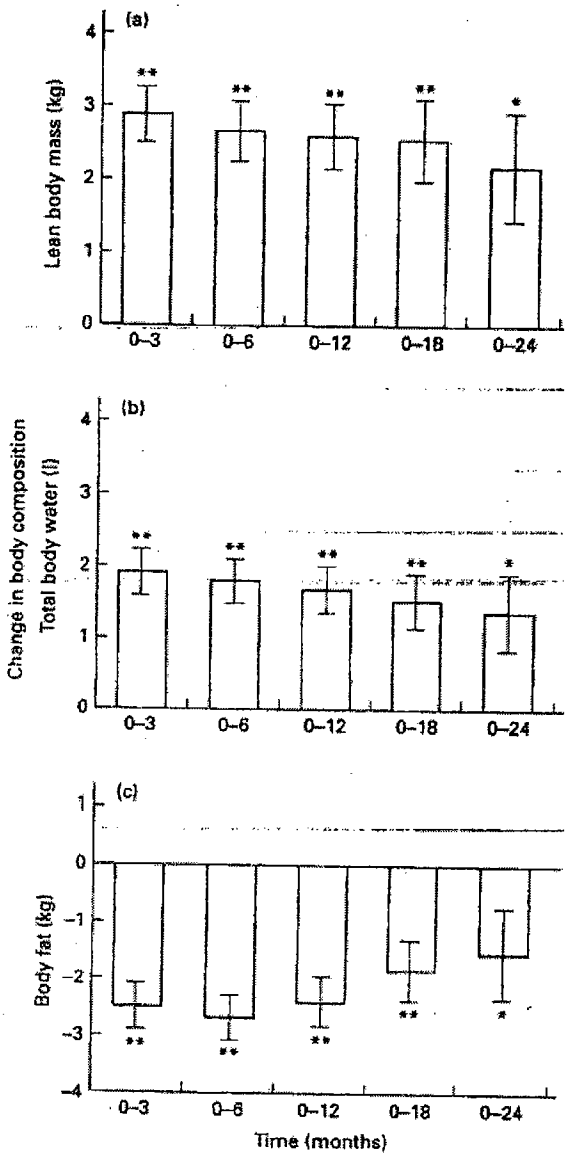

Fig. 1 Changes in body composition parameters during the whole trial (pooled data). a, lean body mass; b, total body water; c, body fat. Results are expressed as mean and SEM. *$P<0.01$, **$P<0.001$. The number of patients available for analysis of pooled data was 148 at baseline, 137 after 3 months, 130 after six months, 105 after 12 months, 98 after 18 months and 46 after 24 months.

Patients in both the placebo and the GH treatment group had improvements on the QOL questionnaire. Compared to placebo, patients in the GH group tended to perform slightly better for emotions, energy, and sleep although the difference did not reach significance.
With GH the number of full days of sick leave/6 months decreased from 12.17 ± 3.90 days (SEM) to 7.15 ± 3.50 days after six months (p=0.009), 2.93 ± 1.55 days after 12 months (p=0.01), 0.39 ± 0.17 days after 18 months (p<0.001) and 3.3 ± 2.51 days after 24 months

(p=0.026); no changes were seen in the placebo group. Similarly, the hospitalization rate went down from 14.9 to 7% after 6 months and remained at this level thereafter (p=0.12); it did not change during the placebo period.

Safety:

The authors report that about one third of patients on GH experienced fluid-related adverse events, most often within the first 3 months. More than half of the patients with fluid retention had more than one fluid-retention episode. In 20 patients no action was taken, in 20 the GH dose was reduced, in 5 patients treatment was interrupted and in 5 treatment was stopped. Most fluid-related adverse events disappeared at the time of the next visit. Fluid retention could not be predicted by any of the baseline parameters.
Incidence of adverse events during the pacebo-controlled phase of the clinical trial are presented in authors' Table 2, below. The adverse events are divided as "related to fluid retention" (clearly in excess as a group and as individual AEs when compared to placebo) and adverse events "not related to fluid retention" (with the exception of depression, dyspepsia, and nervousness, similar between the two treatment groups).

Table 2 Incidence of adverse events during the first six months (placebo-controlled period).

Side effects	rhGH ($n=71$)	Placebo ($n=77$)
Related to fluid retention		
Arthralgia	15·4%	2·4%
Peripheral oedema	12·6%	1·2%
Generalised oedema	5·6%	0%
Myalgia	4·2%	0%
Paraesthesia	2·8%	0%
Stiffness in extremities	2·8%	1·2%
Carpal tunnel syndrome	2·8%	0%
Not related to fluid retention		
Depression	2·8%	1·3%
Dyspepsia	2·8%	0%
Nervousness	2·8%	1·3%
Hyperuricaemia	1·4%	1·3%
Flu	1·4%	1·3%
High blood pressure	1·4%	1·4%
Headaches	1·4%	1·3%
Tendinitis	1·4%	1·2%
Tiredness	0%	1·3%
Insomnia	0%	2·6%
Cutaneous rash	0%	2·8%

Withdrawals from the clinical trial are presented as "cumulative drop-out rates" (10.1% at six months, 29% after 1 year and 38% after two years). Two thirds of these patients stopped treatment because of insufficient subjective improvement. Two patients discontinued the trial because of "diabetic values for fasting glucose and HbA1c" (one patient was in the placebo group).

Other safety findings associated with GH treatment (and not present in the placebo group) included:

- a statistically significant but small drop in both systolic (-3.58 ±16.32 mmHg) and diastolic blood pressure (-2.49±11.3 mmHg) after 12 months of GH treatment
- a statistically significant rise in mean fasting plasma glucose after 6 months and through 24 months (approximately 0.30 to 0.36mmol/L)
- an initial mean HbA1c rise at 6 months (0.17%) attenuated after 18 and 24 months
- a transient decrease in mean serum T4 and a transient increase in serum T3 at 6 months
- a drop in serum creatinine at 6 months maintained thereafter (approximately 3-4 µmol/L

Conclusions:

This study confirms beneficial effects of GH treatment on body composition consistent with those previously published for similar GH doses. These beneficial effects were seen early in the trial (3 months) and were maintained, although to a lower extent, for up to two years of treatment. The results of the validated QOL questionnaire showed beneficial trends but the findings were not statistically significant. In contrast, the number of full sick days and hospitalizations were clearly reduced with GH treatment relative to placebo. The safety findings (primarily related to fluid retention) were those well recognized to occur in association with GH during the treatment of adult GHD.

8) Rodriguez-Arnao et al.: Serum collagen croslinks as markers of bone turn-over during GH replacement therapy in growth hormone deficient adults (*Clinical Endocrinology, 1998, 48, 455-462)*

This study was a randomized, double-blind, placebo-controlled 6-month study followed by a 6-month open-label treatment phase that evaluated the effects of GH replacement therapy on markers of bone metabolism. It enrolled 35 adults (17 women and 18 men; mean age 39.8 years; range 21.1-59.9 years), all with adult GHD. GH was administered at a dose of 0.125 IU/kg/week (i.e. 0.04 mg/kg/week) for the first four weeks, followed by 0.25 IU/kg/week (0.08 mg/kg/week) thereafter. Bone formation was analyzed using serum bone alkaline phosphatase and serum osteocalcin. Bone resorption was analyzed using serum pyridoline (PYR) and serum deoxypyridoline (DPYR). Bone mineral density (BMD) was also assessed via dual X-ray absorptiometry (DEXA).

Efficacy:

Before GH treatment, serum IGF-I levels were below the age-corrected normal levels in most patients; 12 patients (34%) had serum IGF-I levels in the normal range. GH treatment resulted in significant, albeit variable, increases in serum IGF-I levels with some in supraphysiological range (for 11 patients or 31% they were above the upper limit of normal). Despite similar GH treatment doses, the serum IGF-I response was more robust in older patients (80% of the 50-60 year olds had supraphysiological levels of IGF-I).
In the placebo group, after 6 months, there were no significant changes in any of the bone markers analyzed, nor in BMD. In contrast, GH treatment was associated with a significant

increase in serum osteocalcin, bone alkaline phosphatase, PYR and DPYR (p=0.03, p=0.004, p=0.003 and p=0.01, respectively); these changes remained elevated over their baseline levels for the subsequent 6 months of GH treatment (p=0.04, p=0.009, p=0.003 and p=0.04, respectively). No changes were observed in BMD in any of the two groups (placebo and GH treatment) after 6 months. However, after 12 months of GH treatment there was a significant increase in BMD at both the lumbar spine and femoral neck (P=0.01 for both sites).

Safety:

No safety data were reported for this clinical study.

Conclusions:

Administration of GH to patients with adult GHD significantly activates bone remodeling with a maximal effect on bone formation and bone resorption after 6 months of treatment. However, consistent with previous studies, a positive change in BMD was seen only after prolonged GH treatment (in this study after 12 months).

9) Abs et al.: GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety (*Clinical Endocrinology),* 1999, 50, 703-713.

This study is primarily a analysis of the safety data collected in KIMS (the Pharmacia & Upjohn International Metabolic Safety Database), a long-term, open-label research program of GH replacement therapy in hypopituitary patients with adult GHD who are treated in a conventional clinical setting. The study enrolled 1034 hypopituitary adult patients with GHD (553 or 53.5% males, 481 or 46.5 females; 759 were non-naïve to GH treatment). The only inclusion criterion was a diagnosis of GHD and the only exclusion criterion was the presence of ongoing malignant neoplasia. The definition of adult GHD was a peak GH response of less than 10 mU/l (3.3 μg/l) during a stimulation test.

GH treatment was initiated (at the time of enrolment for naïve patients, or previously for non-naïve patients) at a maximum dose of 0.125 IU/kg/week (0.04 mg/kg/week). This dose was increased subsequently to a maximum of 0.25 IU/kg/week (0.08 mg/kg/week), according to individual patient requirements. In case of an adverse event presumed to be induced by GH treatment, the dose was reduced by 0.5 IU/day (0.17 mg/day). Although GH dose was based on patients' body weight, dose titration based on tolerability and/or IGF-I serum concentrations was allowed. For the purposes of this analysis, patients who had received a steady GH dose for at least 3 months by the time of their last clinic visit were considered to be on a maintenance dose.

Efficacy:

The serum IGF-I levels (at the time when maintenance GH doses were achieved) are presented for naïve and non-naïve patients in authors' Figure 1, below. Serum IGF-I levels were greater than 2 SD of the normal age-related mean in 16 (15.9%) of 101 naïve patients (Panel "a") and in 81 (23.3%) of 347 non-naïve patients (Panel "b"). Overtreatment with GH was markedly more common in non-naïve than in naïve patient ($p<0.001$ naïve vs. non-naïve).

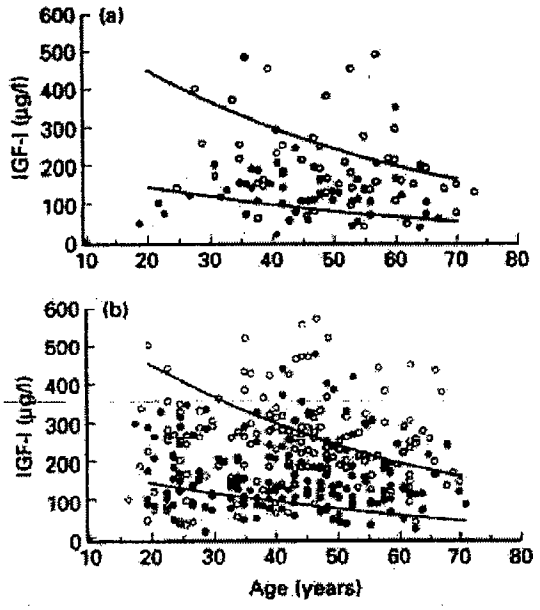

Fig. 1 Age-related serum IGF-I concentration in naive patients (a) and non-naive patients (b) receiving a maintenance dose of GH.

Safety:

The 1034 patients enrolled were treated for a total of 818 patient-years (174 patient-years for the naïve group and 644 patient-years for the non-naïve group). The mean duration of GH treatment was 0.79 years (the range was 0-2.76 years). At the last evaluation 36 (3.5%) patients discontinued GH treatment; of these, 25 discontinued because of AEs, five discontinued because they did not perceive a clinical benefit of GH therapy, and six discontinued for "other" reasons.

306 (29.6%) patients reported 883 adverse events. The most commonly reported AEs were respiratory infection, edema/stiffness, arthralgia/myalgia/pain in the extremities, headache, diarrhea and hypertension. The incidence of AEs was higher in women than in men (1.19 vs. 0.97 AE/year; relative risk, 1.05-1.45, 99% CI). In addition, the incidence of AEs was higher in patients with childhood-onset GHD than in those with adult-onset GHD (1.00 vs. 0.85 AE/year; relative risk, 0.93-1.49), and higher in naïve patients than in non-naïve patients (1.30 vs. 1.01 AE/year; relative risk, 1.00-1.62). The authors report safety information for the following categories: deaths, carbohydrate metabolism abnormalities, cardiovascular disease, neurological/psychiatric/other symptoms, and tumors.

Deaths:

Three patients died due to vascular malformation in the optic chiasm (1), respiratory distress following surgery (1), and increased intracranial pressure after chraniopharyngioma recurrence (1). None of these deaths were reported as "connected" with GH therapy.

Carbohydrate metabolism abnormalities

Six new cases of diabetes mellitus were identified; three of them occurred in patients with obesity at baseline (BMI>30 kg/m^2) and one in a patient with known impairment of glucose intolerance. Following diagnosis of diabetes mellitus, GH was discontinued in one patient, GH dose was reduced in another, and oral antidiabetic treatment was required in three patients. There were no significant changes in mean serum glucose levels and HbA1c between those observed at enrollment and those of the last evaluation.

Cardiovascular disease

Myocardial infarction was reported in 2 patients (both aged 46 years, after receiving GH for 15 and 30 months, respectively). Three patients reported angina pectoris, and 16 patients (ages 27 to 64) developed hypertension.

Neurological/psychiatric, and other symptoms

The number of patients with "neurological, psychiatric and other symptoms" is presented in

Table 4 Number of GHD hypopituitary adult patients reporting neurological, psychiatric and other symptoms during GH replacement

Symptom	Number of patients
Neurological	
Headache	31
Paraesthesia	17
Dizziness	10
Migraine	7
Convulsions	6*
Carpal tunnel syndrome	4
Tremor	2
Leg cramps	2
Psychiatric	
Fatigue	9
Depression	7
Asthenia	4
Anxiety	3
Insomnia	3
Emotional lability	2
Other	
Increased sweating	14
Decreased body weight	4
Flushing	3
Tendinitis	3
Increased body weight	2
Sleep apnoea	2
Snoring	2
Dryness of the mouth	1

*Of whom four known with epilepsy.

Table 4. The authors do not provide an analysis of individual adverse event incidence.

Tumors

New tumors were reported in five patients: basal cell carcinoma (in three Australian patients following 1-2.8 years of GH therapy), malignant teratoma of the testis (in a 23-year old after 1.8 years of GH treatment), and abnormal cervical smear (in a 27-year-old woman). Recurrence of pituitary or CNS tumors was reported in six patients.

Comparison between AEs reported in KIMS and in previous clinical trials

The authors report that the total incidence of AEs in KIMS was lower than that reported in 43 clinical trials (1.07 vs. 6.3 AE/year; relative risk, 0.15-0.19). To what extent this is a consequence of underreporting in a postmarketing study or to the lower GH dose used in KIMS (or both) it is not clear. In general the AEs analyzed in KIMS showed incidence rates comparable to or lower than those previously reported.

Conclusions:

This safety analysis of a large cohort of patients treated with GH for a relatively short period of time (mean duration of 0.79 months) dose not identify any new safety signals. The characteristics of the study (postmarketing, open-label GH use, absence of a control group) limit further conclusions. The study provides supportive evidence that GH replacement therapy is relatively well tolerated in adults with GHD.

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