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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Genotropin® / Somatropin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00555009

PROTOCOL NO.: A6281289

PROTOCOL TITLE: Placebo-Controlled Trial on the Efficacy of Growth Hormone Replacement Therapy in Patients With Growth Hormone Deficiency After Traumatic Brain Injury

Study Centers: A total of 19 centers recruited subjects: Italy (8), France (3), Spain (3), Sweden (2), Netherlands (1), and the United Kingdom (2); and a total of 7 centers enrolled subjects: Italy (2), Sweden (2), France (1), Spain (1), and the United Kingdom (1).

Study Initiation and Completion Dates: 06 March 2008 to 20 January 2009. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives: The primary objective of this study was to establish the effects of growth hormone (GH) replacement in subjects with severe GH deficiency after traumatic brain injury (TBI) on cognitive function.

The secondary objectives of this study were to establish the effect of GH replacement in subjects with severe GH deficiency after TBI on lean body mass and fat mass, Extended Glasgow-Outcome-Scale (GOS-E), Short-form (SF)-36 Health Survey, Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaires and cardiovascular risk profile, as well as to demonstrate the safety of GH treatment in this subject population.

METHODS

Study Design:

This study was to enroll approximately 120 subjects and was to be comprised of 2 phases: a screening phase and a 36-week, multi-center, double-blind, placebo-controlled phase. The screening phase was to last for up to 1 month for subjects who had suffered a TBI and had proven (had undergone dynamic testing within the last 6 months) or suspected (must have been confirmed by dynamic testing during the screening period) GH deficiency (GHD). All subjects who had dynamic testing within 1 year of the brain trauma required retesting prior to

enrollment into the study to ensure that their GHD had not resolved. Subjects may have had other hormone deficiencies, but must have been stabilized by treatment for at least 3 months prior to screening. All subjects must have had proven adequate adrenal reserves if not on sufficient replacement therapy. The double-blind treatment phase was to be 36 weeks during which eligible subjects were to receive placebo or recombinant GH (Genotropin® [somatropin]) in a 1:1 randomization ratio. Subjects randomized to the placebo group were injected subcutaneously (SC) in the same way as somatropin.

Number of Subjects (Planned and Analyzed): A total of 120 subjects were planned to be enrolled (approximately 120 subjects, and, due to early termination of the study, only 10 subjects were enrolled: 4 in the somatropin group and 6 in the placebo group.

Diagnosis and Main Criteria for Inclusion: Subjects were to be males and females between the ages of 18 and 55 years, inclusive. Subjects must have had a previous TBI (more than 1 year and less than 20 years) prior to the screening visit, a GOS-E score ≥5, and proven severe GH deficiency as diagnosed by dynamic testing within the last 6 months. Subjects must have had either a proven isolated GH deficiency without other pituitary hormone insufficiencies or have been receiving stable hormone replacement therapy (excluding GH replacement) for other pituitary dysfunctions, in particular hypothyroidism and hypocortisolism, for at least 3 months prior to screening. Subjects must not have had a history of cranial irradiation, GH replacement therapy in the last 12 months, a history of hypothalamic/pituitary disease which was diagnosed prior to TBI, a history of dementia unrelated to TBI, a history of benign intracranial hypertension, or cognitive or neuromuscular impairment too severe to allow assessment with the CogState™ battery.

Study Treatment: Subjects were randomized to placebo or somatropin. All subjects received somatropin cartridges and a Genotropin Pen 5.3 (a reconstitution device used to mix the diluent and powder within the 2-chamber cartridge, which when mixed together made 1 mL of solution) for self-administration SC on a daily basis for 36 weeks.

Subjects randomized to receive treatment with somatropin were initiated at a dosage of 0.2 mg/day SC in men and 0.3 mg/day SC in women. Insulin-like growth factor I (IGF-I) levels were measured by the central laboratory which was unblinded to the treatment groups to allow dose adaptation. Target IGF-I levels in the somatropin -treated group were between +1 SD (standard deviation) and +2 SD of the age-adjusted and sex-adjusted reference range. Dose adaptation took place monthly until the subject stabilized in the upper half of the normal range. If the investigator diagnosed GH overdose symptoms, they may have chosen to forgo the dose increase at their discretion. Once stable, the subject underwent dose adaptation checks at scheduled visits.

Subjects randomized to the placebo group were treated with placebo which was injected SC in the same way as somatropin. To maintain the blind, the subject was measured in the same way as the treatment group for IGF-I levels. The central laboratory instituted a sham dose titration for placebo subjects. This ensured the continued blinding of study participants and personnel.

Efficacy Evaluations: The primary efficacy evaluation measured the difference in the CogState cognitive function test between the treatment and placebo groups from Baseline to Week 36. Secondary efficacy evaluations included the change in CogState cognitive function tests from Baseline at Weeks 12 and 24, the change from Baseline at Week 36 in lean body mass and fat mass as measured by Dual Energy X-ray Absorptiometry (DXA), the summaries of each item of the SF-36, the change from Baseline at Week 36 of the AGHDA, the change from Baseline at Week 36 in GOS-E scores, the change from Baseline in the cardiovascular risk factors low-density lipoprotein, high-density lipoprotein, total cholesterol, and triglycerides, and the change from Baseline in weight and waist circumference.

Safety Evaluations: Safety evaluations included clinical monitoring, physical examination, vital signs (heart rate, blood pressure), fasting blood glucose, HbA1c levels, adverse events (AEs), and safety laboratory tests.

AEs were encoded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA – Version 11.1).

Statistical Methods: Due to poor recruitment, the study was terminated early; therefore, only minimal safety data was summarized (discontinuations due to AEs and treatment-emergent AEs). All other data collected (including efficacy data) was presented as subject listings only. Safety analyses were descriptive in nature. The safety population included all subjects who received at least 1 dose of the study drug. Disposition and baseline demographics were summarized using summary statistics. All other baseline data were listed.

RESULTS

Subject Disposition and Demography: Due to poor recruitment, the study was terminated early. Only 10 subjects were enrolled, and only 2 of the subjects (both in the somatropin group) completed the 36-week double-blind treatment phase (Table S1). Seven subjects discontinued the study due to termination of the program by the sponsor. One subject in the placebo group discontinued due to no longer being willing to participate in the study.

Table S1. Discontinuations from Study

Number of Subjects	Somatropin (N=4)	Placebo (N=6)
Discontinuation		
Related to Study Drug	2	5
Other [a]	2	5
Not Related to Study Drug	0	1
Subject No Longer Willing to Participate in Study	0	1
Total	2	6

[a] Refers to those subjects whose enrollment was terminated by the sponsor

All subjects were analyzed for AEs, and all but 3 (from the placebo group) were analyzed for labs.

Subjects in this study ranged from 19 to 54 years of age. All subjects in the study were male. Eight of the subjects were white (4 subjects in each group) and 2 subjects were Asian (both in the placebo group). The average weight of subjects was 75.5 kg in the somatropin group and 83.6 kg in the placebo group, and the weight of subjects ranged from 60.1 kg to 93.0 kg. Additionally, all subjects had the primary diagnosis of GH deficiency, and a secondary diagnosis of TBI, as required in the inclusion criteria.

Efficacy Results: Due to the early termination of the study, efficacy analyses were not completed.

Safety Results: There were no deaths, serious adverse events (SAEs), discontinuations due to AEs, or dose reductions/temporary discontinuations due to AEs during the study. There were 4 subjects who experienced a total of 4 AEs during this study, 2 of which were considered treatment-related (somnolence and arthralgia). All AEs were experienced in the somatropin group, and none in the placebo group. Three of the AEs were considered mild in severity, and 1 was considered moderate (lower limb fracture, not related to study drug). An overview of treatment-emergent AEs and treatment-related treatment-emergent AEs is provided in Table S2.

Table S2. Incidence of Adverse Events

	Number of Subjects			
	Somatropin (N=4)		**Placebo (N=6)**	
MedDRA System Organ Class Preferred term	All Causality	Treatment Related	All Causality	Treatment Related
Subjects with adverse events	4	2	0	0
General disorders and administration site conditions	**1**	**0**	**0**	**0**
Pyrexia	1	0	0	0
Injury, poisoning, and procedural complications	**1**	**0**	**0**	**0**
Lower limb fracture	1	0	0	0
Musculoskeletal and connective tissue disorders	**1**	**1**	**0**	**0**
Arthralgia	1	1	0	0
Nervous system disorders	**1**	**1**	**0**	**0**
Somnolence	1	1	0	0
Total number of adverse events	4	2	0	0

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row.
MedDRA = Medical Dictionary for Regulatory Activities, v. 11.1

CONCLUSION: This study was terminated early due to poor recruitment.

- Overall, somatropin was well-tolerated: no safety issues of concern emerged in this study.