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

PROTOCOL NO.: A6281282

PROTOCOL TITLE: Prospective, Randomized, Double Blind Placebo-Controlled Trial on the Efficacy of Growth Hormone Replacement Therapy in Adult Patients With Isolated Growth Hormone Deficiency (PRO ISO-GHD Study)

Study Centers: Two centers in Germany took part in the study and screened subjects for enrollment.

Study Initiation and Final Completion Dates: 26 May 2008 to 17 October 2008.
The study was terminated prematurely on 15 December 2008.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To determine the effects of 52 weeks of growth hormone (GH) replacement therapy on visceral fat mass in adult subjects with isolated GH deficiency (IGHD).

Secondary Objectives:

- To determine the change in quality of life related to GH substitution assessed by disease and non-disease specific questionnaires (Quality of Life-Assessment of Growth Hormone Deficiency in Adults [QoL-AGHDA], 36-Item Short-Form Health Survey [SF-36], and European Quality of Life-5 Dimension [EQ-5D])

- To determine the cognitive function assessed by Verbaler Lern- und Merkfähigkeitstest (VLMT) and by Testbatterie zur Aufmerksamkeitsprüfung (TAP) subtests ‘Alertness’ and ‘Go/NoGo’

- To determine the determination of body fat by anthropometric measurements

- To determine the assessment of cardiovascular risk markers and replacement therapy on visceral fat mass in different subgroups of adult subjects with IGHD

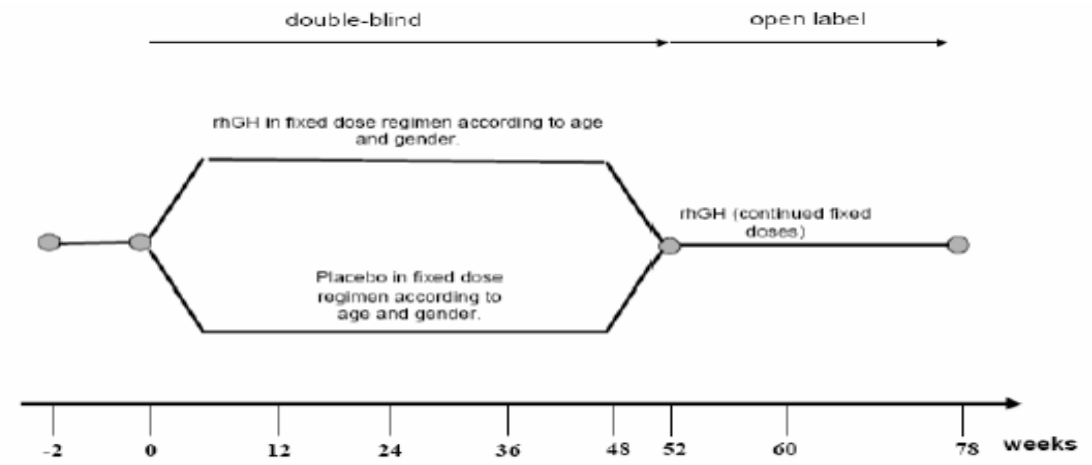
METHODS

Study Design: This was a Phase 3, 52-week, prospective, randomized, placebo-controlled, double blind multi-center study, followed by a 26 week open extension phase (Figure 1 and Table 1).

Subjects with proven or suspected GH deficiency who did not have adrenocorticotropic hormone, thyroid-stimulating hormone, and/or luteinizing hormone/follicle stimulating hormone deficiencies were to be screened and their GH deficiency was to be tested by an insulin tolerance test (ITT). GH deficiency was to be confirmed in case peak GH <3 ng/mL (<5 ng/mL in subjects under 25 years of age respectively). At Baseline (Week 0) eligible subjects with proven isolated GH deficiency were to be randomized in a double-blind manner to receive either placebo or recombinant human GH in a fixed dose regimen according to age and gender, based on average dose data for these parameters from the Kabi International Metabolic Study (KIMS) database. Subjects were to start with half of the fixed dose and were to be adjusted to the full dose after 4 weeks. Subjects were to be subjected to further dose adjustment if their insulin-like growth factor-I (IGF-I) levels exceeded by 2 time standard deviation (+2 SD) or stayed below mean levels according to IGF-I reference data. At Week 52, treatment could be continued in an open label extension phase, where subjects from both groups were to be treated with GH.

The hypothesis was that 52 weeks of GH replacement in subjects with isolated GH deficiency has significant effects on body composition, ie, decreased visceral fat mass. In addition, the study was to provide data about change in quality of life related to GH substitution, measured by a disease specific questionnaire, change of cognitive performance, in cardiovascular risk markers and anthropometric measurements for determination of body fat.

Figure 1. Study Design



rhGH = recombinant human growth hormone.

Table 1. Schedule of Activities

Protocol Activity			Double-Blind Treatment					Open Label Extension Phase		
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	-2 Weeks	**Week 0**	**Week 4**	**Week 13**	**Week 26**	**Week 39**	**Week 52 EOS Visit**	**Week 56**	**Week 65**	**Week 78 EOS Visit**
Informed consent	X									
Medical history and physical examination	X									
Testosterone, LH, FSH	X						X			X
Cortisol, TSH, ft3, ft4	X			X	X		X			X
GH-functional testing with laboratory diagnosis: ITT (fasting)	X[a]									
Hematology	X				X		X			X
Blood chemistry (including HbA1c)	X				X		X			X
Pregnancy test (females only)	X						X			
Check inclusion/exclusion criteria	X	X								
Randomization		X								
Medication dispense		X	X	X	X	X	X	X	X	
Premedication	X									
Compliance check (empty vials)			X	X	X	X	X	X	X	X
MRI (visceral fat mass)		X					X			X
CV risk factors (TSH, HDL, LDL fasting, NT pro BNP)	X[a]						X[a]			X[a]
Anthropometric measurements (height, weight, waist)[b]		X		X	X	X	X		X	X
Vital signs (HR, RR)		X			X		X		X	X
Adverse event assessment	X	X	X	X	X	X	X	X	X	X
Fasting glucose and insulin	X[a]						X[a]			X[a]
Concomitant medication	X	X	X	X	X	X	X	X	X	X
HRQL (QoL-AGHDA)	X	X			X		X			X
HRQL (SF-36, EQ-5D)	X	X			X		X			X
VLMT		X			X		X			X
TAP (Alertness and Go/NoGo)		X			X		X			X
Biomarker analysis of IGF-I (for dose adaptation)		X[c]		X[d]	X	X	X[c]	X[c]	X	X[c]
IGFBP3 analysis		X		X			X			X

CV = cardiovascular; EOS = end of study; EQ-5D = European Quality of Life-5 Dimension; FSH = follicle stimulating hormone; ft3 = free triiodothyronine; ft4 = free thyroxine; GFBP3 = growth factor-binding protein 3; GH = growth hormone; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HR = heart rate; HRQL = health related quality of life; IGF-I = insulin-like growth factor-I; ITT = insulin tolerance test; LDL = low-density lipoprotein; LH = luteinizing hormone; MRI = magnetic resonance imaging; NT pro BNP = N-terminal pro brain natriuretic peptide; QoL-AGHDA = Quality of Life-Assessment of Growth Hormone Deficiency in Adults; RR = respiratory rate; SF-36 = 36-Item Short-Form Health Survey; TAP = testbatterie zur Aufmerksamkeitsprüfung; TG = triglycerides; TSH = thyroid stimulating hormone;

Table 1. Schedule of Activities

VMLT = Verbaler Lern-und Merkfähigkeitstest.
a. Subject had to be fasting.
b. Height was measured at Visit 1 only.
c. IGF-I value was not used for dose adaptation.
d. Subject was informed about dose adaptation by phone.

Number of Subjects (Planned and Analyzed): A total of 50 subjects were planned to be randomized. Due to recruitment difficulties, the study was terminated before any subjects were given study drug; hence no analysis was done.

Diagnosis and Main Criteria for Inclusion: Male and/or female subjects between 18 to 65 years of age having an isolated GH deficiency determined by a previously performed GH stimulation test or the measurement of an IGF-I value below -2 SD according to age and sex adjusted reference data were included in the study.

Subjects with IGHD by childhood onset, diabetes mellitus type 1 or 2, anterior pituitary disease, severe renal, hepatic or cardiac diseases that could cause clinically relevant metabolic changes regarding visceral fat mass or could influence, in the judgment of the Investigator were excluded from the study.

Study Treatment: Nine subjects were enrolled in the study. However, they did not meet the inclusion criteria. Therefore, no subject was randomized or followed up in the study.

Efficacy and Safety Endpoints:

Primary Endpoint: The primary endpoint of this study was the change of visceral fat mass assessed by magnetic resonance imaging scanning after 52 weeks.

Secondary Endpoints:

- Change in quality of life (QoL) from Baseline to Week 52 and additionally to Week 78, assessed by QoL-AGHDA, SF36 and EQ-5D questionnaire
- Change in visceral fat mass in subgroups (Subgroup 1: IGHD due to surgery and/or irradiation of pituitary adenoma and suprasellar tumors; Subgroup 2: history of traumatic brain injury [TBI] or subarachnoid hemorrhage [SAH]) after 52 and 78 weeks
- Change in cardiovascular risk factors (high density lipoprotein, low density lipoprotein, triglycerides, N-terminal pro brain natriuretic peptide) from Baseline to Week 52 and 78
- Change from Baseline in anthropometric parameters: height, weight, waist circumference after 52 and 78 weeks
- Change in alertness (sustained attention) and memory from Baseline to Week 52 and additionally to Week 78, assessed by neuropsychological tests
- Change in executive function and memory in subgroups (Subgroup 1: IGHD due to surgery and/or irradiation of pituitary adenoma and suprasellar tumors; Subgroup 2: history of TBI or SAH) after 52 and 78 weeks
- Change from Baseline to Week 52 and 78 in vital signs (blood pressure, heart rate)
- Change from Baseline to Week 52 and 78 in safety laboratory assessments

- Change in Homeostasis Model Assessment-Index from Baseline to Week 52 and additionally to Week 78

- Incidence and number of adverse events (AEs)

Safety Evaluations: Safety evaluations planned for this study included AE monitoring, clinical laboratory tests, physical examination, vital signs (blood pressure and pulse rate), body height and weight, waist circumference, and ITT at specified time during the study (Table 1).

No safety evaluations were performed in this study as the study was terminated before any subjects were given study drug.

Statistical Methods: The study was terminated before any subjects were given study drug. Therefore statistical method was not applicable.

RESULTS: The study was terminated on 15 December 2008 due to poor recruitment. Although 9 subjects were enrolled, no subject was randomized nor treated with somatropin. No safety reasons contributed to the termination. There were no safety or efficacy data to report for this study and therefore no results are presented here.

CONCLUSION:

Due to recruitment difficulties, the study was terminated before any subjects were given study drug. Therefore no study data are reported and no conclusion can be made.