Integrated Clinical Trial Report

An Open label, Randomized, Crossover, Patient/Parent Preference Trial of Norditropin® SimpleXx™ versus Humatrope®, Nutropin-AQ® and Genotropin™ in Children with Growth Hormone Deficiency

Norditropin® cartridge
(somatropin rDNA origin for injection)
### Title of Trial

An Open label, Randomized, Crossover, Patient/Parent Preference Trial of Norditropin® SimpleXx™ versus Humatrope®, Nutropin-AQ® and Genotropin™ in Children with Growth Hormone Deficiency

### Trial ID

HGH-2060

### Development Phase

Phase IV

### IND Number (US only)

59726

### Generic Name

Somatropin

### Indication

Long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone

### Investigators

Henry Anhalt, Thomas O. Carpenter, Mitchell E. Geffner, Pinchas Cohen, Larry C. Deeb, Martin B. Draznin, Campbell P. Howard, Stephen LaFranchi, Margaret H. MacGillivray, Robery McVie, Leslie Parker Plotnick, Dorothy Shulman, Eva Tsalikian, David T. Wyatt, Michael E. Gottschalk, Paul Saenger,

### Trial Sites

13 sites in the US (See appendix IV)

### Trial Initiated

May 3, 2000

### Trial Completed

April 4, 2001

### Sponsor

Clinical Development
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540

### Local Trial Manager

George Bright, MD

### Statistician

Bob An, Ph.D.

### Medical Writer

Poushali Mukherjea, Ph.D.

### Report Date(s)

February 2, 2002

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.
Synopsis

**TITLE OF TRIAL**
An Open label, Randomized, Crossover, Patient/Parent Preference Trial of Norditropin® SimpleXx™ versus Humatrope®, Nutropin-AQ® and Genotropin™ in Children with Growth Hormone Deficiency

**INVESTIGATORS**

**TRIAL SITES**
13 trial centers across the United States

**PUBLICATIONS**

**TRIAL PERIOD**
May 3 2000 to April 4 2001

**DEVELOPMENT PHASE**
Phase IV

**OBJECTIVES**
The primary objective was to assess patient and parent preferences for Norditropin® cartridge/NordiPen® as compared to three other marketed formulations of growth hormone administered in their respective delivery devices:
- Humatrope® (HumatroPen), Eli Lilly & Co.;
- Nutropin-AQ®, (vial and syringe), Genentech, Inc. and
- Genotropin® (GenotroPen), Pharmacia Corp.

**METHODOLOGY**
This was an open label, randomized, multi-center, crossover trial of four different formulations of growth hormone. Each patient was enrolled in a 4-week crossover study consisting of a 2-3 week screen period followed by two 2-week treatment periods. During the two treatment periods, each patient received 2 weeks treatment, in randomized order, with Norditropin® cartridge administered with the NordiPen® and 2 weeks treatment with one other growth hormone preparation. Patients did not receive the growth hormone formulation in use at study entry.

**NUMBER OF SUBJECTS PLANNED AND ANALYSED**
One hundred and twenty subjects were planned, 112 were randomized and 109 subjects were included in the efficacy analysis. Three patients were excluded due to non-compliance with the protocol.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION**
Patients (ages 8-17) with short stature treated by the Investigator with human growth hormone (dose 2.5 mg or less daily) (Nutropin®-AQ, Humatrope®, or Genotropin™) for at least two months prior to entering the trial. Patients were willing to allow their parents to prepare, dose and administer all injections.

**DURATION OF TREATMENT**
This was a 4-week crossover study consisting of a 2-3 week screen period followed by two 2-week treatment periods.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER**
Humatrope® 6 and 12 mg cartridges, Eli Lilly & Co.
HumatroPen™, delivery device, Eli Lilly & Co.
Nutropin-AQ®, 10 mg vial, Genentech, Inc.
Genotropin®, 1.5, 5.8 and 13.8 mg cartridges, Pharmacia and Upjohn
GenotroPen® delivery device, Pharmacia and Upjohn

CRITERIA FOR EVALUATION - EFFICACY
The two primary efficacy endpoints were patient and parent preference.
The second endpoint is patient preference. The patient will receive an injection of Norditropin® SimpleXx™ with the NordiPen™ and an injection of one other comparison GH. After receiving both injections, the patient will state if he/she prefers one brand or the other.

CRITERIA FOR EVALUATION - SAFETY
Safety was evaluated by recording adverse events.

STATISTICAL METHODS
No statistical tests were performed for this study. For comparison of Norditropin® cartridge vs each of the other GH formulations, the interaction of the treatment sequence and prior GH therapy was evaluated for consistency across previous GH therapy strata by comparing the proportion of patients favoring Norditropin® cartridge for each of the endpoints. Data from the same treatment sequences were pooled for analysis and descriptive statistics, and the 95% confidence interval was calculated for the proportion of patients/parents in favor of Norditropin® cartridge.

DEMOGRAPHY OF TRIAL POPULATION
A total of 112 patients were enrolled in 13 centers in the USA. Of these, 109 patients completed the 4-week treatment period and were included in the analysis. Three patients were excluded due to non-compliance with the protocol. Forty-six patients had received prior Humatrope® treatment, 27 received Genotropin® treatment, and 39 received Nutropin AQ® treatment. The demographic characteristics of the patients are shown in Table below. There were no clinically significant differences in demographic characteristics when analyzed based on previous therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number treated (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) Mean (SD)</td>
<td>12.4 (2.6)</td>
</tr>
<tr>
<td>Boy/ Girl</td>
<td>75/37</td>
</tr>
<tr>
<td>Race C/B/O (N)</td>
<td>96/9/7</td>
</tr>
<tr>
<td>Height (cm) Mean (SD)</td>
<td>142.8 (15.1)</td>
</tr>
<tr>
<td>BMI (kg/m²) Mean (SD)</td>
<td>18.7 (3.3)</td>
</tr>
<tr>
<td>Weight (kg) Mean (SD)</td>
<td>39.1 (12.9)</td>
</tr>
</tbody>
</table>

C: Caucasian; B: black; O: other
*: The majority (87%) of girls were Tanner Stage 1–3
EFFICACY RESULTS

Parents were asked to select answers “Drug A”, “Drug B” or “No Preference” for the following questions: 1) Overall, which GH preparation did you prefer? 2) Which GH preparation was easiest to prepare? 3) Which GH dose was easiest to measure? 4) Which GH shot was easiest to administer? Patients were asked: 5) Which GH injection did you prefer?

SAFETY RESULTS

- Three patients discontinued from the trial due to non-compliance with protocol.
- Nineteen patients reported 26 adverse events; only three of which were possibly/probably related to study drug.
- No SAEs were reported.
- There were no clinically relevant changes in vital signs, physical examinations, ECGs or laboratory tests.

CONCLUSIONS

- An overwhelming majority of both parents and patients voted in favor of Norditropin® cartridge/NordiPen® compared with any of the other formulations, Humatrope®, Genotropin®, or Nutropin AQ®.
- Parent and patient overall preferences for Norditropin® cartridge vs each of the other formulations were statistically significant, as indicated by the 95% confidence intervals.
- The Norditropin® cartridge formulation was preferred by the majority of parents with regard to the secondary endpoints of ease of preparation, dosage and administration.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

A manuscript submitted for publication has been attached to the synopsis for this market support trial.