Sponsor

Novartis

Generic Drug Name

Octreotide acetate

Therapeutic Area of Trial

Acromegalic patients only partially responsive to somatostatin analog monotherapy

Approved Indication

- Treatment of acromegaly
- Treatment of diarrhea and flushing episodes associated with carcinoid syndrome
- Treatment of diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas)

Study Number

CSMS995BDE16

Title

A multicenter, single arm, proof of concept study to investigate in a first stage the efficacy of a combination therapy of octreotide LAR and cabergoline, optionally followed by combination of octreotide LAR and pegvisomant, in acromegalic patients only partially responsive to somatostatin analog monotherapy.

Phase of Development

Phase III

Study Start/End Dates

01-Mar-2006/12-Jan-2010

Study Design/Methodology

This was a Phase III, multi-center, single-arm, proof of concept study of patients who were only partially responsive on first hand to somatostatin analog monotherapy and on second hand to the combination octreotide LAR and cabergoline. Patients who had been only partially responsive to chronic treatment with 30mg/month of octreotide LAR at least 6 months were entered in the first part of the study. During this first part, patients received 30mg octreotide LAR once every 4 weeks and a final dose of 3.5mg cabergoline per week if tolerated (cabergoline was uptitrated from a starting dose of 0.5mg per week over a period of 2 months). Treatment duration was 8 months for a patient whose growth hormone (GH) and insulin like growth factor (IGF-I) levels

were under control. GH and IGF-I were measured at the beginning of the study, after 2, 4, 5, and 8 months.

Subsequently, patients not responding to the combination octreotide LAR and cabergoline after 5 months of therapy received 30mg octreotide LAR once every 4 weeks and pegvisomant 70 mg/week. The study was stopped after 3 months of combination octreotide LAR and pegvisomant.

The study was prematurely discontinued by Sponsor's decision dating on 13-Oct-2009 with 20 patients recruited out of 100 planned due to insufficient recruitment.

Centres

9 centers in Germany and 1 center in Turkey

Publication

None

Objectives

Primary objective(s)

- To demonstrate either the efficacy of an 8-month treatment of a combination therapy with octreotide LAR and cabergoline, or a 5-months treatment with the former combination optionally followed by a further 3-month treatment with octreotide LAR and pegvisomant for patients not responding to the former combination, respectively, to reduce GH and IGF-I levels in acromegalic patients that are only partially responsive to octreotide LAR monotherapy

Secondary objective(s)

- To evaluate the ability of a combination therapy with octreotide LAR and cabergoline to reduce GH and/or IGF-I levels (quantitative analysis) and to normalize GH and/or IGF-I levels in acromegalic patients that are only partially responsive to octreotide LAR monotherapy and the ability of the combination therapy with octreotide LAR and pegvisomant to reduce IGF-I levels by 25% and to normalize IGF-I levels in acromegalic patients that are only partially responsive to octreotide LAR and cabergoline
- The combination therapy with octreotide LAR and cabergoline optionally followed by octreotide LAR and pegvisomant were investigated for their ability to relieve clinical symptoms of acromegaly, their safety and tolerability, their effect on tumor size and their effect on the quality of life

Test Product (s), Dose(s), and Mode(s) of Administration

	Octreotide LAR	Cabergoline	Pegvisomant
Dosage information	30 mg/month	3.5 mg/week (up-titrated from starting dose of 0.5 mg/week)[1]	70mg/week
Mode of administration	Intramuscular injection	Oral	Subcutaneous injection

[1] As specified by protocol amendment 2 (dated 01-Feb-2006), as soon as patients received a dose greater than 1mg cabergoline per week (weeks 3 – 32), this dose was to be administered over several days

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable.

Criteria for Evaluation

Efficacy:

Primary variables

- Therapeutic response defined as a reduction of at least 25%, of both GH_{nadir} and IGF-I levels or normalization of both GH and IGF-I against baseline measurements at V1 (Baseline)

Secondary variables

- Time profile of GH and IGF-I; normalization of GH and IGF, clinical symptoms of acromegaly, tumor size (MRI)
- Health-related quality of life data were collected using the Karnofsky index, the AcroQoL and the SF-36 questionnaires

Safety and tolerability

- Frequency of adverse events and on the number of laboratory values that were evaluated as clinically significant by the investigator. Echocardiography was performed on a routine basis

Pharmacology

Not applicable

Statistical Methods

According to the protocol, a safety population, an intent-to-treat population (ITT) and a per-protocol population were defined. Due to the number of subjects resulting from the premature discontinuation of the study, all analyses were performed solely for the safety (demographics and background characteristics, medication, safety analyses) and ITT populations (efficacy) and exclusively by means of descriptive statistics. No per-protocol analysis was performed.

Data from all centers that participated in this study were combined, so that an adequate number of patients were available for analysis. Data were summarized with respect to demographic and baseline characteristics (including disease characteristics), efficacy observations and measurements and safety observations and measurements. Frequency distributions were provided for categorical variables. Descriptive statistics for continuous variables included mean, standard deviation, minimum, median and maximum, for selected variables in addition coefficient of variation (CV) and two-sided 95%-confidence intervals (95%-CI) were calculated.

No interim analyses were planned or performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male or female patients (aged 18 years or older) with prior surgery of micro- or macroadenoma of the pituitary who had at least 6 months chronic treatment with Somatostatin ana-

logues and the last 3 months treated with the highest dose of Somatostatin analogues (30 mg octreotide LAR or 120 mg lanreotide) were included in this study.

- Lack of suppression of GH nadir to < 1.0 µg/L, after oral administration of 75 g of glucose (OGTT) and IGF-I levels above the normal value ± 2 SD (adjusted for age and gender) proven within 4 weeks prior to visit 1
- If acromegaly symptoms were inadequately controlled as defined in the acromegaly comorbidities and symptom evaluation (as judged by the investigator), an abnormal GH or IGF-I-value as defined in the previous criterion was sufficient.

Exclusion Criteria:

- Requirement of surgery for recent significant deterioration in visual fields or other neurological signs, which are related to the pituitary tumor mass; radiotherapy planned or radiotherapy for acromegaly beside conventional radiotherapy
- Symptomatic cholelithiasis that was clinically relevant
- Psychosis in anamnesis
- Severe cardiovascular dysfunction, relevant liver disease, any medical conditions contraindicated in the Summary of Product Characteristics of all study drugs
- Abnormal clinical laboratory values considered by the Investigator to be clinically significant and which could affect the interpretation of the study results
- Any current or prior medical condition that could interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator; patients with a complete resistance to Somatostatin analogues therapy
- Pregnant or nursing (lactating) women, women of child-bearing potential (WOCBP)
- Treatment with dopamine agonists within the last 6 months
- Prior treatment with GH-receptor-antagonists
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half lives of enrollment, whichever was longer
- History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures
- History of malignancy of any organ system within the past 5 years (with the exception of localized basal cell carcinoma of the skin)
- Inability to complete the entire study for any reason, renal insufficiency, Raynaud-Syndrom or gastrointestinal ulcers/bleeding

Number of Subjects

	Total
Number (%) of patients	
Screened	20
Treated	20
Discontinued	3
Completed	17

Demographic and Background Characteristics

	Safety population N = 20
Gender - n (%)	
Male	11 (55.00%)
Female	9 (45.00%)
Race - n (%)	
Caucasian	20 (100.00%)
Black	0 (0.00%)
Oriental	0 (0.00%)
Other	0 (0.00%)
Mean age (years)	47.1
Standard deviation (SD)	12.2
Range	24.0, 69.0

Primary Objective Result(s)

Number of patients defined as responders (Intention to Treat population; N=20)

Variable		N (%)	95% CI
Responder			
	No	13 (65.00%)	[40.78% - 84.61%]
	Yes	7 (35.00%)	[15.39% - 59.22%]

Secondary Objective Result(s)

Summary statistics for GH by visit and timepoint
Population: Intent To Treat (N=20)

Visit	Timepoint [min]	Statistics [ng/ml] N	Mean	SD	Min	Median	Max	CV [%]
Screening	0	20	2.81	2.28	0.60	1.90	8.00	81.43
	30	20	2.39	2.09	0.10	1.75	7.60	87.41
	60	20	2.21	1.79	0.10	1.60	6.80	81.39
	90	19	2.21	1.67	0.30	1.80	7.20	75.81
	120	20	2.03	1.43	0.50	1.80	7.00	70.22

Visit	Timepoint [min]	Statistics [ng/ml] N	Mean	SD	Min	Median	Max	CV [%]
Week 8	0	14	1.91	1.86	0.40	1.65	7.80	97.48
	30	12	1.62	1.80	0.40	1.05	6.90	111.46
	60	12	1.38	1.39	0.30	1.05	5.60	100.82
	90	12	1.30	1.23	0.40	0.90	4.90	94.89
	120	12	1.14	0.94	0.40	0.65	3.60	82.46

Visit	Timepoint [min]	Statistics [ng/ml] N	Mean	SD	Min	Median	Max	CV [%]
Week 16	0	12	2.17	2.04	0.30	1.00	6.50	94.20
	30	12	1.52	1.28	0.20	1.00	4.60	84.43
	60	12	1.50	1.52	0.30	1.10	5.90	101.58
	90	11	1.39	1.09	0.30	1.00	3.90	78.19
	120	12	1.26	0.87	0.40	1.05	3.20	69.48

Visit	Timepoint [min]	Statistics [ng/ml] N	Mean	SD	Min	Median	Max	CV [%]
Week 20	0	4	2.73	2.00	1.00	2.30	5.30	73.30
	30	4	2.75	1.87	1.20	2.35	5.10	67.87
	60	4	2.63	1.80	1.10	2.40	4.60	68.53
	90	4	2.48	1.92	0.70	2.30	4.60	77.74
	120	4	2.55	2.14	0.50	2.65	4.40	84.02

Visit	Timepoint [min]	N	Statistics [ng/ml] Mean	SD	Min	Median	Max	CV [%]
Week 28	0	5	5.22	8.10	1.30	1.80	19.70	155.12
	30	5	4.42	6.81	1.10	1.40	16.60	154.12
	60	5	4.20	6.99	0.70	1.20	16.70	166.49
	90	5	4.18	7.12	0.70	0.90	16.90	170.26
	120	5	3.94	6.86	0.50	0.90	16.20	174.06

Visit	Timepoint [min]	N	Statistics [ng/ml] Mean	SD	Min	Median	Max	CV [%]
Week 32 / prem discont	0	20	2.75	2.83	0.20	1.65	11.50	102.92
	30	19	2.38	2.89	0.50	1.80	12.60	121.55
	60	20	2.13	3.08	0.10	1.10	13.60	144.46
	90	20	1.98	3.22	0.10	0.90	14.50	162.90
	120	20	1.84	2.72	0.20	0.90	12.20	147.66

Log transformation for IGF-I by visit-ITT (N=20)

		Statistics [ng/ml]		
Visit	N	Geometric mean	Geometric SD	Geometric CV
Screening	20	408.116	1.663	1.00125
Week 8	16	290.150	1.589	1.00160
Week 16	12	304.721	1.723	1.00179
Week 20	6	328.424	1.817	1.00182
Week 28	5	279.242	1.569	1.00161
Week 32 / prem discont	20	269.793	1.724	1.00202

- Concerning acromegaly-related co-morbidities and symptoms, the percentage of patients without arrhythmia, cerebrovascular disease, acromegalic growth, arthralgia, arthropathy, carpal tunnel syndrome, hypopituitarism, impaired glucose tolerance, impaired respiratory function, obstructive sleep apnea syndrome, paraesthesia, and sweating tended to be higher at post screening visits compared to screening. The largest difference was seen for acromegalic growth.
- Visual field assessment was normal for the majority of patients both at screening (75.00%) and at Week 32 / premature discontinuation (70.00%). For the vast majority of patients (85.00%) the current status had not changed.
- The results for subscales of the AcroQoL were comparable between screening and week 32 / premature discontinuation.
- In the SF-36 Health Survey, the values for the scales role physical, and role emotional decreased, general health, vitality and mental health score improved, and the scales physical functioning, bodily pain, social functioning, summary measures of physical health and summary measures of mental health remained roughly the same during the course of the study.

Safety Results

Number (%) of patients with most frequent AEs (in >5% of patients)

	Safety population
Total number (%) of patients	20
Number (%) of patients with AE(s)	14 (70.00%)
AE preferred term	n (%)
Glucose tolerance impaired	3 (15.00%)
Nausea	3 (15.00%)
Arthralgia	2 (10.00%)
Back pain	2 (10.00%)
Constipation	2 (10.00%)
Fatigue	2 (10.00%)
Headache	2 (10.00%)
Hyperhidrosis	2 (10.00%)

Photopsia	2 (10.00%)

Sort order is by decreasing incidence overall

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Safety population
Total number (%) of patients	20
Number (%) of patients with AE(s)	14 (70.00%)
Number (%) of patients with	n (%)
Death	0 (0.00%)
SAE(s)	2 (10.00%)
SAE(s) with suspected relationship to study drug	0 (0.00%)
SAE(s) leading to permanent discontinuation	0 (0.00%)
AE(s) with suspected relationship to study drug	12 (60.00%)
AE(s) leading to dose adjustments or temporary interruption	1 (50.00%)
AE(s) leading to permanent discontinuation	1 (50.00%)
AE(s) requiring concomitant medication	8 (40.00%)

SAEs- Epistaxis (1) and cholecystectomy (1)

Other Relevant Findings

The present study was prematurely terminated due to insufficient recruitment. Due to the low number of patients, the results need to be interpreted with caution.

Date of Clinical Trial Report

27 May 2011

Date Inclusion on Novartis Clinical Trial Results Database

22 Sep 2011

Date of Latest Update