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

PROTOCOL NO.: A6291015

PROTOCOL TITLE: A Double-blind, Proof of Concept Trial of the Use of Pegvisomant to Reduce Urinary Albumin Excretion in Type 1 and Type 2 Diabetic Patients Treated With Angiotensin Convertase Inhibitors/Angiotensin Receptor Blockers, With Persistent Albuminuria

Study Centers: A total of 36 centers took part in the study and randomized subjects; 8 in the United Kingdom (UK), 6 each in Lithuania and South Africa, 5 in India, 4 each in the Czech Republic and Spain, 2 in Denmark, and 1 in Germany.

Study Initiation Date and Final Completion Date: 28 December 2004 to 16 February 2006

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To establish that pegvisomant causes a clinically meaningful decrease in urinary albumin creatinine ratio (UACR) beyond that provided by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Secondary Objectives:

- To demonstrate improvements in renal function and glycemic control
- To demonstrate the safety of pegvisomant in the treatment of subjects with diabetic nephropathy (DN)

METHODS

Study Design: This was a multicenter, double-blind, placebo-controlled, stratified, randomized, parallel-group study. The study was designed to evaluate whether pegvisomant treatment caused a clinically meaningful decrease in UACR beyond that provided by ACEIs and ARBs. A clinically meaningful decrease was defined as either a 30% average decrease in UACR or a significant percentage of subjects (≥70%) showing a 30% decrease in UACR.

A predicted 30% of subjects of Indian subcontinental ethnicity were planned for enrollment and randomization; study randomization was stratified according to whether the subject's

ethnicity originated from the Indian subcontinent. Within each substratum, subjects were randomly allocated in a 2:1 ratio for treatment with pegvisomant or placebo.

Subjects were treated for 24 weeks with primary evaluations after 12 and 24 weeks of therapy, and at a follow-up visit 2 weeks after end of therapy. Subjects who withdrew from the study were not replaced. An overview of study design is presented in Figure 1.

Figure 1. Overview of Study Design

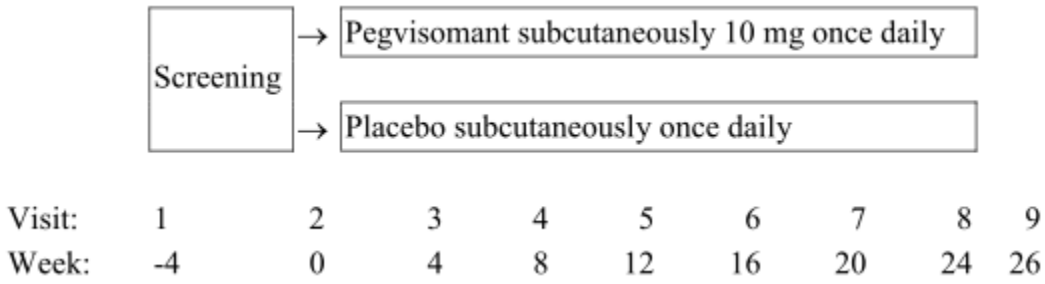

Table 1 presents a schedule of all the protocol-specified procedures.

Table 1. Timetable of Study Procedures

Study Procedure:	Screen V1 Wk -4	Baseline V2 Wk 0	V3 Wk 4	V4 Wk 8	V5 Wk 12	V6 Wk 16	V7 Wk 20	V8 Wk 24	FU V9 Wk 26
Informed written consent	X								
History	X								
Physical examination	X								X
Subject randomization[a]		X							
Vital signs: pulse rate, BP	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Height	X								
Inclusion/exclusion criteria	X	X							
Concomitant medication	X	X	X	X	X	X	X	X	X
Total insulin dose[b]		X			X			X	
Adverse events		X	X	X	X	X	X	X	X
24-hour urinary protein excretion[c]	X							X	
Early morning UACR (3 consecutive samples)[c]	X	X			X			X	X
Biochemistry	X	X	X	X	X	X	X	X	X
Fasting glucose		X						X	
Fasting lipids		X						X	
Fasting IGFBP-1		X						X	
HbA1c		X			X			X	
Haematology	X	X	X	X	X	X	X	X	X
IGF-1	X	X	X	X	X	X	X	X	X
IGFBP-3		X						X	
Pegvisomant concentration		X	X	X	X	X	X	X	X
Antibodies to pegvisomant		X			X				X
Antibodies to GH		X			X				X
Serum bank		X			X			X	
Pregnancy test for females of childbearing potential	X								X
Urinalysis	X	X			X			X	X
12-lead ECG	X								X
Ultrasound for renal size		X						X	
Retinal photography		X						X	
Start pegvisomant/placebo		X							
Adjust study drug dose (if required for safety reasons)[d]			X	X	X	X	X		
Stop pegvisomant/placebo								X	

Window of ±14 days around each visit.
Subjects were to omit morning insulin and fast overnight for Baseline and 24 week visits. Laboratory samples were taken immediately on arrival. The rest of the visit schedule was completed after the subjects had taken breakfast and their normal morning dose of insulin.
BP = blood pressure; ECG = electrocardiogram; FU = follow-up; GH = growth hormone; HbA1C = glycosylated hemoglobin; IGF-1 = insulin growth factor type 1; IGFBP = insulin growth factor binding proteins; Screen = screening; SD = standard deviation; UACR = urinary albumin creatinine ratio; V = visit; Wk = week.

a. Subjects were stratified according to ethnic origin (ie, from the Indian subcontinent or other ethnic origin).
b. Total insulin dose for the 24 hours preceding study visit.
c. Informed consent was obtained at the screening visit before the collection of the 24-hour urine sample and three early morning urine samples. Urine samples were collected at home immediately after the screening visit, refrigerated, and returned to the study site after collection of the final sample. Early morning urine samples for Visits 2, 5, 8 and 9 were collected on the three preceding mornings before the visits.
d. For safety reasons, dose of study drug could be adjusted downwards in 0.25 mL (2.5 mg pegvisomant or placebo) monthly increments, if IGF-1 fell below -3 SD of the age-related mean, or if serum creatinine increased ≥50% above Baseline. The lowest dose permitted was 0.25 mL (2.5 mg pegvisomant or placebo). If the drug had to be stopped, the subject was withdrawn from the study.

Number of Subjects (Planned and Analyzed): A total of 180 subjects (120 randomized to receive pegvisomant, 60 placebo) were planned for enrollment into the study. A total of 343 subjects were screened, 156 were assigned to study treatment (39 in Lithuania, 34 in India, 30 in South Africa, 22 in the Czech Republic, 17 in the UK, 8 in Spain, 5 in Denmark, and 1 in Germany) of which 103 received pegvisomant, and 52 received placebo.

Diagnosis and Main Criteria for Inclusion: Males and females aged between 18 and 70 years, inclusive, with Type 1 or Type 2 DN and with persistent UACR ≥3 mg/mmol, and who received treatment with ACEIs or ARBs were eligible for inclusion in this study. In addition, enrolled subjects were required to have a serum creatinine level of 88-265 µmol/L (1.0-3.0 mg/dL) or a glomerular filtration rate (GFR) of ≥30 mL/min.

Study Treatment: Subjects received double-blind pegvisomant (10 mg) treatment or placebo. Study treatment was self-administered once daily by subcutaneous injection at approximately the same time (first thing in the morning) each day for 24 weeks. For safety reasons, the dose of study drug could be adjusted downwards in 0.25 mL monthly increments (2.5 mg pegvisomant or placebo), if insulin growth factor type 1 (IGF-1) fell below -3 standard deviations of the age-related mean, or if serum creatinine increased ≥50% above Baseline. The lowest dose was to be 0.25 mL (2.5 mg pegvisomant or placebo). If the drug had to be stopped, the subject was to be withdrawn from the study.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint: Proportion of subjects with a UACR that decreased by ≥30% from Baseline to Week 24.

Secondary Efficacy Endpoints:

- Change in protein excretion (based on 24 hour urine) from Screening to Week 24
- Change in GFR from Baseline at 12 and 24 weeks
- Change in renal size from Baseline at 24 weeks
- Proportion of subjects whose total dose of insulin was reduced by ≥20% from Baseline at 12 weeks and 24 weeks
- Proportion of subjects whose fasting glucose fell by ≥10% from Baseline at 24 weeks
- Proportion of subjects whose glycosylated hemoglobin (HbA1c) fell by an absolute change of ≥0.5% from Baseline at 12 weeks and 24 weeks
- Proportion of subjects whose UACR fell by ≥30% from Baseline to 12 weeks

Safety Endpoints:

- Change in serum creatinine at 12 weeks and 24 weeks, compared to Baseline

- Incidence of hypoglycemic reactions (symptomatic hypoglycemia, together with blood glucose ≤2.2 mmol/L [40 mg/dL])

- Proportion of subjects who experienced 1 or more liver function tests (alanine transaminase, aspartate transaminase, bilirubin, alkaline phosphatase), >5.0 times the upper limit of the normal range at any visit after the first dose of pegvisomant and prior to or at Week 24

- Change in cholesterol and fasting triglycerides from Baseline at 24 weeks

- Change in systolic blood pressure (BP) at 12 weeks and 24 weeks compared to Baseline

- Change in diastolic BP at 12 weeks and 24 weeks compared to Baseline

- Urinalysis results at 12 weeks and 24 weeks

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead electrocardiogram, adverse events (AEs), safety laboratory tests, and antibodies to pegvisomant and human growth hormone (GH).

Statistical Methods:

Analysis Sets: The Full Analysis Set (FAS) was known as the Intent-to-Treat (ITT) population in this study. It included all subjects who were randomized into the study; who took at least 1 dose of study medication and had not previously participated in this study.

The Efficacy Evaluable (EE) population included all subjects randomized into the study who took at least 1 dose of study medication; had not previously participated in this study and had both a baseline measurement and who were still in the study at Week 10.

The Safety population included all subjects who took at least 1 dose of study medication.

Statistical Methods: All efficacy endpoints were analyzed using the EE population using the last observation carried forward approach to handling missing data. The primary endpoint was analyzed using a logistic regression (LR) model containing factors for treatment, race (ethnic origin from the Indian subcontinent or not) and the baseline UACR as a covariate. Treatment comparisons were assessed using Type III Wald Chi-Square Statistics. The difference in log odds ratio (OR) (pegvisomant-placebo) was estimated with a 95% confidence interval (CI) (adjusting for treatment, all stratification factors use and the baseline UACR). The treatment comparison was presented using ORs and adjusted 95% CIs, calculated by anti-logging the estimated difference in log OR and associated 95% CI (on the log odds scale) from the LR model, together with the associated p-value. Pegvisomant was to be considered statistically efficacious with respect to this primary endpoint if the lower bound of this 95% CI was >1.

For continuous data, analysis of covariance was used to test the difference between the treatments, by generation of the treatment ratio (pegvisomant/placebo) or treatment difference (pegvisomant-placebo) and the associated 95% CIs.

Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is presented in Table 2.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Pegvisomant	Placebo
Screened = 343		
Assigned to study treatment	156	
Treated	103	52
Completed	91 (88.3)	47 (90.4)
Discontinued	12 (11.7)	5 (9.6)
Related to study drug	4 (3.9)	3 (5.8)
Adverse event	4 (3.9)	3 (5.8)
Not related to study drug	8 (7.8)	2 (3.8)
Adverse event	1 (1.0)	0
Other	2 (1.9)	2 (3.8)
Subject defaulted	5 (4.9)	0
Analyzed for efficacy		
Full analysis set	103 (100.0)	52 (100.0)
Efficacy evaluable	89 (86.4)	44 (84.6)
Analyzed for safety:		
Adverse events	103 (100.0)	52 (100.0)
Laboratory data	102 (99.0)	52 (100.0)
Vitals	103 (100.0)	52 (100.0)
ECG	103 (100.0)	52 (100.0)

Discontinuations occurring after final dose were attributed to the last study treatment received.

Table 3 summarizes the demographic characteristics for the whole study population.

Table 3. Demographic Characteristics

	Pegvisomant			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number (%) of subjects	80	23	103	43	9	52
Age (years):						
<18	0	0	0	0	0	0
18-43	9 (11.3)	9 (39.1)	18 (17.5)	10 (23.3)	3 (33.3)	13 (25.0)
44-69	69 (86.3)	14 (60.9)	83 (80.6)	31 (72.1)	5 (55.6)	36 (69.2)
≥70	2 (2.5)	0	2 (1.9)	2 (4.7)	1 (11.1)	3 (5.8)
Mean	54.2	50	53.2	52.2	52.4	52.3
SD	10.3	12.8	11	11.2	16.4	12.1
Range	26-70	26-66	26-70	27-70	24-70	24-70
Race:						
White	42 (52.5)	20 (87.0)	62 (60.2)	25 (58.1)	6 (66.7)	31 (59.6)
Black	2 (2.5)	1 (4.3)	3 (2.9)	3 (7.0)	0	3 (5.8)
Asian	36 (45.0)	2 (8.7)	38 (36.9)	15 (34.9)	3 (33.3)	18 (34.6)
Weight (kg):						
Mean	81.3	76.5	80.2	88.4	72.3	85.6
SD	15	17.3	15.6	21.3	14.2	21.1
Range	46.7-129.2	41.0-110.0	41.0-129.2	48.6-144.0	53.5-96.7	48.6-144.0
n	80 (100.0)	23 (100.0)	103 (100.0)	43 (100.0)	9 (100.0)	52 (100.0)
Body Mass Index:						
Mean	27.5	29.7	28	29.3	29.9	29.4
SD	4.2	6.5	4.8	5.4	5.7	5.4
Range	18.0-38.0	20.0-39.0	18.0-39.0	18.0-42.0	22.0-40.0	18.0-42.0
n	80 (100.0)	23 (100.0)	103 (100.0)	43 (100.0)	9 (100.0)	52 (100.0)
Height (cm):						
Mean	171.7	160.6	169.2	173	155.7	170
SD	7	8.5	8.7	8.5	7.1	10.5
Range	153.0-197.5	137.0-172.0	137.0-197.5	150.0-192.0	146.0-165.0	146.0-192.0
n	80 (100.0)	23 (100.0)	103 (100.0)	43 (100.0)	9 (100.0)	52 (100.0)

n = number of subjects with specified criteria; SD = standard deviation.

A past medical history was reported for 71 (68.9%) subjects in the pegvisomant group and 35 (67.3%) in the placebo group. Ongoing medical conditions were reported for 100 (97.1%) subjects in the pegvisomant group and 45 (86.5%) in the placebo group. The most common ongoing medical conditions were vascular disorders reported for 86 (83.5%) in the pegvisomant group and 44 (84.6%) in the placebo group (most commonly hypertension) followed by renal and urinary disorders 62 (60.2%) in the pegvisomant group and 25 (48.1%) in the placebo group (most commonly diabetic nephropathy) and eye disorders 58 (56.3%) in the pegvisomant group and 23 (44.2%) in the placebo group (most commonly eyelid ptosis). Past and ongoing medical conditions were similar for the 2 groups at Baseline and typical for the population recruited into the study.

Efficacy Results:

Primary Endpoint Result:

Proportion of Subjects Whose UACR Decreased by ≥30% From Baseline to Week 24:

The percentage of responders was higher in the pegvisomant group than the placebo group; however, the difference between the treatments was not statistically significant (Table 4).

Table 4. UACR Responders at Week 24, Efficacy Evaluable Population (LOCF)

≥30% Reduction in UACR From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Yes	28 (31.46)	10 (22.73)	1.35	(0.54, 3.38)
No	61 (68.54)	34 (77.27)		

The observed responder rates were presented. The OR and CI were determined from the LR where the responder rates are adjusted for covariates.
CI = confidence interval; LOCF = last observation carried forward; LR = logistic regression; OR = odds ratio; UACR = urinary albumin creatinine ratio.

Subgroup analysis for Indian subcontinent subjects showed that the responder rates were slightly lower in the Indian subcontinent subjects in both treatment groups (26.92% in the pegvisomant group and 10.0% in the placebo group) versus non Indian subcontinent subjects (33.3% in the pegvisomant group and 24.5% in the placebo group).

Secondary Endpoints Results:

Proportion of Subjects Whose UACR Decreased by ≥30% From Baseline to 12 Weeks:

Table 5 summarizes the UACR responder rates at Week 12. At this timepoint, the percentage of responders was lower in the pegvisomant group than the placebo group; however, the difference between the treatments was not statistically significant.

Table 5. UACR Responders at Week 12, Efficacy Evaluable Population (LOCF)

≥30% Reduction in UACR From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Yes	15 (16.85)	12 (27.27)	0.48	(0.20, 1.16)
No	74 (83.15)	32 (72.23)		

The observed responder rates are presented. The OR and CI were determined from the LR where the responder rates were adjusted for covariates.
CI = confidence interval; LOCF = last observation carried forward; LR = logistic regression; OR = odds ratio; UACR = urinary albumin creatinine ratio.

The ratios for the adjusted means for change in UACR from Baseline at Weeks 12 and 24 are presented in Table 6. The ratios imply that at each visit both pegvisomant and placebo showed an increase in UACR from Baseline (after allowing for the various factors in the model), however, this increase was seen to be greatest in the placebo treatment group at Week 24.

Table 6. UACR Visit/Baseline Geometric Mean Ratios and Comparison of Treatments at Weeks 12 and 24, Efficacy Evaluable Population (LOCF)

Ratio of Adjusted Means	Pegvisomant	Placebo	Treatment Ratio	95% CI
Week 12/baseline	1.13	1.15	0.98	(0.76, 1.27)
Week 24/baseline	1.09	1.43	0.76	(0.57, 1.03)

CI = confidence interval; LOCF = last observation carried forward; UACR = urinary albumin creatinine ratio.

Change in Protein Excretion (Based on 24-Hour Urine) From Screening at Week 24:

Table 7 summarizes the changes from Baseline in protein excretion at Week 24 for all subjects.

Table 7. Summary Statistics for the Change From Screening of Protein Excretion at Week 24 Efficacy Evaluable Population, Efficacy Evaluable Population (LOCF)

	Pegvisomant N=89	Placebo N=44
Screening		
n	81	43
Geometric mean	0.71	0.57
Arithmetic mean (SD)	1.14 (1.13)	0.91 (0.909)
CV	98.8	99.4
Median (minimum, maximum)	0.8 (0, 5)	0.6 (0, 4)
Week 24		
n	61	36
Geometric mean	0.81	0.86
Arithmetic mean (SD)	1.70 (2.413)	1.39 (1.306)
CV	142.2	93.9
Median (minimum, maximum)	0.6 (0, 11)	1.0 (0, 5)
Change from Screening at Week 24		
n	60	36
Geometric mean	1.01	1.43
Arithmetic mean (SD)	0.42 (1.924)	0.41 (1.159)
CV	461.9	284.1
Median (minimum, maximum)	0 (-3, 8)	0.1 (-1, 5)

Geometric mean for change from Baseline is a ratio of the visit to the Baseline.
CV = coefficient of variance; LOCF = last observation carried forward; N = total number of subjects in the treatment group in the indicated population; n = indicates the total number of subjects contributing to the mean.

Protein excretion had increased from Baseline at Week 24 in both treatment groups and the increase was larger in the placebo group (Table 8).

Table 8. Protein Excretion Visit/Baseline Geometric Mean Ratios and Comparison of Treatments at Week 24, Efficacy Evaluable Population (LOCF)

Ratio of Adjusted Means	Pegvisomant	Placebo	Treatment Ratio	95% CI
Week 24/baseline	1.08	1.43	0.75	(0.53, 1.06)

CI = confidence interval; LOCF = last observation carried forward.

Urinary Albumin: At both Weeks 12 and 24, more responders were observed in the pegvisomant group than the placebo group, however, the number of responders in both groups was low (Table 9).

Table 9. Responders for Urinary Albumin at Weeks 12 and 24, Efficacy Evaluable Population (LOCF)

≥30% Reduction in Urinary Albumin From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Week 12				
Yes	30 (33.71)	11 (25.00)	1.42	(0.56, 3.56)
No	59 (66.29)	33 (75.00)		
Week 24				
Yes	23 (25.84)	8 (18.18)	1.54	(0.59, 4.01)
No	66 (74.16)	36 (81.82)		

The observed responder rates are presented. The OR and CI were determined from the LR where the responder rates were adjusted for covariates.
CI = confidence interval; LOCF = last observation carried forward; OR = odds ratio.

Change in Glomerular Filtration Rate From Baseline at 12 and 24 Weeks:

The changes in GFR were small at Weeks 12 and 24 with both treatment groups. The magnitude of changes was similar with the pegvisomant group at Weeks 12 and 24 and with the placebo group at Week 24 (mean visit/baseline ratios ranging between 0.95 and 0.97). The results of the analyses are summarized in Table 10.

Table 10. GFR Ratio of Change From Baseline at Week 12 and Week 24, Efficacy Evaluable Population (LOCF)

Ratio of Adjusted Means	Pegvisomant	Placebo	Treatment Ratio	95% CI
Week 12/baseline	0.97	1.04	0.93	(0.87, 0.99)
Week 24/baseline	0.96	0.95	1.01	(0.93, 1.10)

CI = confidence interval; GFR = glomerular filtration rate; LOCF = last observation carried forward.

Change in Renal Size From Baseline at 24 Weeks: These data were not summarized and reported in study report and hence are not included here.

Proportion of Subjects Whose Total Dose of Insulin was Reduced by ≥20% From Baseline at 12 Weeks and 24 Weeks:

Although the proportion of responders was higher in the pegvisomant group than the placebo group, the proportion of responders was low in both groups (Table 11).

Table 11. Responders for Insulin Dose at Week 24, Efficacy Evaluable Population (LOCF)

≥20% Reduction in Insulin Dose From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Yes	10 (14.29)	3 (8.82)	1.62	(0.44, 5.92)
No	60 (85.71)	31 (91.18)		

The observed responder rates are presented. The OR and CI were determined from the LR where the responder rates were adjusted for covariates.
CI = confidence interval; LOCF = last observation carried forward; LR = logistic regression; OR = odds ratio.

Proportion of Subjects Whose Fasting Glucose Fell by ≥10% From Baseline at 24 Weeks:

Although the proportion of responders was greater in the pegvisomant group than in the placebo group, there was no significant difference between the groups (Table 12).

Table 12. Responders for Fasting Glucose at Week 24, Efficacy Evaluable Population (LOCF)

≥10% Reduction in Fasting Glucose From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Yes	42 (50.00)	16 (39.02)	1.48	(0.73, 3.00)
No	42 (50.00)	25 (60.98)		

The observed responder rates are presented. The OR and CI were determined from the LR where the responder rates were adjusted for covariates.
CI = confidence interval; LOCF = last observation carried forward; LR = logistic regression; OR = odds ratio.

Proportion of Subjects Whose HbA1c Fell by an Absolute Change of ≥0.5% From Baseline at 12 Weeks and 24 Weeks:

The proportion of responders was less in the pegvisomant group than the placebo group (Table 13).

Table 13. Responders for HbA1c at Week 24, Efficacy Evaluable Population (LOCF)

≥0.5% Reduction in HbA1c From Baseline	Pegvisomant	Placebo	Odds Ratio	95% CI
Yes	36 (40.45)	22 (50.00)	0.69	(0.31, 1.57)
No	53 (59.55)	22 (50.00)		

CI = confidence interval; HbA1c = glycosylated haemoglobin; LOCF = last observation carried forward.

Safety Results:

All-Causality Treatment-Emergent Nonserious Adverse Events (TEAEs): The number of subjects with TEAEs (preferred term) reported by ≥2.0% subjects in either group are summarized in Table 14. Edema peripheral and hypoglycemia were the most common AEs in the pegvisomant group.

Table 14. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All-Causalities) in ≥2% of Subjects in Any Treatment Group

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v9.1) Preferred Term	Pegvisomant n (%)	Placebo n (%)
Number (%) of subjects evaluable for adverse events	103	52
Number (%) of subjects with adverse events	53 (51.5)	27 (51.9)
Eye disorders	14 (13.6)	2 (3.8)
Diabetic retinal oedema	3 (2.9)	0
Diabetic retinopathy	6 (5.8)	1 (1.9)
Gastrointestinal disorders	12 (11.7)	6 (11.5)
Diarrhoea	3 (2.9)	2 (3.8)
Vomiting	3 (2.9)	0
General disorders and administration site conditions	17 (16.5)	9 (17.3)
Asthenia	0	2 (3.8)
Oedema peripheral	10 (9.7)	3 (5.8)
Pyrexia	4 (3.9)	3 (5.8)
Metabolism and nutrition disorders	9 (8.7)	5 (9.6)
Hypoglycaemia	9 (8.7)	5 (9.6)
Musculoskeletal and connective tissue disorders	12 (11.7)	3 (5.8)
Arthralgia	3 (2.9)	1 (1.9)
Back pain	3 (2.9)	0
Pain in extremity	3 (2.9)	2 (3.8)
Nervous system disorders	8 (7.8)	4 (7.7)
Hypoaesthesia	0	2 (3.8)
Paraesthesia	1 (1.0)	2 (3.8)
Vascular disorders	4 (3.9)	1 (1.9)
Hypertension	3 (2.9)	1 (1.9)

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v9.1) coding dictionary applied.
MedDRA (v9.1) = Medical Dictionary for Regulatory Activities (version 9.1); n = number of subjects with adverse events.

Treatment-Related Treatment-Emergent Adverse Events: The treatment related TEAEs are summarized by preferred term in Table 15. Hypoglycemia (4 [3.9%] in the pegvisomant group and 5 [9.6%] in the placebo group) and peripheral edema (5 [4.9%] in the pegvisomant group and 2 [3.8%] in the placebo group) were the commonly reported treatment-related TEAEs.

Two subjects had severe AEs in the pegvisomant group (liver function test abnormal and retinal hemorrhage) that were considered treatment-related and 1 subject had 1 severe AE in the placebo group that was considered treatment-related (hypoglycemia).

Table 15. Treatment-Emergent Treatment-Related Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v9.1) Preferred Term	Pegvisomant (N=103)	Placebo (N=52)
Cardiac disorders		
Atrial fibrillation	1 (1.0%)	0
Atrial flutter	1 (1.0%)	0
Tachycardia	0	1 (1.9%)
Eye disorders		
Retinal haemorrhage	1 (1.0%)	0
Vision blurred	1 (1.0%)	0
Gastrointestinal disorders		
Diarrhoea	1 (1.0%)	0
Nausea	1 (1.0%)	0
Retching	1 (1.0%)	0
Vomiting	1 (1.0%)	0
General disorders and administration site conditions		
Asthenia	0	1 (1.9%)
Fatigue	1 (1.0%)	0
Injection site bruising	1 (1.0%)	0
Injection site hypersensitivity	1 (1.0%)	0
Oedema peripheral	5 (4.9%)	2 (3.8%)
Infections and infestation disorders		
Bronchitis acute	1 (1.0%)	0
Investigations		
ALT increased	1 (1.0%)	0
AST increased	1 (1.0%)	0
Blood creatinine increased	1 (1.0%)	1 (1.9%)
Blood glucose increased	1 (1.0%)	0
Blood pressure increased	1 (1.0%)	0
Blood urea increased	1 (1.0%)	0
Liver function test abnormal	1 (1.0%)	0
Weight increased	0	1 (1.9%)
Metabolism and nutrition		
Hypoglycaemia	4 (3.9%)	5 (9.6%)
Musculoskeletal and connective tissue disorders		
Muscle spasms	1 (1.0%)	0
Pain in extremity	1 (1.0%)	0
Nervous system disorders		
Headache	1 (1.0%)	0
Paraesthesia	1 (1.0%)	0
Respiratory thoracic and mediastinal disorders		
Hiccups	1 (1.0%)	0
Skin and subcutaneous tissue disorders		
Rash	1 (1.0%)	1 (1.9%)
Vascular disorders		
Hypertension	0	1 (1.9%)

AEs and SAEs are not separated out.
Subjects were only counted once per treatment for each row.
MedDRA (v9.1) coding dictionary applied.
AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; MedDRA (v9.1) = Medical Dictionary for Regulatory Activities (version 9.1); N = number of subjects in each group; SAE = serious adverse event.

All-Causality Treatment-Emergent Serious Adverse Events (SAEs): The all-causality treatment-emergent SAEs reported during the study are presented in Table 16.

Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v9.1) Preferred Term	Pegvisomant n (%)	Placebo n (%)
Number (%) of subjects evaluable for adverse events	103	52
Number (%) of subjects with adverse events	11 (10.7)	6 (11.5)
Blood and lymphatic system disorders	0	1 (1.9)
Anaemia	0	1 (1.9)
Cardiac disorders	1 (1.0)	1 (1.9)
Cardiac failure	0	1 (1.9)
Ventricular dysfunction	1 (1.0)	0
Eye disorders	1 (1.0)	0
Retinal vein thrombosis	1 (1.0)	0
Gastrointestinal disorders	1 (1.0)	0
Vomiting	1 (1.0)	0
General disorders and administration site conditions	1 (1.0)	0
Chest pain	1 (1.0)	0
Infections and infestations	5 (4.9)	1 (1.9)
Carbuncle	1 (1.0)	0
Cellulitis	1 (1.0)	0
Gastroenteritis	1 (1.0)	0
Localised infection	0	1 (1.9)
Necrotising fasciitis	1 (1.0)	0
Sepsis	1 (1.0)	0
Urinary tract infection	1 (1.0)	0
Metabolism and nutrition disorders	3 (2.9)	1 (1.9)
Diabetic ketoacidosis	2 (1.9)	0
Hypoglycaemia	1 (1.0)	1 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0
Colon cancer	1 (1.0)	0
Psychiatric disorders	0	1 (1.9)
Abnormal behaviour	0	1 (1.9)
Renal and urinary disorders	0	1 (1.9)
Urethral stenosis	0	1 (1.9)
Skin and subcutaneous tissue disorders	1 (1.0)	0
Skin ulcer	1 (1.0)	0
Vascular disorders	1 (1.0)	1 (1.9)
Deep vein thrombosis	0	1 (1.9)
Hypotension	1 (1.0)	0

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 9.1) coding dictionary applied.
MedDRA (version 9.1) = Medical Dictionary for Regulatory Activities (version 9.1); n = number of subjects with adverse events.

Treatment-Related Treatment-Emergent Serious Adverse Events: Only 2 SAEs in 1 subject in the pegvisomant group were considered treatment related (moderate vomiting and mild hiccups) and 1 subject in the placebo group had severe hypoglycemia reported as an SAE that was considered related to study drug.

Permanent Discontinuations due to Adverse Events: A summary of permanent discontinuations from the study due to AEs is provided in Table 17.

Table 17. Permanent Discontinuations due to Treatment-Emergent Adverse Events

Serial Number	Adverse Event	Intensity	Causality	Outcome
Pegvisomant				
1	Liver function test abnormal	Severe	Study drug	Resolved
2	Injection site hypersensitivity	Moderate	Study drug	Resolved
3	Colon cancer	Severe	Other	Ongoing
4	Diarrhoea and nausea	Moderate	Study drug	Resolved
5	Fatigue	Mild	Study drug	Unknown
Placebo				
6	Asthenia	Moderate	Study drug	Resolved
7	Blood creatinine increased	Moderate	Study drug	Ongoing
8	Rash	Moderate	Study drug	Resolved

Dose Reductions or Temporary Discontinuations due to Adverse Events: A total of 11 subjects had temporary discontinuations or dose reductions during the study due to AEs. Two subjects had dose reductions due to elevated blood creatinine (1 in each group), all other subjects had temporary discontinuations. Three subjects (1 in the pegvisomant group and 2 in the placebo group started with a temporary discontinuation but later discontinued permanently due to these AEs). Hence 6 subjects in the pegvisomant group and 2 in the placebo group had dose reductions or temporary discontinuation of study treatment (Table 18).

Table 18. Temporary Discontinuations or Dose Reductions due to Treatment-Emergent Adverse Events

Serial Number	Adverse event	Dose Reduction or Temporary Discontinuation	Intensity	Causality	Outcome
Pegvisomant					
1	Sepsis and urinary tract infection	Temp discont.	Severe	Other	Resolved
2[a]	Nausea and diarrhoea	Temp discont.	Moderate	Study drug	Resolved
3	Blood creatinine increased	Dose reduced	Mild	Study drug	Resolved
4	Vomiting	Temp discont.	Moderate	Study drug	Resolved
	Cellulitis	Temp discont.	Moderate	Other	Resolved
	Diabetic ketacidosis	Temp discont.	Severe	Other	Resolved
	Hiccups	Temp discont.	Mild	Study drug	Resolved
5	Tachycardia	Temp discont.	Mild	Other	Resolved
	Diabetic ketoacidosis	Temp discont.	Moderate	Disease under study	Resolved
	Hyponatraemia	Temp discont.	Severe	Disease under study	Resolved
6	Rash erythaematous and rash maculo-papular	Temp discont.	Moderate	Other	Ongoing
7	Necrotising fascitis	Temp discont.	Severe	Disease under study	Resolved
	Blood creatinine increased	Temp discont.	Moderate	Disease under study	Resolved
	Blood urea increased	Temp discont.	Severe	Study drug	Resolved
	Hypotension	Temp discont.	Severe	Other	Resolved
Placebo					
8	Abnormal behaviour	Temp discont.	Severe	Other	Resolved
9[a]	Asthenia and hypertension	Temp discont.	Moderate	Study drug	Resolved
10[a]	Blood creatinine increased	Temp discont.	Mild	Study drug	Resolved
11	Anaemia	Temp discont.	Severe	Disease under study	Resolved
	Cardiac failure	Temp discont.	Severe	Concomitant treatment	Resolved

a. These subjects later discontinued permanently due to these events but are presented for completeness.
Temp discont. = temporary discontinuation.

Deaths: There were no deaths during the study.

Change in Serum Creatinine at 12 Weeks and 24 Weeks: The changes in serum creatinine were small at Weeks 12 and 24 with both treatment groups. The magnitude of changes were similar with the pegvisomant group at Weeks 12 and 24 and with the placebo group at Week 24 (Table 19).

Table 19. Summary of Analysis for Change From Baseline of Serum Creatinine (mg/dL)

	N	Week 12/Baseline Adjusted Mean	Treatment Ratio	95% CI	p-Value
At Week 12					
Pegvisomant	89	1.03	1.06	(1.01, 1.12)	0.0267
Placebo	44	0.97			
At Week 24					
Pegvisomant	89	1.04	1.03	(0.98, 1.09)	0.2748
Placebo	44	1.01			

One subject had an unusual reading at Week 24, so excluded from the analysis.
CI = confidence interval; N = number of subjects in each group.

Incidence of Hypoglycemic Reactions: Only 1 subject (in the placebo group) experienced a hypoglycemic reaction, which occurred between Baseline and Week 12.

Change in Systolic and Diastolic Blood Pressure at 12 Weeks and 24 Weeks Compared to Baseline: Table 20 presents a summary of mean changes from baseline in systolic and diastolic BP.

Table 20. Mean Baseline and Mean Changes from Baseline

	Pegvisomant			Placebo		
	N	Mean	SD	N	Mean	SD
Sitting diastolic BP (mmHg)						
Baseline	98	79.28	9.1	50	80.44	7.26
Week 12	94	-0.33	8.46	48	-2.46	8.48
Week 24	95	0.77	8.92	52	-1.10	10.42
Sitting systolic BP (mmHg)						
Baseline	98	135.82	15.46	50	136.76	16.32
Week 12	94	-2.70	14.74	48	-3.75	17.00
Week 24	95	-1.47	16.92	52	-3.35	17.92

Baseline was defined as Day 0 reading.
BP = blood pressure; N = number of subjects evaluated in each group; SD = standard deviation.

Other Safety Related Findings: A total of 71 (70%) subjects in the pegvisomant group and 44 (85%) in the placebo group with normal baseline had a laboratory abnormality during the study meeting the specified criteria. Most commonly, the laboratory abnormalities were insulin, urine glucose ≥1, random glucose, and urine protein ≥1. The profile of laboratory abnormalities was broadly similar for the two groups.

A total of 101 (100.0%) subjects in the pegvisomant group and 51 (98.0%) in the placebo group with abnormal baseline values had a laboratory abnormality during the study meeting the specified criteria. Most commonly, the laboratory abnormalities were for insulin growth factor binding proteins (IGFBP)-1 and IGFBP-3, random glucose and HbA1c. The profile of laboratory abnormalities was similar for the 2 groups.

At both Weeks 12 and 24, the pegvisomant group showed larger decreases in IGF-1 than the placebo group (Table 21).

Table 21. Total and Free IGF-1 Change From Baseline at Week 12 and Week 24 (LOCF)

Adjusted Means (µg/L)	Pegvisomant	Placebo	Mean Difference (Pegvisomant - Placebo)	SE of Difference	95% CI
Total IGF-1					
Week 12	-51.58	-10.53	-41.05	6.58	(-54.06, -28.04)
Week 24	-43.33	-6.43	-36.90	6.69	(-50.14, -23.66)
Free IGF-1					
Week 12	-22.03	53.66	-75.69	22.28	(-119.79, -31.59)
Week 24	-35.99	11.70	-47.69	22.24	(-91.70, -3.68)

CI = confidence interval; IGF-1 = insulin growth factor-1; LOCF = last observation carried forward; SE = standard error.

In general, the changes from Baseline to last observation were small and similar for the 2 groups, with the exception of low density lipoprotein cholesterol and fasting glucose (Table 22).

Table 22. Median Change From Baseline to Last Observation for LDL Cholesterol and Fasting Glucose

Parameter	Pegvisomant			Placebo		
	n	Baseline	Change	n	Baseline	Change
LDL cholesterol (mg/dL)	89	102	8	44	102	-2
Plasma glucose fasting (mg/dL)	93	160	-16	46	152	6

LDL = low density lipoprotein; n = number of subjects in each group.

In the pegvisomant group, 10 subjects were positive for antibodies to GH at Week 12 (maximum titer 1/128), 7 subjects remained positive at Week 26 and 3 additional subjects tested positive at Week 26 only (maximum titer 1/32), giving a total of 13 subjects with positive results for GH antibodies during the study. No subjects in the placebo group developed antibodies to GH during the study.

Two subjects were positive for antibodies to pegvisomant with titers of 1/16 and 1/64 at Week 26. A further 11 subjects had anti-pegvisomant antibodies detected at Week 26 (including 2 who also had antibodies detected at Week 12), although the levels were too low to obtain a titer. Five subjects who tested positive for antibodies to pegvisomant were also positive for antibodies to GH, including both subjects with antibody titers against pegvisomant.

CONCLUSION: Proof of concept has not been achieved. Although a significant reduction in serum IGF-1 was achieved. It is possible that the degree of GH receptor antagonism obtained was insufficient to reduce intrarenal GH action and, or IGF-1 to a level that would reduce urinary albumin excretion. No new concerns were raised with regard to safety.