CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-426/N-000
Drug Name:	OMNITROPE™ (somatropin [rhGH] for injection)
Indication(s):	Long-term treatment and replacement therapy for growth hormone deficiency in children and adult (2 indications)
Applicant:	Biochemie U.S., Inc.
Date(s):	Received 07/30/03; user fee (10 months) 05/30/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Todd Sahlroot, Ph.D., Statistical Team Leader
	S. Edward Nevius, Ph.D., Division Director
Medical Division:	Div. of Metabolic and Endocrine Drug Products (HFD-510)
Clinical Team:	Dragos Roman, M.D., Medical reviewer
	David Orloff, M.D., Team Leader and Division Director
Project manager:	Monika Johnson, PharmD
Keywords:	NDA review, clinical study, non-inferiority, historical data

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

After 9 months of treatment with OMNITROPE Lyophilized powder using the Active Pharmaceutical Ingredient (API) manufactured by Covance, USA, the previously untreated growth hormone deficient (GHD) children showed statistically comparable results in heights, growth rates, and related standardized scores when compared with that of the Genotropin®-treated children. Specifically, the observed treatment difference between the 2 study groups for the main efficacy variable of interest, height velocity standard deviation score (HVSDS), was 0.6440, favoring the OMNITROPE treatment. However, it was also shown that OMNITROPE could be worse than Genotropin® by as much as 0.8303 (less than 1 standard deviation away from the mean of normal children of the same age and gender) according to the 95% lower confidence limit.

The change in height between Months 9 and 15 when subjects were treated with OMNITROPE Lyophilized powder using the API manufactured by Biochemie, Austria, was shown to be similar to that between Months 6 and 9 when OMNITROPE Lyophilized powder using the API manufactured by Covance, USA, was given. In other words, Biochemie API was able to maintain the growth rate seen in the later stage of treatment with Covance API. However, due to the study design limitations, whether Biochemie API could have produced the same steep growth curve as seen in the early stage of treatment with Covance API remains unknown.

It was shown that the height, growth rate, and related standardized scores after 9 months of treatment with OMNITROPE Lyophilized powder were all significantly improved over that at baseline. Similar findings were also observed at Month 15.

Since there was lack of a valid concurrent control for the to-be-marketed drug product (OMNITROPE Lyophilized powder using the API manufactured by Biochemie, Austria), historical data from the current submission, the prescribing information of Nutropin Depot, and some published literature were utilized as a supplementary tool. Despite the fact that there might be some bias in the selection of historical data due to differences in patient population, study design, etc, the mean height velocity and its 95% confidence interval after 12 months of OMNITROPE treatment (9 months with Covance API, then 3 months with Biochemie API) was well within the historical range.

In summary, the data have demonstrated that OMNITROPE Lyophilized powder, regardless of the manufacturing site of API, was efficacious in increasing height and in stimulating height velocity of previously untreated GHD children. The difference in height between the growth hormone treated children and the normal age- and gender-matched children was

gradually decreased as the treatment continued. In addition, the rate of growth was reversed from slower than that of normal children of the same age and gender to faster than that of normal ones during the early stage of the treatment.

If the sponsor had used the to-be-marketed drug product from the beginning of the Phase III clinical program and included a valid control group, the analysis of the data and interpretation of the results would have been much more straightforward.

1.2 Brief Overview of Clinical Studies

This submission to NDA 21-426 seeks approval of OMNITROPE™ Lyophilized powder (using the API manufactured by Biochemie, Austria) for long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.

Three Phase III open-label clinical trials were conducted in the same cohort of patients from 7 European centers. A total of 89 previously untreated children with GHD were randomized to receive either OMNITROPE Lyophilized powder (using the API manufactured by Covance, USA) or Genotropin® for 6 months in the EP2K-99-PhIII study, which was extended for an additional 3 months (EP2K-00-PhIIIFo). Eighty-six subjects completed the 2 studies and entered the 6-month EP2K-00-PhIII^{AQ}, Part A study, where the Genotropin®-treated subjects in the first 2 studies were given OMNITROPE Liquid and OMNITROPE Lyophilized powder-treated subjects continued to receive OMNITROPE Lyophilized powder, but with the API manufactured by Biochemie, Austria. The reason of changing from Covance API to Biochemie API was because Covance product contained too high an amount of host cell proteins (HCPs) causing unexpected development of anti-GH antibodies.

The primary efficacy variables included height, height standardized for age and gender standard deviation score (HSDS), height velocity, height velocity standard deviation score (HVSDS), and projected final height. The standard deviation scores were calculated by the sponsor using means and standard deviations of height or height velocity of normal subjects of the same age and gender from nation-specific standard curves. Among the 5 primary efficacy variables, HVSDS was the main variable of interest.

1.3 Statistical Issues and Findings

In this reviewer's opinion, the issues that may impact the overall conclusions of the study are more related to the study design aspects, as mentioned in Section 3.1.1 of the main body of the review. For example, the to-be-marketed product, OMNITROPE Lyophilized powder with Biochemie API, was compared with a product that is not approved, and was tested only during Months 9-15 of the whole Phase III clinical program. Note that there were some

erroneous calculations made by the clinical investigators for height velocity at baseline and the sponsor is still in the process of discussing the issue with the investigators, as stated in the 4/27/2004 submission. This reviewer has re-calculated the Month 0 height velocity herself and found that the difference between the investigators and this reviewer's calculation was at the 2nd decimal place of mean values, in which case should cause no impact on the overall conclusions. In general, this reviewer's findings based on the data submitted agree with the sponsor's conclusions.

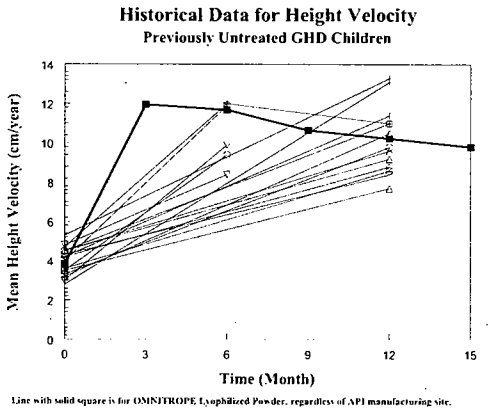
The table below presents the summary statistics for the height-related parameters for the OMNITROPE Lyophilized powder-treated children. During the 15-month growth hormone treatment period, a significant linear growth over time was observed for the previously untreated children with GHD. The standardized differences in height between the growth hormone treated children and the normal age- and gender-matched children were gradually decreased as the treatment continued. The most rapid growth occurred in the early stage of the treatment, when the height velocity was accelerated from 4 cm/year at baseline to 12 cm/year at Month 3. Once the so-called "catch-up growth" was reached, the rate of growth started to attenuate. The mean height velocity standard deviation score was reversed from a negative value at baseline to positive values at all post-treatment time points, indicating that under the growth hormone treatment, the rate of growth of previously untreated GHD children became higher than that of normal children of the same age and gender.

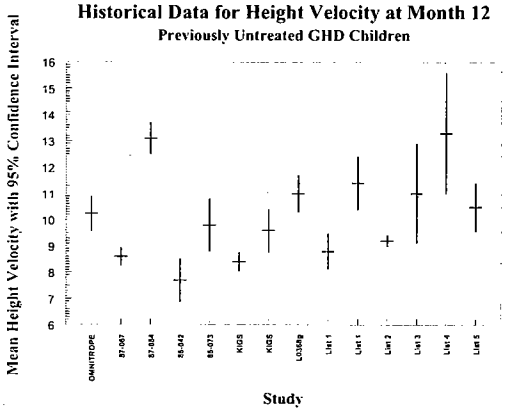
ITT	OMNITROPE Lyophilized Powder (Raw Mean ± S.D. (N))			
	Height	HSDS	Height Velocity	HVSDS
Month 0	113.339 ± 13.334 (44)	-2.9899 ± 0.7221 (43)	3.8136 ± 1.2296 (44)	-2.4341 ± 1.2994 (44)
Month 3	116.652 ± 13.296 (42)	-2.7146 ± 0.6916 (41)	11.9576 ± 3.9353 (42)	7.5265 ± 4.9958 (41)
Month 6	119.540 ± 13.073 (42)	-2.4266 ± 0.6737 (42)	11.6728 ± 3.0312 (42)	7.2852 ± 4.2131 (41)
Month 9	121.852 ± 13.058 (42)	-2.2670 ± 0.6822 (42)	10.6508 ± 2.5671 (42)	6.0516 ± 3.6730 (41)
Month 12	124.017 ± 12.891 (42)	-2.1007 ± 0.6977 (42)	10.2289 ± 2.1731 (42)	**3.8148 ± 3.7292 (41)**
Month 15	126.095 ± 12.953 (42)	-1.9957 ± 0.7213 (42)	9.8019 ± 1.9013 (42)	**3.3823 ± 2.5524 (41)**

Months 12 and 15 HVSDS (in bold) were calculated with respect to the height at Month 9.

According to this reviewer's analyses, height, HSDS, height velocity, and HVSDS at Month 9 (with Covance API) and Month 15 (with Biochemie API) were all highly significantly improved over that at baseline. The change in height during Months 9-15 when Biochemie API was used was not statistically different from that during Months 6-9 when Covance API was used, implying that (1) a stable growth rate was obtained and (2) Biochemie API was able to maintain the growth rate produced in the later stage of treatment with Covance API.

Due to lack of a valid concurrent control for the to-be-marketed drug product, this reviewer collected historical data from the sponsor's Table 22 in Mo0-12 report.pdf, the prescribing information of Nutropin Depot, and some published literature as supportive evidence, to see if the efficacy of OMNITROPE Lyophilized powder was similar to that of the historical data, which were all from the same recombinant growth hormone family with closely matched study populations. The following 2 figures depict that the mean height velocities of OMNITROPE-treated children at 6- and 12-month time points were within the historical range, and the mean and 95% confidence interval at 12 months were within 9 to 12 cm/year, where the majority of historical data were.





The percentage of OMNITROPE-treated children with anti-GH antibodies was gradually increased as the treatment with Covance API continued, but was gradually decreased once Biochemie API was used. This finding may be a confirmation of Biochemie API being a cleaner product than Covance API that contained too high an amount of HCPs. No statistical difference in HVSDS at Months 9 and 15 were observed between the children with and without anti-GH antibodies, meaning that the presence of anti-GH antibodies had no significant impact on the treatment efficacy.

No significant difference in mean HVSDS at Month 9 was observed between the Omnitrope and Genotropin groups, indicating that the growth rates of the 2 study groups, relative to that of the normal children of the same age and gender, may be comparable over a 9-month treatment period. However, although the mean HVSDS at Month 9 adjusted for the baseline in the Omnitrope group was slightly larger than that in the Genotropin group (treatment difference 0.6440), it could actually be smaller by as much as 0.8308 according to the 95% lower confidence limit. Note that the equivalence interval the sponsor defined for HVSDS was (-2.8, 2.8).

All post-treatment mean IFG-1 serum levels were numerically larger than that at baseline when the GHD children were treated with OMNITROPE Lyophilized powder. In addition, the numbers of children with IGF-1 serum level below the limit of calibration (LOC) were smaller during the growth hormone treatment period. Similar response patterns were also observed for IGFBP-3 serum levels.

2. INTRODUCTION

2.1 Overview

Biochemie GmbH has submitted the results from 3 Phase III clinical studies conducted in the same cohort of previously untreated prepubertal children with growth hormone deficiency (GHD) and growth retardation, to NDA 21-426 for OMNITROPE™ (somatropin (rhGH) injection, EP2000), a new preparation of recombinant human growth hormone. The associated intended indication is long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. The sponsor is also seeking approval for long-term replacement therapy in GHD adults. Per medical officer, since there were no clinical studies performed with OMNITROPE™ in GHD adults, the intended indication for GHD adults would not be the focus of the review.

The original clinical development program included an open, randomized, active-controlled, 6-month Phase III study (EP2K-99-PhIII), which was extended for an additional 3 months (EP2K-00-PhIIIFo). During the 9-month treatment period, OMNITROPE Lyophilized powder (using the Active Pharmaceutical Ingredient (API) manufactured by Covance, USA) was compared with Genotropin® (using the API manufactured by Pharmacia/Upjohn, Sweden). It was found that Covance API contained too high an amount of host cell proteins (HCPs), which caused unexpected development of anti-GH antibodies in the patients. Therefore, a revision on the clinical program was made. The patients who had been treated with OMNITROPE Lyophilized powder (using the API manufactured by Covance, USA) and Genotropin® for 9 months were switched to OMNITROPE Lyophilized powder and OMNITROPE Liquid (both using the API manufactured by Biochemie, Austria), respectively, for 6 months (EP2K-00-PhIII^{AQ}, Part A). Subsequently, all patients were given OMNITROPE Liquid for 15 months (EP2K-00-PhIII^{AQ}, Part B).

Note that OMNITROPE Liquid is not an approved drug product and OMNITROPE Lyophilized powder with the API manufactured by Biochemie, tested only during Months 9-15 treatment period, is the drug product that the sponsor is seeking approval for. Since the EP2K-00-PhIII^{AQ}, Part B study involved only OMNITROPE Liquid treatment, it was not reviewed for the efficacy evaluation.

According to the sponsor, it was demonstrated by in-depth physicochemical characterization and comparability exercises that Covance API and Biochemie API are fully comparable in all quality aspects with the sole exception of HCP content. If the reviewing chemist thinks that the two APIs are basically the same drug substance, the 9-month clinical data from Covance API (see the table below for study highlights) can then fully support the efficacy and safety of the to-be-marketed drug product (using the API manufactured by Biochemie, Austria).

Protocol No./Study Design/Location	Treatment (N)	Age/Gender/Race	Primary Endpoint
EP2K-99-PhIII Phase III, open, multicenter, randomized, controlled, 2-group parallel study over 6 months 6 in Poland and 1 in Hungary	0.03 mg/kg/day (Covance) OMNITROPE™ Lyophilized powder (44) 0.03 mg/kg/day Genotropin® (45)	2 – 14 years (Mean = 7.6) M:49 (55%) F: 40 (45%) White: 89 (100%)	Height HSDS Height velocity HVSDS Projected final height
EP2K-00-PhIIIFo A follow-up study to provide an additional 3 months of data from children who completed the previous 6-month study; same locations as above	0.03 mg/kg/day (Covance) OMNITROPE™ Lyophilized powder (42) 0.03 mg/kg/day Genotropin® (44)		same as above
EP2K-00-PhIII^{AQ}, Part A Phase III, open, multicenter, 2-group parallel study for children who completed the previous 6- & 3-month studies; same locations as above	0.03 mg/kg/day (Biochemie) OMNITROPE™ Lyophilized powder (42) 0.03 mg/kg/day (Biochemie) OMNITROPE™ Liquid (44)		same as above

N = Number of subjects randomized and received medication

2.2 Data Sources

The data files this reviewer used are velocity.sd2, serum.sd2, ghab_t.sd2, and demog.sd2, submitted electronically by the sponsor on 12/9/2003. They are in EDR \\Cdsesub1\n21426\N_000\2003-12-09\Sas\Derived. Files with extension .sd2 are SAS internal files. The sponsor did not provide SAS transport files (.xpt), nor the data definition file (define.pdf) at the time of submission. In response to this reviewer's request, a data definition file (DDTs.ZIP) was received on 3/9/2004 via e-mail. The study reports this reviewer reviewed are located in \\Cdsesub1\n21426\N_000\2003-08-08\clinstat\GHD_children. The bookmarks and hypertext links in those reports were done very poorly which made the review task very difficult.

The sponsor's naming conventions for variables were confusing and inconsistent across data files, especially for the date variables, which were crucial for calculating height velocity and its standardized score (HVSDS). Also, this reviewer had a difficult time to verify or recalculate height velocity and HVSDS because the sponsor did not create SAS date formats consistently among some of the date variables.

This reviewer has found some erroneous calculations made by the clinical investigators for height velocity at Month 0 (based on growth data prior to inclusion in the clinical trial). The sponsor has been informed and is in the process of discussing the issue with the investigators.

They expect that the changes are minor and will not affect the final conclusions, as stated in the 4/27/2004 submission. This reviewer has re-calculated the Month 0 height velocity using the raw data of height prior to study entry recorded in growhis2.sd2. The difference between the investigators and this reviewer's calculation was found at the 2nd decimal place of mean values, and therefore, has no impact on the overall conclusions.

There were some historical data collected in this review report, which were used as supportive evidence. They were extracted from the sponsor's Table 22 in Mo0-12 report.pdf under \\Cdsesub1\n21426\N_000\2003-08-08\clinstat\GHD_children\Other\Month 0 to 12 report, the prescribing information of Nutropin Depot, and some published literature.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

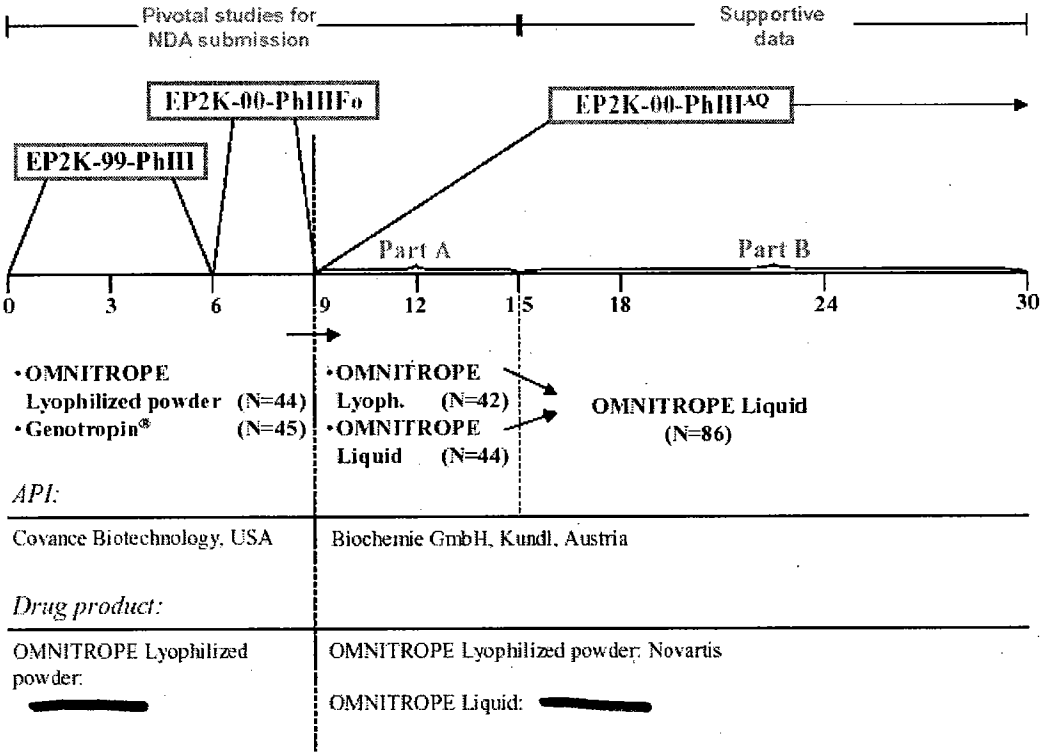
3.1.1 Study Design and Endpoints

Protocol EP2K-99-PhIII was a 6-month study started on 2/15/2000 and Protocol EP2K-00-PhIIIFo was a 3-month follow-up study started on 9/5/2000. Subsequently, Protocol EP2K-00-PhIII^{AQ}, Part A started on 12/11/2000 and lasted for 6 months. All 3 studies were Phase III, open, multicenter (in Europe), comparative trials conducted in the same cohort of previously untreated (naïve) GHD children. The first 2 studies were to compare OMNITROPE Lyophilized powder with Genotropin®. The third (Part A) study was to compare Lyophilized powder with Liquid formulations of OMNITROPE; the subjects treated with OMNITROPE Liquid were the ones taking Genotropin® in the first 2 studies (see the design diagram below). Protocol EP2K-00-PhIII^{AQ}, Part B, was a 15-month study and consisted of only OMNITROPE Liquid treatment.

The API of OMNITROPE was manufactured by Covance, USA for the EP2K-99-PhIII/EP2K-00-PhIIIFo studies, while Biochemie, Austria was the manufacturing site for the EP2K-00-PhIII^{AQ}, Part A study. The reason of changing from Covance to Biochemie was because Covance product contained too high an amount of HCPs causing unexpected development of anti-GH antibodies. As a consequence, OMNITROPE Lyophilized powder (using the API manufactured by Biochemie, Austria) is the to-be-marketed product that the sponsor is seeking approval for under this NDA.

The primary efficacy variables included height, height standardized for age and gender standard deviation score (HSDS), height velocity, and height velocity standard deviation score (HVSDS, main efficacy variable of interest). They were measured at Months 0, 3, 6, 9, 12, and 15. Projected final height which was collected at Months 0, 9, and 15 was also one of the primary efficacy variables. The secondary efficacy variables included insulin-like

growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) serum levels that were measured at Months 0, 1, 3, 6, 9, 12, and 15.



Based on consultation with the medical officer, projected final height would not be the focus of the review. The efficacy in HVSDS with respect to anti-GH antibody was evaluated according to the medical officer's request.

In this reviewer's opinion, there are some aspects of the design that may be inappropriate and introduce bias to the final results. For example, no clinical study was conducted to show equivalence in efficacy and safety between the APIs of OMNITROPE manufactured by Covance (Months 0-9) and Biochemie (Months 9-15). Therefore, whether the Months 0-9 clinical data can support the Months 9-15 data is questionable. Since there was no washout period between Months 0-9 and Months 9-15 treatment periods, how much efficacy and safety OMNITROPE Lyophilized powder with the API manufactured by Biochemie actually produced remains unknown. For subjects entering the EP2K-00-PhIII^{AQ}, Part A study, since they had been exposed to different growth hormone treatments for 9 months and were not re-randomized prior to entry, the comparability of "baselines" at Month 9 is in doubt. The to-be-marketed product, OMNITROPE Lyophilized powder, tested during Months 9-15 was compared with an uncontrolled (unapproved) comparator, OMNITROPE Liquid. Moreover, it is not clear if those studies were designed for an equivalence or non-inferiority trial since

there were no hypotheses given in the protocols. For the purpose of this review and regulatory interest, those studies were treated as non-inferiority trials.

It was stated in the EP2K-99-PhIII protocol that to detect a difference between the treatment groups of equal to 1 SD of the HVSDS score at the 5% level with 80% power, 40 patients per treatment group were to be recruited. This reviewer could not verify the sample size due to inadequate information such as common standard deviation in the protocol.

3.1.2 Statistical Methods

EP2K-99-PhIII/EP2K-00-PhIIIFo (Months 0-9)

Height-related efficacy variables at Month 9 were analyzed by ANCOVA techniques using treatment as the main factor and Month 0 baseline as the covariate (the sponsor's model). Treatment-by-baseline for parallelism of the slopes and treatment-by-site interaction terms were tested for HVSDS initially by this reviewer; no significance at $p \leq 0.10$ was found in both cases. Since all the study sites were inspected by either an independent auditing team or the EMEA, and there was a significant overall site-to-site difference in baseline HVSDS, this reviewer also analyzed the data by including site in the model and found no difference in the conclusions. In addition, a paired t-test was performed for the Omnitrope group to examine if growth rate after 9 months of treatment was significantly improved over that at baseline.

The equivalence interval (or non-inferiority margin) for the primary efficacy endpoint HVSDS the sponsor defined was ±2.8, equal to the standard deviation of HVSDS of Genotropin® in the study TRN 86-073, as cited in the sponsor's study report. This reviewer could not find any background rationale regarding the choice of 2.8. Based on a memo of a conference call on 2/14/2001 for IND 58,980, the sponsor noted a 2.6-cm per year for growth velocity to be a clinically important difference, even though 2-cm was agreed to by the involving medical officer and statistician. How much standardized score a 2.6-cm per year of height velocity should be translated to was not indicated in that memo. There were several Genotropin® trials (NDA 20-280) conducted in naïve patients for the same clinical indication as the OMNITROPE™ submission. Unfortunately, none of those were placebo controlled, which makes the acquisition of a sensible margin from statistical grounds much more difficult. Therefore, no non-inferiority margin was used as a criterion to draw conclusions in this review report.

EP2K-00-PhIII^{AQ}, Part A (Months 9-15)

Since OMNITROPE Liquid is not an approved drug product, comparing Lyophilized powder with it does not actually give any direct inference for the efficacy of powder formulation. Due to the limitations of the study design, this reviewer thinks that comparisons with

baseline values (within-patient analysis) and with historical data (as a supplementary tool) may be the best approaches to assess the efficacy of OMNITROPE Lyophilized powder (using the API manufactured by Biochemie, Austria) during Months 9-15.

Specifically, a paired t-test was performed to examine if growth rate after 15 months of OMNITROPE Lyophilized powder treatment, regardless of the manufacturing site of API, was significantly improved over that at Month 0 baseline. In addition, since the subjects in the EP2K-00-PhIII^{AQ}, Part A study were previously treated in the EP2K-99-PhIII/EP2K-00-PhIIIFo studies (without washout period), it would be interesting to see if treatment effect produced by Covance API was maintained by Biochemie API. Therefore, a paired t-test was performed to see if growth rate of Months 9-15 was similar to that of Months 0-9, 3-9, or 6-9. Since most historical data were up to 12 months, the above analyses were also done for the 12-month time point. Note that the sponsor calculated height velocity and HVSDS at Months 12 and 15 relative to the height measured at Month 9, e.g., height velocity = ((post-treatment height – Month 9 height)/(post-treatment visit date – Month 9 visit date)) × 365.25. This reviewer re-calculated height velocity with respect to the height obtained at Month 0, e.g., ((post-treatment height – Month 0 height)/(post-treatment visit date – Month 0 visit date)) × 365.25, for the purpose of the first paired t-test analysis mentioned above. However, since the sponsor did not provide the means and standard deviations of normal children of the same age and gender from nation-specific standard curves, this reviewer could not re-calculate HVSDS for any intervals of interest.

The sponsor analyzed all the primary efficacy variables without any multiplicity adjustment. Since sample size and equivalence interval were obtained based on HVSDS, it is reasonable to claim that HVSDS was the most important primary efficacy variable. In other words, this reviewer did not strongly feel the necessity of the adjustment either.

3.1.3 Subject Disposition

There were 89 subjects randomized to the 6-month EP2K-99-PhIII study: 44 and 45 for the Omnitrope and Genotropin groups, respectively. A total of 3 subjects withdrew from the study, where 2 were from the Omnitrope group due to violation of protocol inclusion criteria and 1 from the Genotropin group due to non-compliance (major protocol violations). They all discontinued from the study before their Month 3 visits. All the other 86 subjects (42 for the Omnitrope and 44 for the Genotropin groups) completed the 6-month study and stayed through the EP2K-00-PhIIIFo and EP2K-00-PhIII^{AQ} Part A studies.

The efficacy analyses were performed on the intention-to-treat (ITT) population that consisted of all the subjects randomized to the EP2K-99-PhIII study, as defined by the sponsor. Since 3 subjects withdrew from the study before the first post-treatment standing

height was collected, only 86 subjects in the ITT set were available for the height-related efficacy analyses, which became the same analyses as using the per-protocol (PP) population.

3.1.4 Demographic and Baseline Characteristics

No statistically significant differences in baseline age, weight, height, HSDS, height velocity, and HVSDS at Month 0 were observed between the Omnitrope and Genotropin groups (Table 1). Subject distributions in gender and study site were also similar between the 2 study groups. All patients were prepubertal at Month 0 and Caucasian.

Table 1 – Demographic and Baseline Characteristics of Randomized Subjects at Month 0

Characteristic		Omnitrope	Genotropin	Total
Age (year):	Mean ± SD	7.82 ± 2.56 (44)	7.38 ± 2.84 (45)	7.60 ± 2.70 (89)
	Median	8	7	7
	Range	3 – 13	2 – 14	2 – 14
Gender:	Male (%)	28 (63.64)	21 (46.67)	49 (55.06)
	Female (%)	16 (36.36)	24 (53.33)	40 (44.94)
Weight (kg):	Mean ± SD	20.77 ± 6.04 (44)	20.14 ± 7.51 (45)	20.45 ± 6.79 (89)
	Median	20.0	19.0	19.5
	Range	11.7 – 37.2	8.8 – 46.0	8.8 – 46.0
Height (cm):	Mean ± SD	113.34 ± 13.33 (44)	109.35 ± 15.68 (45)	111.32 ± 14.62 (89)
	Median	111.8	109.8	109.8
	Range	86.4 – 142.6	75.7 – 143.0	75.7 – 143.0
HSDS:	Mean ± SD	-2.99 ± 0.72 (43)	-3.14 ± 0.89 (43)	-3.06 ± 0.81 (86)
	Median	-2.84	-2.89	-2.86
	Range	-4.90 – -1.77	-6.36 – -2.09	-6.36 – -1.77
Height velocity (cm/year):				
	Mean ± SD	3.81 ± 1.23 (44)	3.96 ± 0.83 (45)	3.89 ± 1.04 (89)
	Median	3.9	4.1	4.0
	Range	1.0 – 6.1	1.8 – 5.6	1.0 – 6.1
HVSDS:	Mean ± SD	-2.43 ± 1.30 (44)	-2.34 ± 1.12 (45)	-2.39 ± 1.21 (89)
	Median	-2.1	-2.0	-2.1
	Range	-6.0 – 0.4	-5.5 – -1.0	-6.0 – 0.4
Study Site	01 – Poland (%)	3 (6.82)	3 (6.67)	6 (6.74)
	02 – Poland (%)	8 (18.18)	8 (17.78)[a]	16 (17.98)
	03 – Poland (%)	3 (6.82)	3 (6.67)	6 (6.74)
	04 – Poland (%)	9 (20.45)	10 (22.22)	19 (21.35)
	05 – Poland (%)	6 (13.64)[a]	7 (15.56)	13 (14.61)
	06 – Poland (%)	7 (15.91)	7 (15.56)	14 (15.73)
	07 – Hungary (%)	8 (18.18)[a]	7 (15.56)	15 (16.85)

[a] Including a withdrawn subject

3.1.5 Efficacy Results and Discussion

Following are the sponsor's efficacy findings based on the 15-month data of ITT population.

- After 9 months of treatment, OMNITROPE Lyophilized powder (using the API manufactured by Covance, USA) and Genotropin® showed comparable results for the clinical efficacy parameters of height, HSDS, growth velocity, HVSDS, and projected height. Specifically, the 95% confidence interval of the mean difference in HVSDS between treatment groups was –0.83 to 2.12, which lies entirely within the pre-defined equivalence interval (-2.8, +2.8). Both products also showed comparable results for the pharmacodynamic efficacy parameters of IGF-1 and IGFBP-3 serum levels.

- After 6 months of treatment, OMNITROPE Lyophilized powder (using the API manufactured by Biochemie, Austria) and OMNITROPE Liquid (using the API manufactured by Biochemie, Austria) showed comparable results for the clinical efficacy parameters of height, HSDS, growth velocity, HVSDS, and projected height. Both products also showed comparable results for the pharmacodynamic efficacy parameters of IGH-1 and IGFBP-3 serum levels.

Basically, the reviewer confirmed the sponsor's findings. The following sections present the results of this reviewer's own analyses using the data submitted on 12/9/2003.

Height. As Table 2 shows, the mean heights of previously untreated GHD children in both the Omnitrope and Genotropin groups were increased over time; and as Figure 1 and Lack-of-Fit test reveal, the growths during the course of the study were in a linear fashion. In fact, a significant linear growth over time was observed in both the study groups based on regression analyses. In addition, the paired t-test results show that the mean heights in the Omnitrope group at Month 9 (using Covance API) and Months 12 and 15 (using Biochemie API) were all significantly increased over that at baseline.

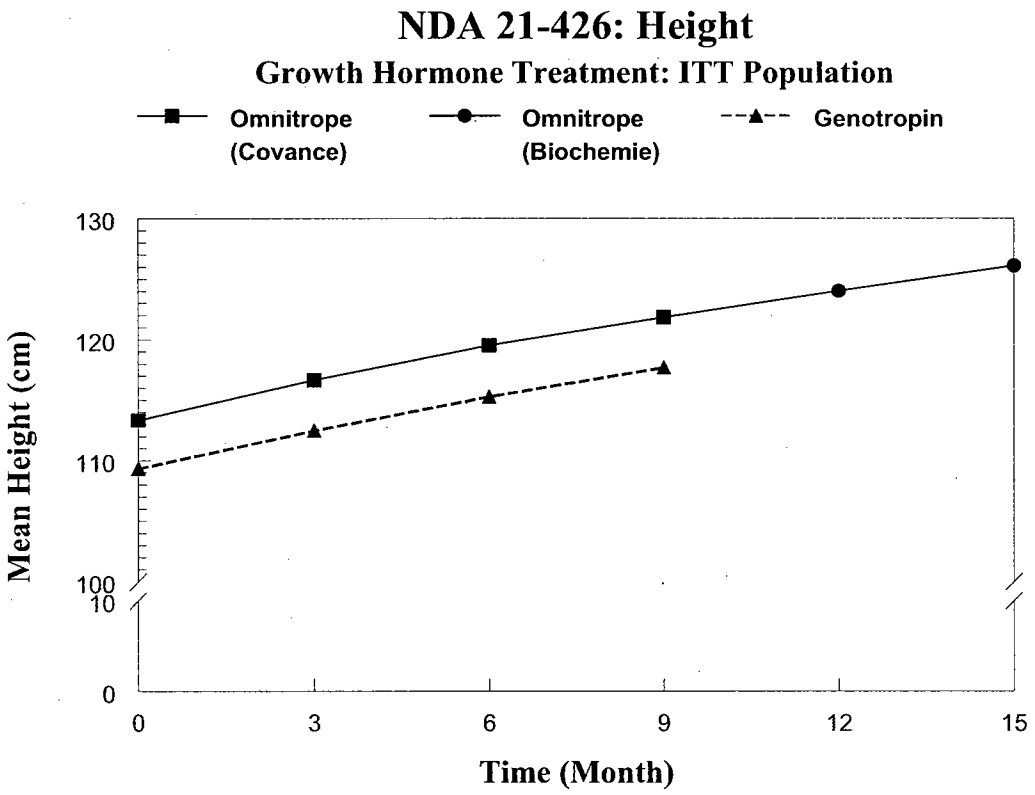
No significant difference in mean height at Month 9 was observed between the Omnitrope and Genotropin groups, indicating that the 2 study groups may be comparable in inducing growth over a 9-month treatment period. Although the mean height at Month 9 adjusted for the baseline in the Omnitrope group was slightly larger than that in the Genotropin group (treatment difference 0.2338 cm), it could actually be smaller by as much as 0.5923 cm according to the 95% lower confidence limit.

Table 2 – Results for Height (cm)

	Omnitrope	Genotropin	Treatment Difference	p-value	(LCL, UCL)
Raw mean height ± standard deviation (N)					
Month 0	113.339 ± 13.334 (44)	109.347 ± 15.681 (45)			
Month 3	116.652 ± 13.296 (42)	112.480 ± 15.468 (44)			
Month 6	119.540 ± 13.073 (42)	115.293 ± 15.063 (44)			
Month 9	121.852 ± 13.058 (42)	117.711 ± 14.712 (44)	8.2143	<.0001	(7.610, 8.819)
Month 12	124.017 ± 12.891 (42)		10.3786	<.0001	(9.705, 11.052)
Month 15	126.095 ± 12.953 (42)		12.4571	<.0001	(11.721, 13.194)
Least-squares mean height ± standard error (N)					
Month 9	119.85 ± 0.2956 (42)	119.62 ± 0.2887 (44)	0.2338	0.5750	(-0.5923, 1.0598)

Shaded numbers are the results of pre- (Month 0) and post-treatment analysis for the Omnitrope group.
Lack-of-fit test p-values for the Omnitrope and Genotropin groups are 0.9924 and 0.9879, respectively.
Regression slope p-values for the Omnitrope and Genotropin groups are <.0001 and 0.0066, respectively.

Figure 1



Height Standard Deviation Score (HSDS). The decreasing negative scores over time in both the Omnitrope and Genotropin groups, as shown in Table 3 and Figure 2, indicate that the standardized differences in height between the growth hormone treated children and the normal age- and gender-matched children were decreased over time. In other words, the heights of previously untreated GHD children under either growth hormone treatment were gradually improved and close to the average height of normal children of the same age and gender over the course of the study.

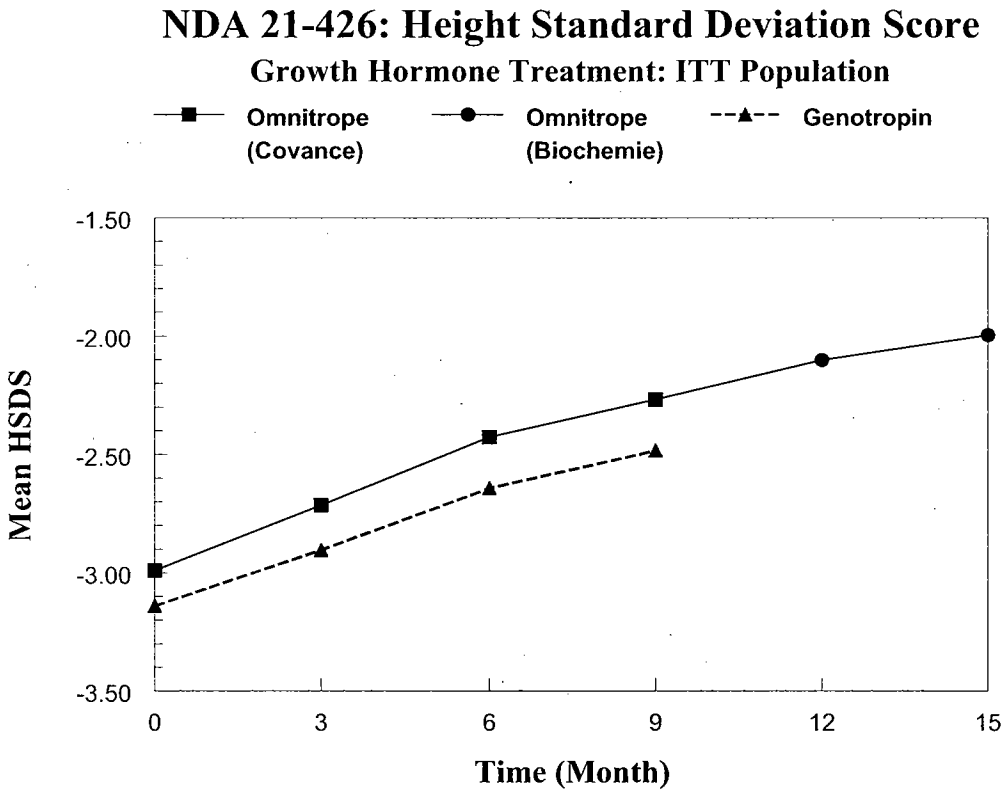
In general, all the statistical findings for HSDS are similar to the ones observed for Height mentioned in the preceding section.

Table 3 – Results for Height Standardized for Age and Gender Standard Deviation Score (HSDS)

	Omnitrope	Genotropin	Treatment Difference	p-value	(LCL, UCL)
Raw mean height standard deviation score ± standard deviation (N)					
Month 0	-2.9899 ± 0.7221 (43)	-3.1383 ± 0.8895 (43)			
Month 3	-2.7146 ± 0.6916 (41)	-2.9032 ± 0.8997 (43)			
Month 6	-2.4266 ± 0.6737 (42)	-2.6413 ± 0.7796 (43)			
Month 9	-2.2670 ± 0.6822 (42)	-2.4829 ± 0.7270 (43)	0.7851	<.0001	(0.6528, 0.9174)
Month 12	-2.1007 ± 0.6977 (42)		0.9405	<.0001	(0.7948, 1.0862)
Month 15	-1.9957 ± 0.7213 (42)		1.0474	<.0001	(0.8866, 1.2081)
Least-squares mean height standard deviation score ± standard error (N)					
Month 9	-2.2866 ± 0.0620 (41)	-2.4138 ± 0.0612 (42)	0.1272	0.1486	(-0.0464, 0.3009)

Shaded numbers are the results of pre- (Month 0) and post-treatment analysis for the Omnitrope group.
Lack-of-fit test p-values for the Omnitrope and Genotropin groups are 0.7461 and 0.9297, respectively.
Regression slope p-values for the Omnitrope and Genotropin groups are <.0001 and 0.0001, respectively.

Figure 2



Height Velocity. As Table 4 shows, the height velocity in both the Omnitrope (using Covance API) and Genotropin groups were increased from approximately 4 cm/year at baseline to 12 cm/year at Month 3, and then were gradually decreased throughout the rest of the 9-month comparative trial. The height velocity in the Omnitrope group was further decreased at Months 12 and 15 when Biochemie API was used.

No significant difference in mean height velocity at Month 9 was observed between the Omnitrope and Genotropin groups, indicating that the growth rates of the 2 study groups may be comparable over a 9-month treatment period. However, it is worth noting that the mean height velocity at Month 9 adjusted for the baseline in the Omnitrope group was slightly smaller than that in the Genotropin group (treatment difference -0.23 cm/year), and it could be smaller by as much as 1.37 cm/year according to the 95% lower confidence limit.

The paired t-test results showed that after 9 months of treatment with OMNITROPE Lyophilized powder (using Covance API), the mean height velocity (10.65 cm/year) was highly significantly increased over that at baseline (3.81 cm/year). The significance was still seen, with mean height velocity = 9.80 cm/year, after a total of 15 months growth hormone

treatment (using Covance API for 9 months, then Biochemie API for 6 months). Similar finding was also observed for the 12-month analysis.

Table 4 – Results for Height Velocity (cm/year) Calculated w.r.t. Month 0 Height

	Omnitrope	Genotropin	Treatment Difference	p-value	(LCL, UCL)
Raw mean height velocity ± standard deviation (N)					
Month 0	3.8136 ± 1.2296 (44)	3.9622 ± 0.8321 (45)			
Month 3	11.9576 ± 3.9353 (42)	12.0373 ± 4.1326 (44)			
Month 6	11.6728 ± 3.0312 (42)	11.5535 ± 3.1339 (44)			
Month 9	10.6508 ± 2.5671 (42)	10.7233 ± 2.8971 (44)	6.9222	<.0001	(5.9800, 7.8644)
Month 12	10.2289 ± 2.1731 (42)		6.5004	<.0001	(5.6934, 7.3073)
Month 15	9.8019 ± 1.9013 (42)		6.0733	<.0001	(5.3369, 6.8098)
Least-squares mean height velocity ± standard error (N)					
Month 9	10.5688 ± 0.4095 (42)	10.8016 ± 0.4000 (44)	-0.2328	0.6862	(-1.3745, 0.9090)

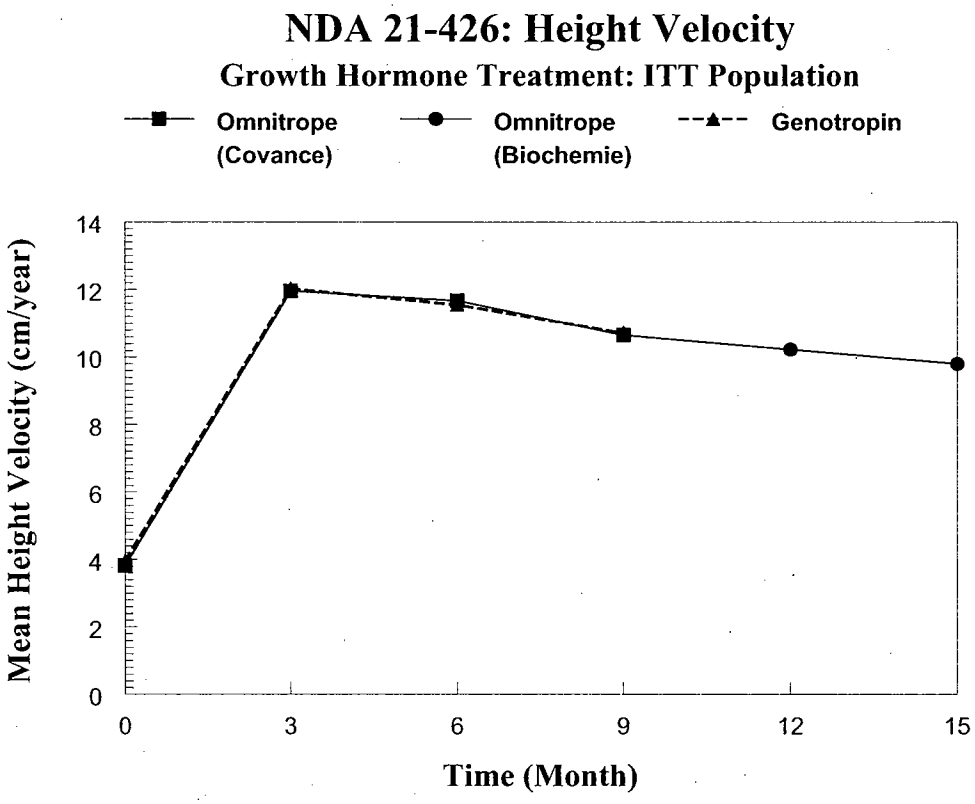
Month 0 height velocity was the growth rate prior to treatment.
Months 3, 6, 9, 12, and 15 height velocities here refer to Months 0-3, 0-6, 0-9, 0-12, and 0-15 height velocities, respectively.
Shaded numbers are the results of pre- (Month 0) and post-treatment analysis for the Omnitrope group.

As Table 5 shows, the growth rate increased by Biochemie API between Months 9 and 15 was significantly less than that observed during Months 0-9 period when Covance API was used. This finding can probably be explained by the fact that the most rapid growth stimulated by OMNITROPE was occurred during the first 3 months, immediately after the treatment was initiated for those previously untreated GHD children (see Figure 3). The rate of growth started to decelerate once the so-called "catch-up growth" was reached, and finally became stable, as shown by no significant difference in growth rate between Months 6-9 and Months 9-15 periods. The latter finding also implies that Biochemie API was able to maintain the height velocity stimulated by Covance API in the later stage of treatment (i.e., in Months 6-9). However, due to the study design limitations, it can not be determined if Biochemie API would have been able to produce the same steep growth curve as seen in the early stage of treatment using Covance API (i.e., in Months 0-3). Similar findings were also observed for Month 12 analyses.

Table 5 – Comparing Height Velocity (cm/year) between Covance API and Biochemie API

		Months 9-12: Raw Mean ± SD (N) 8.9045 ± 2.8893 (42)			Months 9-15: Raw Mean ± SD (N) 8.4895 ± 1.8035 (42)		
Months	Raw Mean ± SD (N)	Post-Pre	p-value	(LCL, UCL)	Post-Pre	p-value	(LCL, UCL)
0-9	10.6508 ± 2.5671 (42)	-1.7463	0.0028	(-2.82, -0.67)	-2.1613	<.0001	(-2.96, -1.36)
3-9	10.0380 ± 2.6092 (42)	-1.1335	0.0586	(-2.28, 0.01)	-1.5484	0.0012	(-2.42, -0.68)
6-9	8.7247 ± 3.1784 (42)	0.1798	0.7967	(-1.18, 1.54)	-0.2352	0.6813	(-1.35, 0.88)

Figure 3



Height Velocity Standard Deviation Score (HVSDS). As Table 6 and Figure 4 show, the mean scores in both the Omnitrope and Genotropin groups were reversed from negative values at baseline to positive values at all post-treatment time points, indicating that under the growth hormone treatments, the rates of growth of previously untreated GHD children became higher than that of normal children of the same age and gender. Specifically, the largest standardized difference in height velocity between the growth hormone treated children and the normal age- and gender-matched children occurred at Month 3 in both the study groups. The differences were gradually decreased as the treatments continued

throughout the rest of the 9-month comparative trial. The sponsor did not calculate the height velocity standard deviation scores at Months 12 and 15 with respect to Month 0 height. This reviewer could not compute them either due to lack of information of means and standard deviations from nation-specific standard growth curves that the sponsor used. The positive mean scores at Months 12 and 15 with respect to Month 9 height reveal that the GHD children treated with Biochemie API (previously treated with Covance API for 9 months without a washout period) still grew more rapidly than the normal children did.

No significant difference in mean HVSDS at Month 9 was observed between the Omnitrope and Genotropin groups, indicating that the growth rates of the 2 study groups, relative to that of the normal children of the same age and gender, may be comparable over a 9-month treatment period. However, it is worth noting that although the mean HVSDS at Month 9 adjusted for the baseline in the Omnitrope group was slightly larger than that in the Genotropin group (treatment difference 0.6440), it could actually be smaller by as much as 0.8308 according to the 95% lower confidence limit. Note that the equivalence interval the sponsor defined for HVSDS was (-2.8, 2.8).

Table 6 – Results for Height Velocity Standard Deviation Score (HVSDS)

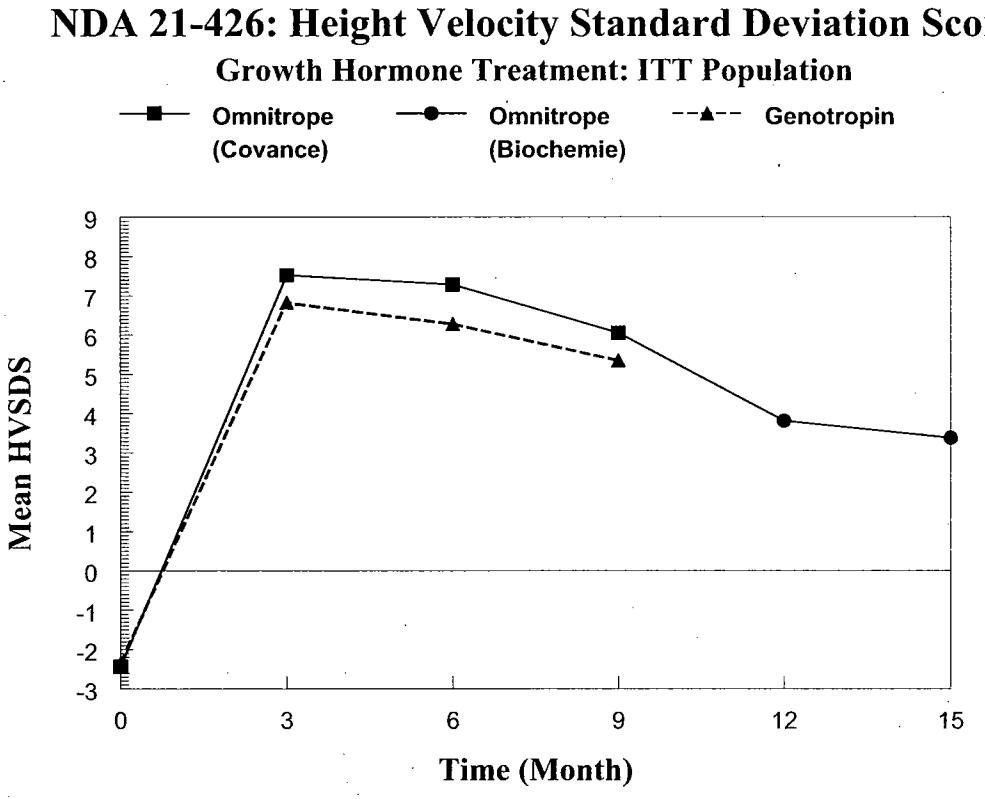
	Omnitrope	Genotropin	Treatment Difference	p-value	(LCL, UCL)
Raw mean height velocity standard deviation score ± standard deviation (N)					
Month 0	-2.4341 ± 1.2994 (44)	-2.3378 ± 1.1224 (45)			
Month 3	7.5265 ± 4.9958 (41)	6.8268 ± 4.9254 (44)			
Month 6	7.2852 ± 4.2131 (41)	6.2818 ± 3.4490 (44)			
Month 9	6.0516 ± 3.6730 (41)	5.3600 ± 3.1649 (44)	8.5394	<.0001	(7.3091, 9.7697)
Month 12	3.8148 ± 3.7292 (41)		-2.2368	0.0034	(-3.647, -0.827)
Month 15	3.3823 ± 2.5524 (41)		-2.6693	<.0001	(-3.709, -1.630)
Least-squares mean height velocity standard deviation score ± standard error (N)					
Month 9	6.0270 ± 0.5330 (41)	5.3830 ± 0.5145 (44)	0.6440	0.3876	(-0.8308, 2.1188)

Month 0 value was the height velocity standard deviation score prior to treatment.
Months 3, 6, and 9 HVSDS here refer to Months 0-3, 0-6, and 0-9 HVSDS, respectively.
Months 12 and 15 HVSDS here refer to Months 9-12 and 9-15 HVSDS, respectively.
Shaded numbers are the results of pre- and post-treatment analysis for the Omnitrope group, i.e., Month 0 versus Months 0-9, Months 0-9 versus Months 9-12, and Months 0-9 versus Months 9-15, respectively.

The paired t-test results showed that after 9 months of treatment with OMNITROPE Lyophilized powder (using Covance API), the mean HVSDS (6.0516) was highly

significantly increased over that at baseline (-2.4341). The significance was also seen when it was compared with a total of 6 months of OMNITROPE treatment using Biochemie API (Months 9-15). This finding implies that the growth rate in the Omnitrope group during Months 0-9 with Covance API, relative to that of the normal age- and gender-matched children, was significantly higher than the growth rate stimulated by Biochemie API during Months 9-15 treatment period. Once again, due to lack of information of means and standard deviations of normal children, this reviewer could not compute HVSDS for Months 6-9, and therefore, could not determine if Biochemie API was able to maintain the treatment effect produced by Covance API with respect to HVSDS.

Figure 4



IGF-1 and IGFBP-3 Serum Levels. As Table 7 shows, all post-treatment mean IFG-1 serum levels were numerically larger than that at baseline in both the Omnitrope and Genotropin groups. In addition, the numbers of GHD children with IGF-1 serum level below the limit of calibration (LOC) were smaller during the growth hormone treatment periods. Similar response patterns were also observed for IGFBP-3 serum levels.

Table 7 – Descriptive Statistics for IGF-1 (ng/mL) and IGFBP-3 Serum Levels (μg/mL)

	IGF-1 Serum Levels				IGFBP-3 Serum Levels			
	Omnitrope		Genotropin		Omnitrope		Genotropin	
Month 0	158.6 ± 92.0 (20)	24	157.7 ± 43.0 (20)	25	3.47 ± 1.31 (40)	4	3.48 ± 1.01 (36)	9
Month 1	205.4 ± 98.6 (36)	5	190.8 ± 88.0 (33)	12	4.22 ± 0.82 (41)	0	3.99 ± 1.00 (45)	0
Month 3	199.6 ± 97.9 (34)	8	193.1 ± 78.3 (33)	11	4.10 ± 1.31 (42)	0	4.07 ± 1.26 (44)	0
Month 6	257.2 ± 127.8 (38)	4	248.4 ± 131.2 (40)	4	3.84 ± 1.29 (42)	0	3.75 ± 1.25 (44)	0
Month 9	291.1 ± 174.0 (35)	7	301.9 ± 182.9 (38)	6	4.62 ± 2.97 (40)	2	3.99 ± 1.53 (43)	1
Month 12	304.2 ± 150.4 (41)	1			4.22 ± 1.08 (42)	0		
Month 15	300.1 ± 225.2 (39)	3			4.61 ± 1.29 (42)	0		

Shaded numbers are the total number of children with serum level below the limit of calibration (LOC).

3.2 Evaluation of Safety

Safety is not the focus of this review. See Dr. Dragos Roman's review for safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on HVSDS at Month 9 were consistent across the subgroups of sex and age (≤7, >7), as no significant treatment-by-subgroup interactions were observed ($p > 0.10$ in both cases). No statistical difference in HVSDS was observed between the Omnitrope and Genotropin groups at Month 9 within the same gender or age group. Based on the descriptive statistics shown in Table 8, the female or younger (≤7 years old) GHD children, relative to the normal children of the same sex and gender, tended to grow more rapidly than the male or older ones, respectively, at Months 9 and 15. No subgroup analysis was done for race since all the study subjects were Caucasian.

Table 8 – Descriptive Statistics for Subgroups of Sex and Gender (Raw Mean ± S.D. (N))

Treatment (Month)	Height Velocity Standard Deviation Score (HVSDS)			
	Sex (M)	Sex (F)	Age (≤7)	Age (>7)
Omnitrope (9)	5.9242 ± 3.5031 (27)	6.2974 ± 4.1071 (14)	7.3763 ± 3.9818 (19)	4.9075 ± 3.0246 (22)
Genotropin (9)	4.5919 ± 2.6028 (20)	6.0001 ± 3.4914 (24)	6.1919 ± 2.6871 (28)	3.9043 ± 3.4880 (16)
Omnitrope (15)	3.1052 ± 2.6518 (27)	3.9166 ± 2.3482 (14)	3.8471 ± 2.2050 (19)	2.9808 ± 2.8066 (22)

4.2 Other Special/Subgroup Populations

Although there was a significant overall site-to-site difference in HVSDS at Month 9, the response patterns of the 7 study sites were similar between the 2 study groups (treatment-by-

site interaction $p > 0.10$). No statistical difference in HVSDS at Month 9 was observed between the Omnitrope and Genotropin groups within each study site. Similar findings were also seen for pubertal status (1 = prepubertal, 2 = pubertal). The prepubertal GHD children at Months 9 and 15, relative to the normal children of the same sex and gender, tended to grow more rapidly than the pubertal ones.

Anti-GH Antibodies

As shown in Table 9, the percentage of children with anti-GH antibodies in the Omnitrope group was gradually increased as the treatment with Covance API continued, but was gradually decreased once Biochemie API was used. This finding may be a confirmation of Biochemie API being a cleaner product than Covance API that contained too high amount of HCPs. Specifically, the percentage of children with anti-GH antibodies was significantly decreased from Month 9 to Months 12 and 15 based on Cochran's Q test ($p = 0.0215$ and 0.0225, respectively).

Table 9 – Number of Patients with and without Anti-GH Antibodies

		Omnitrope		Genotropin	
	API	Absent	Present	Absent	Present
Month 0	Covance	44/44 (100%)	0/44 (0%)	45/45 (100%)	0/45 (0%)
Month 3	Covance	31/42 (73.81%)	11/42 (26.19%)	44/44 (100%)	0/44 (0%)
Month 6	Covance	28/42 (66.67%)	14/42 (33.33%)	43/43 (100%)	0/43 (0%)
Month 9	Covance	17/41 (41.46%)	24/41 (58.54%)	43/44 (97.73%)	1/44 (2.27%)
Month 10	Biochemie	23/42 (54.76%)	19/42 (45.24%)		
Month 12	Biochemie	26/42 (61.90%)	16/42 (38.10%)		
Month 15	Biochemie	27/42 (64.29%)	15/42 (35.71%)		

To examine if the existence of anti-GH antibodies had any impact on treatment efficacy, the following subgroup analyses were done for HVSDS at Month 9. First, the efficacy of children without anti-GH antibodies in the Omnitrope group was compared with that in the Genotropin group. Second, within the Omnitrope group, the children without anti-GH antibodies were compared with the children having the antibodies. Note that there was only 1 subject in the Genotropin group developing the antibody at Month 9 (Table 9).

As shown in Table 10, no statistical difference in HVSDS at Months 9 and 15 were observed between the children with and without anti-GH antibodies in the Omnitrope group, indicating that the presence of anti-GH antibodies had no significant impact on the treatment efficacy. In addition, for the children without anti-GH antibodies, the mean HVSDS at Month 9 of the Omnitrope group was statistically similar to that of the Genotropin group.

Table 10 – Descriptive Statistics for Subgroups of Anti-GH Antibodies (Raw Mean HVSDS ± S.D. (N))

	Month 9		Month 15	
HVSDS	Omnitrope	Genotropin	Omnitrope	Genotropin
Absent	6.4808 ± 4.3468 (17)	5.3431 ± 3.2004 (43)	3.2600 ± 2.5990 (27)	
Present	5.6347 ± 3.1976 (23)	6.0885 ± NA (1)	3.6181 ± 2.5385 (14)	

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In this reviewer's opinion, the issues that may impact the overall conclusions of the study are more related to the study design aspects, as mentioned in the section 3.1.1. For example, the to-be-marketed product, OMNITROPE Lyophilized powder with Biochemie API, was compared with a product that is not approved, and was tested only during Months 9-15 of the whole Phase III clinical program. To investigate if the to-be-marketed product itself was efficacious, this reviewer has performed several types of analyses as discussed in the previous sections. Lastly, this reviewer collected some historical data (see section 2.2 above for data sources) from the same recombinant growth hormone family with closely matched study populations, as a supplementary tool, to see if the efficacy of OMNITROPE Lyophilized powder was similar to that of the historical data.

The majority of historical data here are for height velocity (Table 11) and most of them are up to 12 months. Those historical mean height velocities are plotted in Figure 5 along with the growth curve of OMNITROPE Lyophilized powder. It depicts that the mean height velocities of OMNITROPE-treated children at 6- and 12-month time points were within the historical range. To examine the data more closely, the means and 95% confidence intervals at 12 months are plotted in Figure 6. As one can see, most of the information in Figure 6 is around 9 to 12 cm/year and the 12-month confidence interval of height velocity for OMNITROPE is well in it.

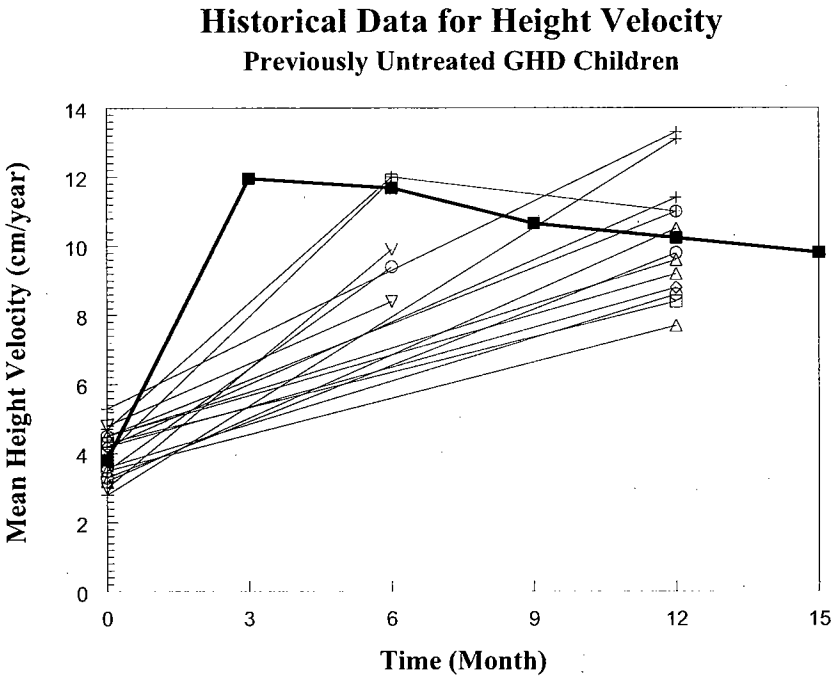
Table 11 – Historical Data of Height Velocity (cm/year) of Previously Untreated GHD Children

Study Number	Treatment	N	Month 0	Month 6	Month 12	C.I. of Last Time Point
NDA 20-280 Genotropin® (from the current submission)						
87-067	0.5-0.7 IU/kg/wk (4 IU/mL)	42	3.6 ± 0.6		8.6 ± 1.1	(8.27, 8.93)
87-084	0.5-0.7 IU/kg/wk (4 IU/mL)	59	2.8 ± 1.0		13.1 ± 2.5	(12.5, 13.7)
86-042	0.5-0.7 IU/kg/wk (4 IU/mL)	16	3.5 ± 1.5		7.7 ± 1.7	(6.87, 8.53)
86-073	0.5-0.7 IU/kg/wk (4 IU/mL)	22	3.3 ± 0.6		9.8 ± 2.4	(8.80, 10.8)
87-062	0.5-0.7 IU/kg/wk (4 IU/mL)	7	3.0 ± 1.3	9.9 ± 2.5		(8.05, 11.8)
KIGS	0.5-0.7 IU/kg/wk (4 IU/mL)	169	4.3 ± 1.8		8.4 ± 2.4	(8.04, 8.76)
KIGS	0.5-0.7 IU/kg/wk (16 IU/mL)	37	4.5 ± 1.3		9.6 ± 2.6	(8.76, 10.4)
NDA 19-676 Nutropin® (from the current submission)						
85-041	0.1 mg/kg SC tiw	44	4.0 ± 1.6	11.9 ± 4.0		(10.7, 13.1)
NDA 20-522 NutropinAQ® (from the current submission)						
L0368g	0.043 mg/kg/day	61	4.7 ± 2.3	12.0 ± 3.5	11.0 ± 2.9	(10.3, 11.7)
NDA 19-640 Humatrope® (from the current submission)						
GDAD/AH	0.18 mg/kg/wk divided in 3 or 7 inj.	158	3.5 ± 1.9	9.4 ± 2.1		(9.07, 9.73)
NDA 21-075 Nutropin Depot (from the prescribing information)						
03-002/004	0.75 or 1.5 mg/kg, 1x or 2x/month	89	4.8 ± 2.4	8.4 ± 2.2		(7.94, 8.86)
Other Historical Data of Nutropin listed under NDA 21-075 (from the published literature)						
List 1	0.1 mg/kg, 3x/week	28	4.2 ± 1.7		8.8 ± 1.8	(8.13, 9.47)
	0.05 mg/kg, 6x/week	23	4.2 ± 1.7		11.4 ± 2.5	(10.4, 12.4)
List 2	37 µg/kg/day, 3-7x/week	523	4.5 ± 2.8		9.2 ± 2.4	(8.99, 9.41)
List 3	19 µg/kg/day	10	4.5 ± 2.8		11.0 ± 3.0	(9.14, 12.9)
List 4	38 µg/kg/day	11	5.3 ± 2.2		13.3 ± 3.9	(11.0, 15.6)
List 5	0.1 mg/kg, 3x/week	22	3.2 ± 1.0		10.5 ± 2.2	(9.58, 11.4)

1. Information in this table came from the sponsor's Table 22 in Mo0-12 report.pdf, the prescribing information of Nutropin Depot, and some published literature.

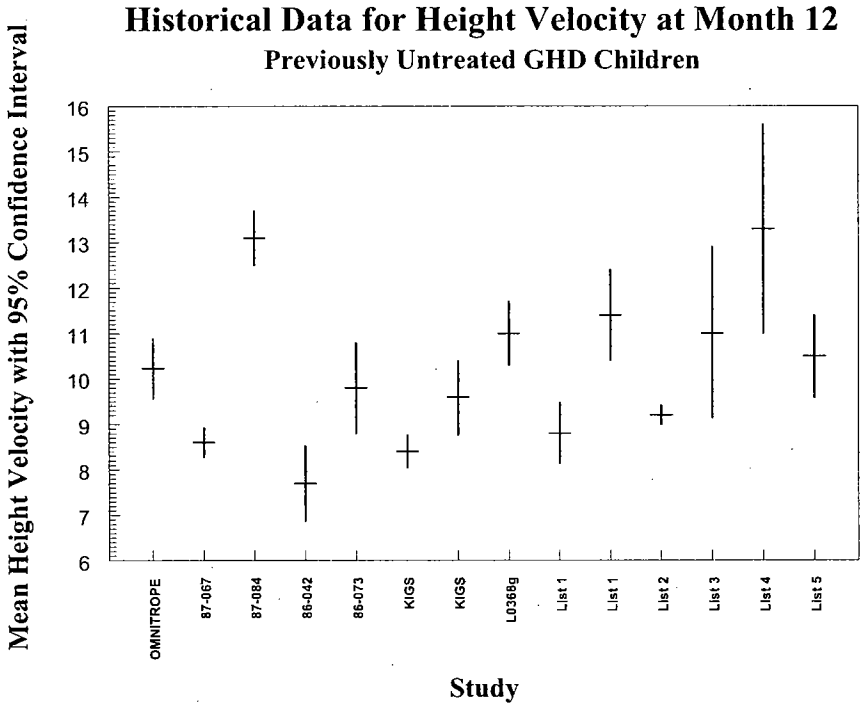
2. List 1 = MacGillivray et. al. (J Clin Endocrin + Metabol, 1996); List 2 = Blethen (1993); List 3 = De Muinck (1994); List 4 = De Muinck (1994); List 5 = Kaplan et. al. (The Lancet, 1986)

Figure 5



Line with solid square is for OMNITROPE Lyophilized Powder, regardless of API manufacturing site.

Figure 6



5.2 Conclusions and Recommendations

After 9 months of treatment with OMNITROPE Lyophilized powder using the API manufactured by Covance, USA, the previously untreated GHD children showed statistically comparable results in heights, growth rates, and related standardized scores when compared with that of the Genotropin®-treated children. Specifically, the observed treatment difference between the 2 study groups for the main efficacy variable of interest, HVSDS, was 0.6440, favoring the OMNITROPE treatment. However, it was also shown that OMNITROPE could be worse than Genotropin® by as much as 0.8303 (less than 1 standard deviation away from the mean of normal children of the same age and gender) according to the 95% lower confidence limit.

The change in height between Months 9 and 15 when subjects were treated with OMNITROPE Lyophilized powder using the API manufactured by Biochemie, Austria, was shown to be similar to that between Months 6 and 9 when OMNITROPE Lyophilized powder using the API manufactured by Covance, USA, was given. In other words, Biochemie API was able to maintain the growth rate seen in the later stage of treatment with Covance API. However, due to the study design limitations, whether Biochemie API could have produced the same steep growth curve as seen in the early stage of treatment with Covance API remains unknown.

It was shown that the height, growth rate, and related standardized scores after 9 months of treatment with OMNITROPE Lyophilized powder were all significantly improved over that at baseline. Similar findings were also observed at Month 15.

Since there was lack of a valid concurrent control for the to-be-marketed drug product (OMNITROPE Lyophilized powder using the API manufactured by Biochemie, Austria), historical data from the current submission, the prescribing information of Nutropin Depot, and some published literature were utilized as a supplementary tool. Despite the fact that there might be some bias in the selection of historical data due to differences in patient population, study design, etc, the mean height velocity and its 95% confidence interval after 12 months of OMNITROPE treatment (9 months with Covance API, then 3 months with Biochemie API) was well within the historical range.

In summary, the data have demonstrated that OMNITROPE Lyophilized powder, regardless of the manufacturing site of API, was efficacious in increasing height and in stimulating height velocity of previously untreated GHD children. The difference in height between the growth hormone treated children and the normal age- and gender-matched children was gradually decreased as the treatment continued. In addition, the rate of growth was reversed

from slower than that of normal children of the same age and gender to faster than that of normal ones during the early stage of the treatment.

If the sponsor had used the to-be-marketed drug product from the beginning of the Phase III clinical program and included a valid control group, the analysis of the data and interpretation of the results would have been much more straightforward.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D., Statistical Team Leader
Ed Nevius, Ph.D., Director of Division of Biometrics II

CC: HFD-510/MJohnson, DOrloff, DRoman
HFD-715/ENevius, TSahlroot, CLiu
HFD-700/CAnello

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia Liu
8/31/04 10:38:54 AM
BIOMETRICS

Todd Sahlroot
9/1/04 10:42:15 AM
BIOMETRICS
concur