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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Somavert[®]/ Pegvisomant

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See. USPI

NATIONAL CLINICAL TRIAL NUMBER: 00151437

PROTOCOL NO: A6291017

PROTOCOL TITLE: A Multicenter, Open-Label Study for the Compassionate Use of Pegvisomant in Acromegalic Patients Refractory to Conventional Therapy and for Patients Who Received the Product During the Clinical Development Program

Study Center(s): The study was conducted at 4 centers in Canada

Study Initiation and Completion Dates: 12 November 2004 to 30 April 2007

Phase of Development: Phase 4

Study Objective(s):

- To provide pegvisomant for compassionate use to patients with acromegaly refractory to conventional therapy, who were not eligible for ongoing clinical trials and to patients who completed previous clinical trial(s) during Clinical Development Program and who were responsive to pegvisomant
- To evaluate the safety and tolerability of pegvisomant

METHODS

Study Design:

This was a multicenter, open-label, nonrandomized, variable dose protocol. The study was intended to enroll a maximum of 30 study subjects, including a maximum of 15 subjects refractory to conventional therapy and naïve to pegvisomant and up to 15 subjects who received pegvisomant and completed clinical trials PEGA-0435-003 or PEGA-0435-005.

Treatment with pegvisomant started at baseline. Subject who were naïve to pegvisomant were instructed to begin daily subcutaneous injections of 10 mg/day. Subjects completing one of the preceding pegvisomant trials were continued at their individualized stable dose, not exceeding 30 mg/day.

Recommendations were to measure serum IGF-1 concentrations every four to six weeks and to make the dose adjustments according to laboratory results and Assessment of Signs and Symptoms of Acromegaly Questionnaire, in order to maintain the serum IGF-1 concentration within the age-adjusted normal range and alleviate the signs and symptoms of acromegaly. Timing of assessments was estimated approximately at every 3 months and each clinic had its own schedule of study visits.

The duration of exposure to pegvisomant was dependent on subjects' response to the therapy and approval date of pegvisomant by Health Canada, but no later than April 30, 2007. This extension allowed continuing access to treatment for the enrolled patients and provincial governments to evaluate and determine if SOMAVERT[®] will be listed on their formularies.

Number of Subjects (Planned and Analyzed): The study intended to enroll a maximum of 30 study subjects, including a maximum of 15 subjects refractory to conventional therapy and naïve to pegvisomant and up to 15 subjects who received pegvisomant and completed clinical trials PEGA-0435-003 or PEGA-0435-005.

Of the 19 enrolled subjects, the majority (total of 15 subjects) were treated for more than one year (median of 548 days; range 51-861 days).

Diagnosis and Main Criteria for Inclusion:

Subjects with acromegaly were included in this study if they were responsive to pegvisomant during study PEGA-0435-003 or study PEGA-0435-005 and had completed the entire course of the study or subjects who were shown to be unresponsive or intolerant to conventional pharmacotherapy (somatostatin analogue or somatostatin analogue along with a dopamine agonist) based on the investigator's assessment and who were ineligible to participate in trial PEGA-0435-005.

Study Treatment:

Subjects who were naïve to pegvisomant were instructed to begin daily subcutaneous injections of 10 mg of SOMAVERT[®]. Subjects at stable doses of pegvisomant completing trials PEGA-0435-003 or PEGA-0435-005 were continued at their individualized stable dose.

Treatment with pegvisomant started at the baseline visit. New subjects starting pegvisomant were required to be seen every 4 to 6 weeks initially for dose adjustment. Each subject was provided with supplies for up to 3 months. Investigators had to obtain documented approval from Pfizer Canada before dispensing an additional 3-month supply. The duration of exposure to pegvisomant was dependent on subject response to the therapy and approval date of pegvisomant by Health Canada. It was intended that the end of treatment visit for all study subjects would be no later than April 30, 2007. This extension allowed continuing access to treatment for the enrolled patients and provincial governments to evaluate and determine if SOMAVERT[®] will be listed on their formularies.

Efficacy Evaluations:

The baseline visit could be performed on the same day as the screening visit. These visits included administration and interpretation of the Signs and Symptoms of Acromegaly Questionnaire; collection of blood for the analysis of the serum IGF-1 concentration (to be performed every 4 to 6 weeks and after each dose adjustment); collection and recording of the information on the concomitant medications; training the subject on the administration of pegvisomant; dispensing of the drug along with the instructions for use, and recording adverse events (AEs) information, if any.

Each subsequent study visit would be scheduled at approximately 3-month intervals. These visits included administration and interpretation of the Signs and Symptoms of Acromegaly Questionnaire; collection of blood for the analysis of the serum IGF-1 concentration; collection and recording of the information on the concomitant medications; recording AE information; collection of the returned used and unused vials; recording therapy compliance; and dispensing drug supply for the next 3-month period.

The End of Treatment visit included: administration and interpretation of the Signs and Symptoms of Acromegaly Questionnaire; collection of blood for the analysis of the serum IGF-1 concentration; collection and recording of the information on the concomitant medications; recording AE information; collection of the returned used and unused vials; recording therapy compliance; and completing the Subject Summary page in the CRF.

There were no formal efficacy endpoints established for this study, however, signs and symptoms of acromegaly were assessed according to five individual signs (ie, headache, perspiration, arthralgia, fatigue, and soft tissue swelling) and were evaluated on a nine-point ordinal scale (from 0 to 8), where 0 = absent, 2 = mild, 4 = moderate, 6 = severe but not incapacitating, or 8 = severe and incapacitating. In addition to the five signs/symptoms listed above, an overall health status was added to the questionnaire, which was also rated from 0 to 8.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: N/A

Safety Evaluations:

Assessments were as follows:

- Periodic imaging scans of the sella turcica, due to a concern of potential tumor growth while on the pegvisomant therapy. There is no available proof that this condition has been observed during the experimental stages, but this was considered theoretically possible.
- Monitoring of glucose and doses of anti-diabetic drugs, due to a potential of increase in glucose tolerance while on the pegvisomant therapy.

- Observation for clinical signs and symptoms of a GH-deficient state. Then pegvisomant dose adjustments would be made to maintain serum IGF-1 concentration within the age-adjusted normal range.
- Serum ALT, AST, TBIL and ALP levels were to be obtained prior to initiating the pegvisomant therapy and then repeated periodically.

Statistical Methods:

Since this was a non-randomized single group Phase 4 compassionate use study, no formal statistics were specified in the study protocol. The statistical analysis was descriptive and exploratory. In these analyses, missing values were handled using the last observation carried forward (LOCF) methodology, ie, wherever the relevant result was missing, the nearest (preceding) post-baseline result was used in the analysis. Continuous data were presented using descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum) for each study visit excluding the screening visit. For each study visit excluding the screening visit, categorical data were also presented using descriptive statistics (eg, percentage and absolute frequencies).

The full analysis set (FAS) included all subjects who took at least one dose of the study medication and had a post-baseline efficacy measure (at least one assessment with Acromegaly Signs and Symptoms Questionnaire or IGF-1 post-baseline score). Efficacy tables were produced and efficacy analysis was carried out using the FAS. For reporting purposes, the overall health status and each sign and symptom of questionnaire were evaluated separately.

Safety parameters included treatment emergent adverse events, including analysis of serious adverse events (SAEs), medical history and concomitant medications, withdrawals from the study and subject discontinuations due to adverse events (AEs). Standard safety tables were produced. The number and percentage of subjects experiencing treatment-emergent adverse events were presented for the safety analysis set, ie, those subjects who received at least one dose of pegvisomant in the context of this particular study. The incidence of treatment-emergent adverse events was tabulated by dose; prior to tabulation the adverse events were coded into MedDRA preferred terms. The incidence of serious adverse events was also tabulated.

RESULTS

Subject Disposition and Demography:

Of the 19 subjects enrolled, 10 were males and 9 females, with the mean age of 41 and 45.6 years, respectively. Both genders were well represented in the study. The mean age of the whole group was 43.2 years. Overall, the mean weight for male and female patients was 120.2 and 96.1 kg, respectively. The mean weight and height of all subjects was 108.8 kg and 176.7 cm, respectively.

Table S1. Subject Evaluation Groups

	Number of Subjects
Screened	19
Assigned to Study Treatment	19
Treated	19
Completed	15
Discontinued	4
Analyzed for efficacy	
Full analysis set	19
Analyzed for safety	
Adverse events	19
Safety	19

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.

Two subjects withdrew voluntarily (subject 1 withdrew his informed consent with an explanation that he was discouraged by necessity of daily injections; subject 2 failed to reschedule an appointment, despite several attempts by study personnel to contact him; he was considered lost to follow up)

Table S2. Discontinuations from Study

	Number of Subjects (N=19)
Discontinuations	
Related to Study Drug	2
Adverse event	1
Laboratory abnormality	1
Not Related to Study Drug	2
Subject defaulted	2
Total	4

Efficacy Results:

Both mean and median values of IGF-1 serum levels noticeably decreased during the study, with the nadir for mean and median occurring at month 18 of study treatment. The acromegalic symptoms assessed by means of the Acromegaly Signs and Symptoms Questionnaire were somewhat more difficult to manage, with the best controllable symptom being soft tissue swelling. Progression of the perspiration and headache symptoms were also relatively well controlled, but joint pain and fatigue were more difficult to manage.

Table S3 represents evolution of IGF-1 blood levels during pegvisomant therapy. Both mean and median values significantly decreased during the study, with the nadir for mean and median IGF-1 levels occurring after 18 months of pegvisomant continuous treatment. The normal ranges of somatomedin C differ from one laboratory to another, and also depend on subject's age and gender. Overall, there was a clear observable effect of the study treatment on IGF-1 level normalization.

Table S3. IGF-1– Last Observation Carried Forward^a

Month	Number of Subjects	Mean	Std Dev	Median	Minimum	Maximum
Month 0	19	379.63	128.51	388	141	594
Month 3	19	334.00	147.84	307	121	588
Month 6	19	313.26	110.69	297	107	556
Month 9	19	287.74	117.96	267	98	563
Month 12	19	270.21	88.04	261	107	434
Month 15	19	253.74	72.39	258	152	380
Month 18	19	252.68	79.49	246	126	407
Month 21	19	256.26	89.73	258	124	451
Month 24	19	258.74	78.84	258	152	417
Month 27	19	255.32	83.64	263	147	417

^a Only those results with units of ug/L were used. The nearest test to the 3-month time point was used (either scheduled or unscheduled)

Pharmacokinetic, Pharmacodynamic, and/or Other Results: N/A

Safety Results:

Study subjects demonstrated a very good tolerability to pegvisomant, for a long duration of the therapy. There were no SAEs related to the study therapy and no deaths for duration of the study. The majority of AEs were of mild to moderate severity. Frequently observed AEs were those related to different types of infections, and there was also a relatively significant number of AEs related to the nervous and gastrointestinal systems. Two subjects were withdrawn from the study due to increased liver enzymes. Finally, there were two cases of treatment-induced hypoglycemia, a caution of which had been provided in the study protocol. Overall, the safety profile of the pegvisomant therapy was found to be satisfactory and suitable for a long-term treatment.

Table S4. Incidence and Severity of Treatment-Emergent Adverse Events (all causalities)^a

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Mild	Mod.	Sev.
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	0	1	1
Coagulopathy	1	0	1	0
Splenomegaly	1	0	0	1
CARDIAC DISORDERS	1	0	0	1
Atrial fibrillation	1	0	0	1

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Severity		
		Mild	Mod.	Sev.
ENDOCRINE DISORDERS	2	1	1	0
Adrenal insufficiency	2	1	1	0
Androgen deficiency	1	0	1	0
GASTROINTESTINAL DISORDERS	7	1	4	2
Abdominal distension	2	0	2	0
Abdominal pain upper	2	0	1	1
Constipation	2	0	1	1
Flatulence	1	1	0	0
Gastroesophageal reflux disease	1	0	1	0
Rectal hemorrhage	1	0	1	0
Toothache	1	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6	2	3	1
Chest pain	3	0	3	0
Fatigue	3	1	1	1
Injection site bruising	1	1	0	0

^a If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row. For the TESS algorithm, any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. This includes data up to 999 days after last dose of study drug. MedDRA (v10.0) coding dictionary applied.

Table S4 (cont). Incidence and Severity of Treatment – Emergent Adverse Events (all causalities)^a

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Severity		
		Mild	Mod.	Sev.
IMMUNE SYSTEM DISORDERS	1	0	0	1
Seasonal allergy	1	0	0	1
INFECTIONS AND INFESTATIONS	10	1	5	4
Bronchitis	2	0	1	1
Diverticulitis	1	0	0	1
Ear infection	3	0	3	0
Fungal infection	1	0	1	0
Influenza	3	1	1	1
Localized infection	1	0	1	0
Nasopharyngitis	6	2	4	0
Otitis media	1	0	0	1
Pharyngitis	1	0	1	0
Sinusitis	3	0	2	1
Urinary tract infection	2	1	1	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	0	0	2
Cartilage injury	1	0	1	0
Contrast media reaction	1	0	0	1
Procedural pain	1	0	1	0
Transmission of drug via semen	1	0	0	1

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Severity		
		Mild	Mod.	Sev.
INVESTIGATIONS	9	1	3	5
Blood pressure decreased	1	0	0	1
Blood urine present	1	1	0	0
Hepatic enzyme increased	2	0	1	1
Thyroxine decreased	1	0	1	0
Tri-iodothyronine free decreased	1	0	1	0
Weight decreased	2	0	2	0
Weight increased	5	1	1	3
METABOLISM AND NUTRITION DISORDERS	1	0	1	0
Hypercholesterolaemia	1	0	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8	2	5	1
Arthralgia	2	1	1	0
Back pain	3	1	1	1
Joint swelling	1	0	1	0
Muscle twitching	2	0	2	0
Musculoskeletal pain	2	0	2	0
Pain in extremity	2	0	2	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3	1	1	1
Acrochordon	1	0	1	0
Neoplasm	1	1	0	0
Uterine leiomyoma	1	0	0	1

^a If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row. For the TESS algorithm, any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. This includes data up to 999 days after last dose of study drug. MedDRA (v10.0) coding dictionary applied.

Table S4 (cont). Incidence and Severity of Treatment – Emergent Adverse Events (all causalities)^a

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Severity		
		Mild	Mod.	Sev.
NERVOUS SYSTEM DISORDERS	10	1	5	4
Amnesia	1	0	1	0
Carpal Tunnel syndrome	1	0	1	0
Coordination abnormal	1	0	0	1
Dizziness	2	0	2	0
Dysgeusia	1	1	0	0
Facial neuralgia	1	0	1	0
Headache	4	0	1	3
Hypoesthesia	1	1	0	0
Syncope	1	0	1	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	0	0	1
Pregnancy	1	0	0	1
PSYCHIATRIC DISORDERS	1	0	1	0
Insomnia	1	0	1	0

System Organ Class and MedDRA (v10.0) Preferred Term	Number of Subjects Evaluable for AE (N=19)			
	n	Severity		
		Mild	Mod.	Sev.
RENAL AND URINARY DISORDERS	2	1	1	0
Nephrolithiasis	1	0	1	0
Pollakiuria	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6	3	1	2
Asthma	1	0	0	1
Cough	2	1	0	1
Epistaxis	2	1	1	0
Pharyngolaryngeal pain	1	0	0	1
Sinus disorder	1	1	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5	1	3	1
Alopecia	5	1	4	0
Dermal cyst	1	0	0	1
Rash	1	1	0	0
VASCULAR DISORDERS	1	0	1	0
Hypertension	1	0	1	0
Total preferred term events	114	22	63	29

^a If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row. For the TESS algorithm, any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. This includes data up to 999 days after last dose of study drug. MedDRA (v10.0) coding dictionary applied.

Six SAEs were formally reported in a total of 5 subjects. The following SAEs were reported during the study: sinusitis, transmission of drug via semen, blood pressure decrease and uterine leiomyoma, atrial fibrillation, and diverticulitis. None of the reported events were considered related to the study treatment by either Investigator or Sponsor, and none caused permanent discontinuation from the study.

CONCLUSION:

The results of the efficacy analysis confirmed that pegvisomant is capable of controlling serum IGF-1 levels in acromegalic subjects refractory to conventional therapy for a prolonged period (up to 27 months). Given the tendency for progression in the acromegalic population refractory to conventional treatments, the results obtained of some acromegaly symptomatology stabilization may be considered reassuring.

The tolerability of pegvisomant was shown to be good for the study duration; however, previous data on reversible hepatotoxicity requiring therapy discontinuation was confirmed. The majority of reported AEs were of mild-to-moderate severity, and overall, the safety profile of pegvisomant was found to be satisfactory and suitable for a long-term treatment. Further Phase 4 studies with a larger sample size may be warranted to investigate the safety profile in a wider population. However, given the very low incidence of this disease in Canada and given that most acromegalic Canadian patients use standard therapy with somatostatin analogs, such a study may be challenging.