

SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Genentech, Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Nutropin AQ®	Volume:	
Name of Active Ingredient: Somatropin (rDNA origin)	Page:	

Title of Study: A Phase II, Multicenter, Randomized, Controlled, Open-Label Study of the Safety and Efficacy of Nutropin AQ® (Somatropin [rDNA Origin] Injection) for the Treatment of Growth Restriction in Children with Cystic Fibrosis

Phase of Development: II

Investigators: A list of investigators is provided in Appendix 16.1.4.

Study Centers: Twenty-four study centers in the United States participated in this study.

Publications: No publications have resulted from this study.

Study Period: 12 April 2004 to 9 May 2007.

Objectives

Primary:

The primary objective was to determine the safety and efficacy of Nutropin AQ in treating growth restriction and increasing lean body mass (LBM) in children with cystic fibrosis (CF) and growth restriction.

Secondary:

The secondary objective was to evaluate the effects of Nutropin AQ treatment on pulmonary function, disease-related exacerbations, and exercise tolerance in children with CF and growth restriction

Methodology

This was a Phase II, multicenter, randomized, controlled, open-label trial of the safety and efficacy of Nutropin AQ administered subcutaneously (SC) daily in pre-pubertal children with CF and growth restriction.

This was an 18-month study. Subjects were randomized in a 1:1 ratio to receive either Nutropin AQ at a daily dose of 0.043 mg/kg (corresponding to a weekly Nutropin AQ dose of 0.3 mg/kg) or to no Nutropin AQ treatment for a period of 12 months. After completion of Month 12, subjects in the Nutropin AQ group discontinued treatment with Nutropin AQ and were observed for approximately an additional 6 months. Subjects enrolled in the control group remained in the control group through approximately Month 18. All subjects were enrolled for a period of 18 months.

A Data Monitoring Committee (DMC) was established to conduct periodic reviews of safety for this open-label study to meet oversight requirements for sites conducting the study in the National Institutes of Health (NIH)-approved Clinical Research Centers.

Number of Subjects (Planned and Analyzed):

Approximately 100 pre-pubertal boys and girls with CF and restricted growth were to be enrolled at approximately 30 sites. Study enrollment was more difficult than anticipated, which would have extended the enrollment period beyond what was feasible. This led to a decision to stop enrollment prior to the targeted 100 subjects. No data were analyzed before stopping enrollment. A total of 68 subjects were randomized at the 24 sites participating in the study.

Diagnosis and Main Criteria for Inclusion:

Subjects were to have CF as diagnosed by sweat or genetic testing, were to be between the ages of 5 and 12 years for girls and between 5 and 13 years for boys, were to be able to perform

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pulmonary function tests in a reproducible manner, were to be $\leq 10^{\text{th}}$ percentile in height, and were to be Tanner Stage 1 at baseline.

Test Product, Dose and Mode of Administration, Batch Number:

Subjects randomized to the Nutropin AQ group received Nutropin AQ at a daily dose (SC injection) of 0.043 mg/kg (corresponding to a weekly dose of 0.3 mg/kg). Lot numbers were L73938, L86961, M03159, M04115, M45013, M11728, M45013, and M67917.

Duration of Treatment:

The total duration of treatment was 12 months.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Subjects randomized to the control group received no Nutropin AQ treatment.

Criteria for Evaluation

Efficacy:

Analyses of primary and secondary efficacy endpoints included all randomized subjects according to their assigned treatment (intent-to-treat). Efficacy comparisons were based on the randomized treatment group. Analyses of other endpoints included all randomized subjects and were performed on the treatment groups as randomized.

Safety:

Safety analyses included all subjects who received at least one injection of Nutropin AQ or, in the untreated control group, subjects who had baseline assessments.

Statistical Methods

Primary Endpoint:

The co-primary efficacy endpoints were change from baseline in height SDS (defined as the SD score calculated as $[\text{height} - \text{mean height}] / \text{height SD}$, where the mean and SD are specific to sex and age) and change in LBM (kg) at Month 12. Height SDS was calculated using sex- and age-specific height reference norms provided by CDC. LBM was measured by DEXA scan. The Nutropin AQ group was compared with the control group using Student's t-test and the Hochberg-Bonferroni method of accounting for multiple comparisons was applied (Hochberg 1988). Using this procedure, if both tests had a p-value < 0.05 , then the comparison for both tests was considered statistically significant. Otherwise, if the test for either endpoint had a p-value < 0.025 , the comparison for that endpoint was considered statistically significant.

Secondary Endpoints:

Unless otherwise specified, each secondary efficacy endpoint was analyzed by comparing the mean change from baseline to Month 12 between treatment groups.

The following were compared between Nutropin AQ and the control group: weight (kg), FVC (L), FEV₁ (L), FEF_{25%-75%} (L/sec), and 6-minute walk distance (m), using the Student's t-test.

The number of exacerbations requiring IV antibiotics from baseline to Month 12 and the number of exacerbations requiring any antibiotics from baseline to Month 12 were summarized by treatment group using descriptive statistics. The start date of each respiratory exacerbation requiring antibiotics was defined as the start date of antibiotic use, provided that there were at least 7 days after the end date of any previous antibiotic treatment. Antibiotic treatment for a pulmonary

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exacerbation that began within 7 days of the previous antibiotic treatment for a respiratory exacerbation was considered as part of the same event. Once subjects were treated with any antibiotics and if the treatment event defined above included IV antibiotics, it was considered an IV antibiotic event. The time to first exacerbation requiring IV antibiotics and the time to first exacerbation requiring any antibiotic were compared between the treatment groups using a log-rank test. Kaplan-Meier survival curves were presented for each group.

Summary of Results and Conclusions

Efficacy and Pharmacokinetic/Pharmacodynamic Conclusions:

In growth-restricted, pre-pubertal CF subjects, Nutropin AQ treatment, at a dose of 0.3 mg/kg/week for 1 year, improved height velocity, as indicated by the change in height SDS. Nutropin AQ treatment was also associated with greater weight gain, resulting, in part, from an increase in LBM. Improvements in growth velocity and increases in weight/LBM did not persist beyond the Nutropin AQ treatment period, as assessed by re-evaluation at 6 months post-treatment (Month 18).

Pulmonary function data, expressed by FEV₁, FVC, and FEF_{25-75%}, did not demonstrate a clear benefit for Nutropin AQ treatment compared with no treatment, except for a statistically significant difference in FVC between treated and untreated subjects at Month 12. Both the untreated and Nutropin AQ groups demonstrated a statistically significant change from baseline to Month 12 in FEV₁ and FVC; only the difference in FVC between study groups was statistically significant, favoring Nutropin AQ. One possible explanation for the absence of significant differences in pulmonary function tests between treated and untreated subjects is the large variability in the tests. The number of subjects required to provide adequate power to detect differences in pulmonary function tests would be larger than would be feasible to enroll. Thus, the study was not powered to demonstrate statistically significant differences in these tests.

No clinically meaningful differences in the number of respiratory tract infections were found between the untreated and Nutropin AQ groups.

The difference (increase) between baseline and Month 12 in the number of meters walked during the 6-minute walk test was significant for the Nutropin AQ group but not for the untreated group. However, no significant between-group differences at 12 months were demonstrated.

Per protocol, only subjects in the Nutropin AQ group had samples taken for antibody testing. Although there was no expectation that a subject naïve to GH treatment would be positive for GH antibodies, 1 subject in the treated group was positive at both baseline and Month 6. The antibody incidence rate of 24%, (8/33) in this study is consistent with past study data, which show an antibody incidence rate of approximately 25–30%. In the Nutropin 86-053 Phase II, open-label, idiopathic short-stature study, the antibody incidence rate was 26% (31/117) based on assays at Month 6.

Safety Conclusions:

The overall number of subjects with at least 1 adverse event was similar in the two groups. There was some imbalance in numbers for the following adverse events: streptococcal pharyngitis (2 subjects in the untreated group vs. 9 subjects in the Nutropin AQ group), nasal congestion and inflammations (14 vs. 4), gastrointestinal signs and symptoms (4 vs. 1), and hyperglycemic conditions (2 vs. 8). Nutropin AQ can induce insulin resistance, and CF can also lead to IGT and the development of CFRD.

Serious adverse events that occurred during the study were mostly pulmonary exacerbations and were reported equally by the two study groups. Two serious adverse events related to

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abnormalities in glucose metabolism were reported in the Nutropin AQ group; one of them led to the subject's discontinuation from the study. Another reason for study discontinuation was intracranial hypertension as evidenced by papilledema (n = 1); 9 subjects discontinued from the study on their own request. One subject died because of respiratory failure, which occurred during the 6-month observation period 1 month after discontinuing Nutropin AQ; this was not considered by the investigator to be related to study drug.

Overall Conclusions:

In growth-restricted pre-pubertal CF patients, Nutropin AQ treatment at a dose of 0.3 mg/kg/week for 1 year improved height velocity, as indicated by the change in height SDS. Nutropin AQ treatment was also associated with greater weight gain, resulting, in part, from an increase in LBM. Improvements in growth velocity and increases in weight/LBM did not persist beyond the Nutropin AQ treatment period as assessed by re-evaluation at 6 months after treatment.

Three subjects in the untreated group and 1 subject in the Nutropin AQ group used megestrol acetate as an appetite stimulant. Megestrol is a progestin, a sex steroid, and could possibly have an influence on growth. Two subjects in each study group were reported to use a CNS stimulant (methylphenidate) for ADHD. In a recent NCGS analysis in hundreds of subjects with ADHD, no difference was observed in the first-year response to GH treatment between a group using CNS stimulants for ADHD and a control group with GH treatment only (data presented at Pediatric Academic Societies' 2008 Annual Meeting). Many subjects with CF are undernourished and this can, of course, interfere with growth. This is true for untreated CF subjects, but probably also for GH-treated CF subjects. In this study, the mean height velocity for the first year was 8.2 cm/year for the Nutropin AQ group. In a previous Genentech-sponsored study, GH-deficient subjects using the same dose had a mean height velocity of 10.5 cm/year. This apparent reduction in growth response may be indicative of a certain amount of GH resistance, which has also been described in other GH-treated populations with chronic illnesses like chronic kidney disease where the first-year height velocity is also lower.

The results for most of the secondary endpoints failed to show significant differences between the untreated and Nutropin AQ groups. The pulmonary function data, as expressed by the pulmonary function tests (FEV₁, FVC and FEF_{25-75%}), did not demonstrate a clear benefit for Nutropin AQ treatment. FEV₁ and FVC demonstrated statistically significant changes from baseline to Month 12 for both the untreated and the Nutropin AQ groups. A statistically significantly larger increase in FVC was seen in the Nutropin AQ group compared with the untreated group for the change from baseline to Month 12, but not for other pulmonary function measures. Different approaches to expressing pulmonary function were examined, including absolute volumes and percent predicted values of the three selected pulmonary function tests. One reasonable explanation for the lack of benefit of Nutropin AQ is the considerable variability seen in these measures. This was acknowledged to be likely a priori, and the sample size required to power the study would have been prohibitive.

No significant differences in the number of respiratory tract infections were found between the untreated and Nutropin AQ groups.

The difference (increase) between baseline and Month 12 in the number of meters walked during the 6-minute walk test was significant for the Nutropin AQ group, but not for the untreated group. However, no significant difference between the groups in change from baseline was demonstrated.

Overall, Nutropin AQ was well tolerated. No clinically significant differences in adverse events or serious adverse events were found between the two study groups, except for a higher incidence of abnormalities in glucose metabolism and reports of streptococcal pharyngitis in the Nutropin AQ group. The higher incidence of glucose homeostasis abnormalities in the Nutropin AQ group was not unexpected. In general, abnormalities in glucose metabolism are part of the CF disease,

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and become more frequent and prominent as patients with CF get older. Because Nutropin AQ can induce insulin resistance, which is reversible in most cases, and given the time-dependent inherent glucose abnormalities of CF, it is not surprising to find subjects with glucose homeostasis abnormalities during an 18-month observation period. The differences in reported streptococcal pharyngitis may have resulted from ascertainment bias, with subjects in the Nutropin AQ group being under closer scrutiny compared with subjects in the untreated group. No good explanation exists for the higher number of nasal congestion and inflammations in the untreated group. Thyroid function assessment by free T4 and TSH showed no abnormalities at Month 12. CF subjects are thought to have normal thyroid function in general, given that iodine-containing expectorants are no longer used.

The significant increases in height SDS, weight, and LBM in during the 12 months of treatment in this study could be expected to increase lung volume, which might contribute to a better overall outcome in these patients.

Date of the Report

14 April 2008