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COMPOUND NUMBER: PHA-794428

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: 00308464

PROTOCOL NO.: A6391003

PROTOCOL TITLE: A Double Blind Parallel Group Randomized Multiple Dose Study to Evaluate the Pharmacodynamic Response and Safety of PHA-794428 in Adult Growth Hormone Deficient Patients

Study Centers: A total of 32 centers randomized subjects; 3 Belgium; 2 Czech Republic, 4 Denmark, 3 France, 3 Germany, 4 Italy, 1 Netherlands, 2 Slovakia, 3 Spain, 4 Sweden and 3 in the United Kingdom.

Study Initiation and Completion Dates: 13 July 2006 to 10 December 2007 (Early Termination)

Phase of Development: Phase 2

Study Objectives

- To explore the safety, toleration and humoral response of PHA-794428 after multiple weekly injections in adult growth hormone deficiency (AGHD) patients.
- To explore the dose response relationship of PHA-794428 after multiple weekly subcutaneous injections in AGHD patients.
- To explore the pharmacokinetic/pharmacodynamic relationships with PHA-794428 after single and multiple injections.

METHODS

Study Design: This was a randomized double-blind placebo controlled, multiple-dose, parallel group study. The study included a screening visit followed by 13 study visits. Subjects received 6 weekly injections of either PHA-794428 or placebo at Visits 2, 5, 6, 9, 10 and 11. Subjects were randomized into 1 of 4 treatment groups (Groups A to D) or placebo (Group E).

Groups A, B and C received 1, 3 and 4 mg PHA-794428 respectively for the first 3 weeks followed by 2, 6 and 8 mg PHA-794428 respectively for the remaining 3 weeks. Group D received 4 mg PHA-794428 for 6 weeks. Group E received placebo. The schedule of assessments is summarized in Table S1.

Table S1.Schedule of Activities

	Visit														
Protocol Activity	**Screen**	**Baseline[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Follow-up**
Week	**0**	**1**			**2**	**3**			**4**	**5**	**6**			**7**	
Informed Consent	X														
Randomization		X													
Inclusion/ Exclusion Criteria	X	X													
Stop rhGH[b]	X														
Study Treatment		X			X	X			X	X	X				
Medical History	X														
Physical Examination	X														X
BP and PR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[c]	X	X			X	X			X	X	X			X	X
Biochemistry[c]	X				X	X			X	X	X			X	X
Testosterone/ oestradiol[c,d]	X														X
Thyroid Hormones[e]	X														X
oGTT Glucose	X													X	
Fasting Glucose, Insulin, HbA1c, Fasting Lipids[c]		X							X					X	
IGF-1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGFBP-3, ALS	X	X							X					X	
PK		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHA-794428/hGH ab		X							X						X
Pharmacogenomic		X													
Virology	X														
Urinalysis (Dipstick)	X	X			X	X			X	X	X			X	X
Urine Drug Screen	X														
Pregnancy Test	X														X
Electrocardiogram	X														X
Draize Scores		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gracely Box Score		X			X	X			X	X	X				
AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRTI[f]									X					X	

rhGH = recombinant growth hormone, BP = blood pressure, PR = pulse rate, ab = antibody, AE = adverse event, PRTI = patient reported treatment impact, oGTT = oral glucose tolerance test, IGF-1 insulin-like growth factor 1, IGFBP-3 = IGF binding protein-3, ALS = acid labile subunit, hGH = human growth hormone, PK = pharmacokinetics, HbA1c = glycated hemoglobin

[a] Baseline occurred between 3 and 4 weeks after screening for non-naïve subjects.

[b] In pre-treated subjects.

[c] Laboratory samples were taken immediately before injection of PHA-794428 or placebo.

[d] Unless female was receiving oral contraceptive pill or hormone replacement therapy.

[e] Free triiodothyronine and free thyroxine.

[f] At Visits 9 and 14 or at subject discontinuation.

Number of Subjects (Planned and Analyzed): 120 subjects were planned and 105 were treated and included in the PK and safety analyses.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 25 to 60 with severe AGHD as defined by the Growth Hormone Research Society guidelines were included. Subjects receiving growth hormone (GH) treatment underwent a 3 week washout. Subjects were excluded if they had uncontrolled pituitary tumor growth or diabetes mellitus.

Study Treatment: Non-naïve subjects stopped their recombinant GH (rhGH) treatment at least 3 weeks before starting treatment with PHA-794428 or placebo. PHA-794428 or placebo was administered in a blinded fashion as a single subcutaneous injection in the same thigh, by qualified study staff. After the first cases of injection site lipoatrophy were reported the protocol was amended to include an injection site rotation plan. Subjects received a total of 6 injections at weekly intervals as described in Table S2.

Table S2.Dose Groups

Treatment Group	PHA-794428 Dose (mg)	
	Weeks 1-3	Weeks 4-6
A	1	2
B	3	6
C	4	8
D	4	4
E	Placebo	Placebo

Efficacy Evaluations (None)

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Pharmacokinetic: Analysis of PHA-794428 Analysis

A blood sample (2 mL) was collected at all visits from baseline to follow-up. Samples were analysed using a validated analytical method.

Pharmacodynamic: Analysis of IGF-1, IGFBP-3 and ALS

A blood sample (2 mL) was collected at screening and all visits including the follow-up visit. IGF-1, IGFBP-3 and ALS were used as biomarkers for PHA-794428 activity. Samples were analysed using a suitably validated immunoassay.

Determination of Anti-hGH/PHA-794428 Antibodies

A blood sample (2 mL) was collected at Visit 2 and Visit 8 or follow-up. Samples were used to characterise any immunogenic response.

Safety Evaluations: Adverse events (AEs), safety laboratory assessments, weight, pulse rate and blood pressure were monitored throughout the study.

Pain was assessed using the Gracely Box Score 30 minutes post-injection at Visits 2, 5, 6, 9, 10 and 11.

Erythema, eschar formation and oedema were assessed by Draize scoring at 30 minutes post-injection at all visits post screening.

A patient reported treatment impact (PRTI) questionnaire was collected at Visits 9 and 14 or at subject discontinuation.

The PRTI comprised 3 domains:

- Patient global satisfaction assessment.
- Patient global preference assessment.
- Patient willingness to use drug.

Statistical Methods:

The PK, PD (IGF-1), outcomes research and safety endpoints were tabulated and summarized by treatment.

Safety data will be presented using descriptive statistics unless otherwise stated.

RESULTS

Subject Disposition and Demography:

Table S3 summarizes subject evaluation groups. One hundred and twenty subjects were planned 157 subjects were screened and 105 subjects were assigned treatment. Eighty-six subjects completed Period 1 (injections 1-3) and 51 completed Period 2 (injections 4-6). All subjects were assessed for safety 105 subjects were analyzed for PK in Period 1 and 86 in Period 2; 100 subjects were analyzed for PD IFGBP-3, IGF-1 and ALS in Period 1 and 81 in Period 2.

The baseline characteristics weight, age, height and male to female ratios were similar for all treatment groups. The majority of subjects were white with a mean age of 45.8 years ranging from 28 to 60 years; the mean height was 164.9 cm ranging from 151.0 to 179.0 cm. The highest incidence of present endocrine disorders were hypopituitarism (59 subjects [56.2%]), GHD (39 subjects [37.1%]) and diabetes insipidus (13 subjects [12.4%]). The most common drug treatments prior to the start of study drug were levothyroxine (67 [63.8%]), hydrocortisone (61 [58.1%]), somatropin (54 [51.4%]) and pituitary and hypothalamic hormones (22 [20.9%]). Mean doses of prior GH treatment were similar across the different treatment groups and ranged from 0.1 to 1.2 μg/kg; the overall mean dose was 0.45 μg/kg. Three subjects had nondrug treatments prior to the start of the study and 7 subjects had concomitant nondrug treatments, these treatments were not considered clinically important.

The majority of subjects received 3 doses in both periods.

Table S3.Subject Evaluation Groups

		PHA-794428								
Treatment Group		**A**		**B**		**C**		**D**		**E**
Number of Subjects		**Period 1 1 mg**	**Period 2 2 mg**	**Period 1 3 mg**	**Period 2 6 mg**	**Period 1 4 mg**	**Period 2 8 mg**	**Period 1 4 mg**	**Period 2 4 mg**	**Period 1 Placebo**	**Period 2 Placebo**
Screened	157										
Assigned to Study Treatment	105										
Treated		29	25	26	20	26	23	13	9	11	9
Completed		25	13	20	11	23	14	9	7	9	6
Discontinued		4	12	6	9	3	9	4	2	2	3
Related to Study Drug		4	12	6	9	3	9	4	2	2	3
AE		1	2	0	1	0	1	0	1	0	0
Other		3	10	6	8	3	8	4	1	2	3
Analysed for PK											
PK Concentration Analysis Set		29	25	26	20	26	23	13	9	11	9
Analysed for PD											
IGFBP-3 Concentration Analysis Set		29	25	26	20	24	21	13	9	9	7
IGF-1 Concentration Analysis Set		29	25	26	20	24	21	13	9	9	7
ALS Concentration Analysis Set		29	25	26	20	24	21	13	9	9	7
Analysed for Safety											
AE		29	25	26	20	26	23	13	9	11	9
Laboratory Data		29	25	26	20	26	23	13	9	11	9

PK = pharmacokinetic, PD = pharmacodynamic, FAS = full analysis set, AE = adverse event

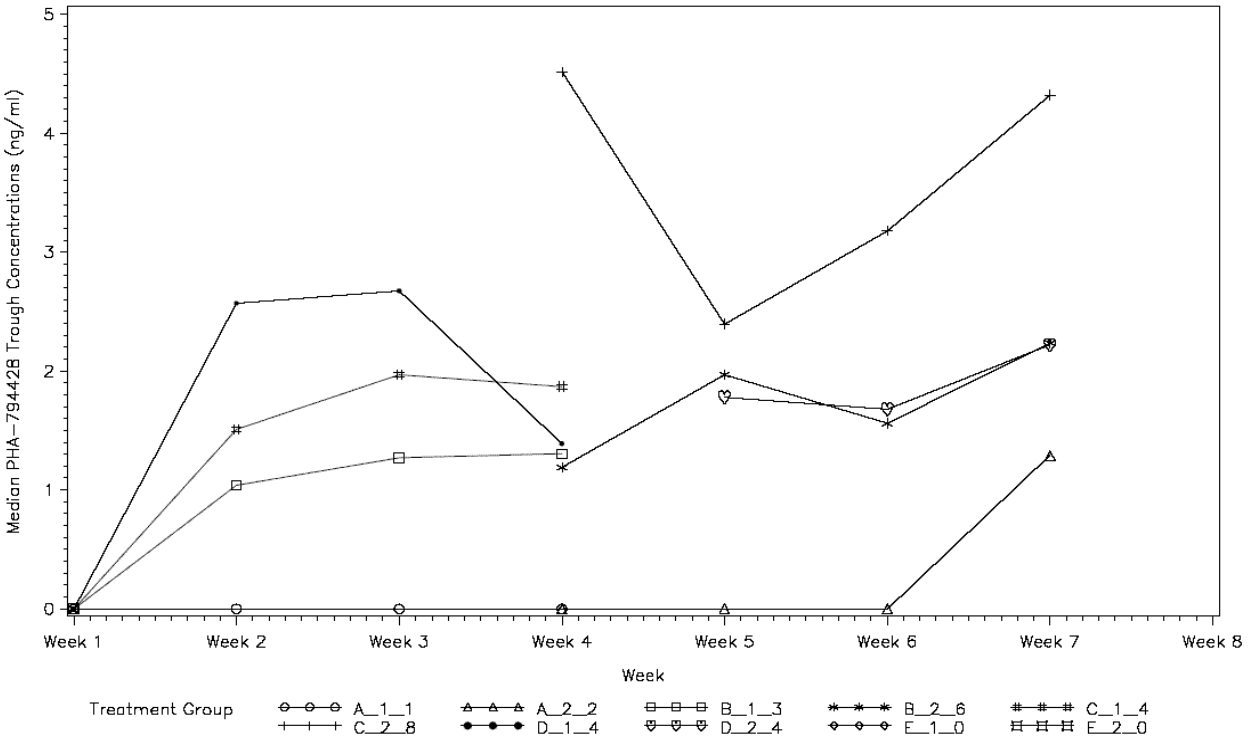
Efficacy Results: (None)

Pharmacokinetic, Pharmacodynamic

PHA-794428 Analysis

Median trough PHA-794428 concentrations versus week are presented in Figure S1. PHA-794428 trough concentrations were similar in Periods 1 and 2 for all groups except Treatment C (4 mg to 8 mg). PHA-794428 trough concentrations between male and female subjects or naïve and non-naïve subjects were similar.

Figure S1. Median PHA-794428 Trough Concentrations Versus Week



Summary statistics were calculated by setting concentration values below the lower limit of quantification to half the lower limit of quantification. The lower limit of quantification was 0.5 ng/mL.

Pharmacodynamic

Determination of IGF-1

Mean IGF-1 concentrations increased with increasing PHA-794428 dose from Period 1 (Week 4) to Period 2 (Week 7) for all PHA-794428 treatment groups except Treatment D (4 mg administered in both periods) where IGF-1 concentrations were similar during Period 1 and 2 (Table S4). Lower IGF-1 levels were observed in females compared to males in the same treatment group (Figure S2). Baseline treatment status did not affect IGF-1

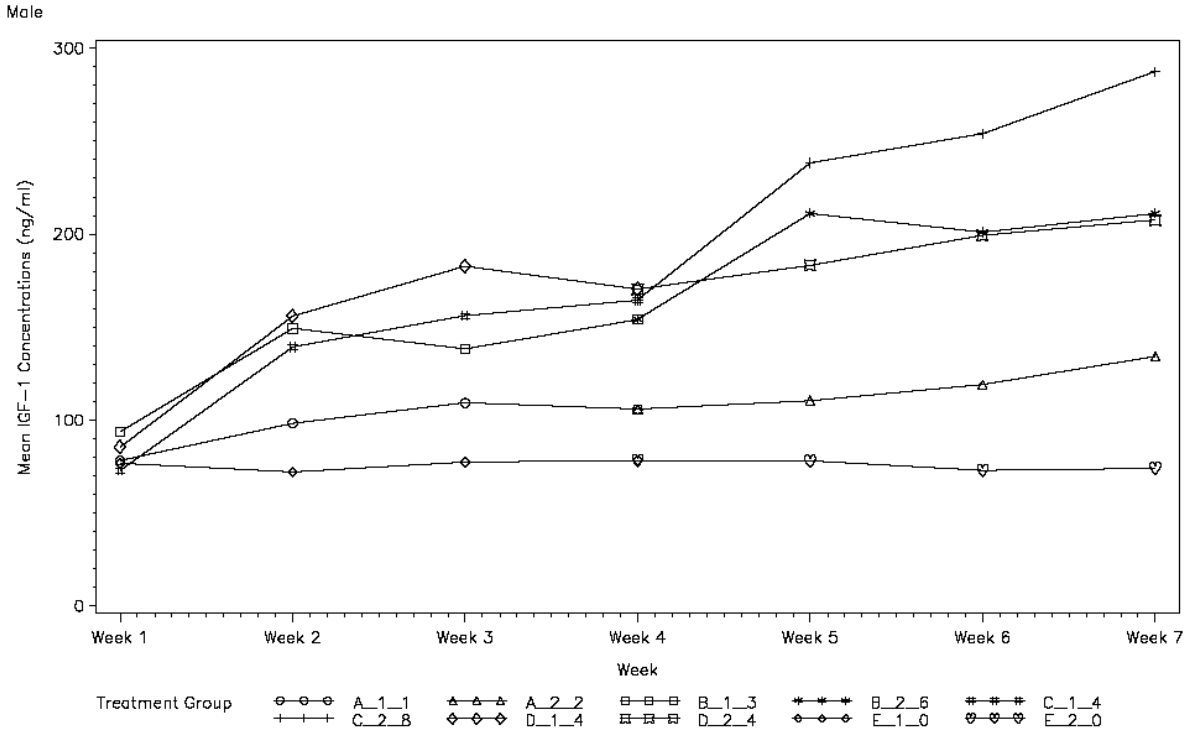
concentrations post PHA-794428 dosing, similar IGF-1 levels within each treatment group were observed for naïve and non-naïve subjects.

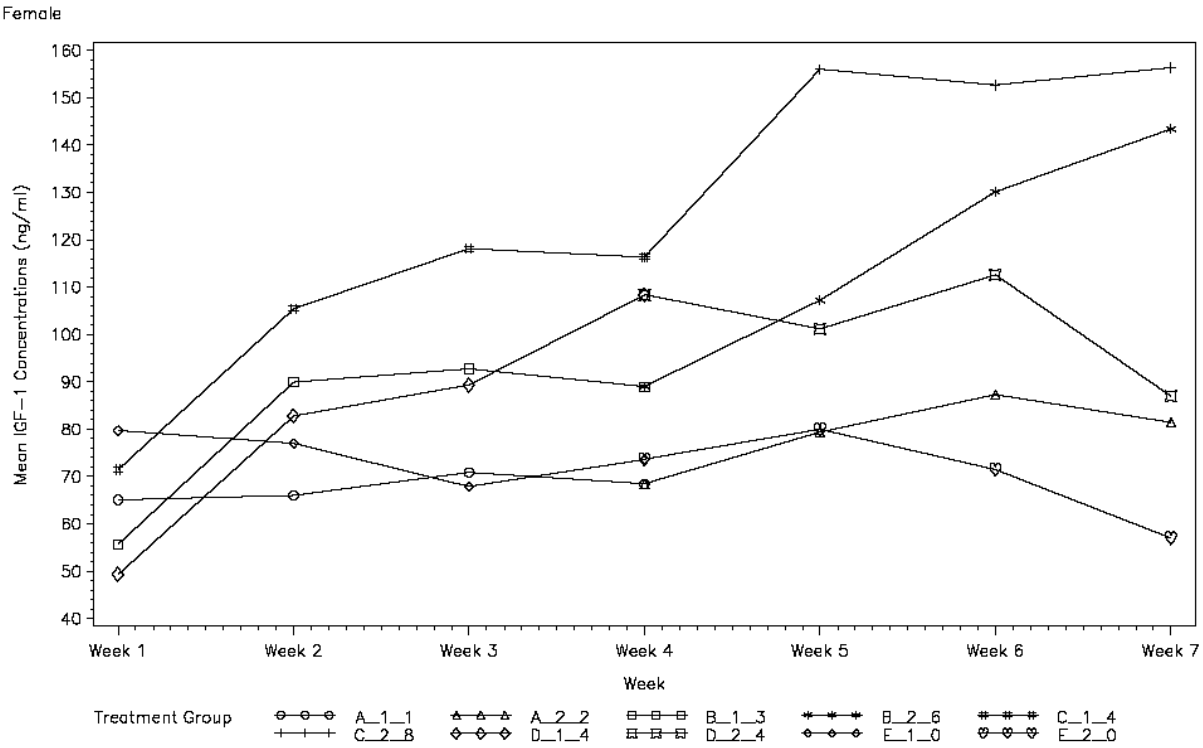
Table S4. IGF-1 Change from Baseline to Week 4 and Week 7 by Dose Group

	PHA-794428 Treatment Group									
	A		B		C		D		E	
IGF-1 (mg/mL)	Week 4 (1 mg)	Week 7 (2 mg)	Week 4 (3 mg)	Week 7 (6 mg)	Week 4 (4 mg)	Week 7 (8 mg)	Week 4 (4 mg)	Week 7 (4 mg)	Week 4 (PBO)	Week 7 (PBO)
N	25	13	20	11	21	13	9	7	7	4
Mean	13.6	28.0	47.4	90.4	67.0	157.5	64.8	71.6	-12.5	-16.0
(SD)	(22.1)	(34.8)	(25.6)	(63.1)	(45.6)	(78.3)	(26.7)	(56.5)	(14.9)	(10.9)
Min, Max	-45.0, 44.0	-36.0, 69.0	-11.0, 96.0	-17.0, 172.0	-1.0, 143.0	26.0, 296.0	23.0, 98.0	0.0, 176.5	-41.0, 8.0	-27.0, -1.0

PBO = placebo, SD = standard deviation

Figure S2. IGF-1 Versus Week by Gender





Summary statistics were calculated by setting concentration values below the lower limit of quantification to half the lower limit of quantification. The lower limit of quantification was 20 ng/mL.

Determination of IGFBP-3 and ALS

Mean IGFBP-3 concentrations were similar in Periods 1 and 2 for all treatment groups (Table S5), a dose response was not evident except for Group A. There was no difference in IGFBP-3 concentrations between males and females or between naïve and non-naïve subjects.

Table S5. IGFBP-3 Change from Baseline to Week 4 and Week 7 by Dose Group

	PHA-794428 Treatment Group									
	A		B		C		D		E	
IGFBP-3 (mg/L)	Week 4 (1 mg)	Week 7 (2 mg)	Week 4 (3 mg)	Week 7 (6 mg)	Week 4 (4 mg)	Week 7 (8 mg)	Week 4 (4 mg)	Week 7 (4 mg)	Week 4 (PBO)	Week 7 (PBO)
N	25	13	20	11	21	14	9	7	7	4
Mean (SD)	0.46 (0.5)	0.8 (0.4)	0.8 (0.6)	1.0 (0.9)	1.2 (0.8)	1.8 (0.9)	1.1 (0.7)	1.2 (1.0)	-0.1 (0.4)	-0.3 (0.3)
Min, Max	-0.7, 1.5	0.0, 1.4	-0.5, 2.0	-0.3, 2.6	0.2, 2.7	0.2, 3.4	0.2, 2.0	-0.1, 2.4	-0.6, 0.5	-0.7, 0.0

Source: 13.4.10.1.1
PBO = placebo, SD = standard deviation,

Mean ALS concentrations increased with increasing PHA-794428 dose from Period 1 (Week 4) to Period 2 (Week 7) for all PHA-794428 treatment groups except Treatment D

(4 mg administered in both periods) where ALS concentrations were similar during Period 1 and 2 (Table S6). There was no difference in ALS levels between males and females or naïve and non-naïve subjects.

Table S6. ALS Change from Baseline to Week 4 and Week 7 by Dose Group

	PHA-794428 Treatment Group									
	A		B		C		D		E	
ALS (miu/mL)	Week 4 (1 mg)	Week 7 (2 mg)	Week 4 (3 mg)	Week 7 (6 mg)	Week 4 (4 mg)	Week 7 (8 mg)	Week 4 (4 mg)	Week 7 (4 mg)	Week 4 (PBO)	Week 7 (PBO)
N	25	13	20	11	21	14	9	7	7	4
Mean	78.4	216.2	279.6	355.9	312.6	456.8	230.7	287.4	3.3	-40.0
(SD)	(185.6)	(236.5)	(227.4)	(284.0)	(206.0)	(255.5)	(279.8)	(342.0)	(83.3)	(69.6)
Min, Max	-279.0, 457.0	-317.0, 609.0	-85.0, 627.0	63.0, 851.0	-98.0, 672	-92.0, 817	-115.0, 563.0	-91.0, 827.0	-139.0, 143.0	-144.0, 4.0

PBO = placebo, SD = standard deviation

Serum hGH Antibodies

The majority of subjects were negative for hGH antibodies at baseline and follow-up.

Serum PHA-794428 Antibodies

The majority of subjects were negative for PHA-794428 antibodies at baseline and follow-up.

Safety Results

Adverse Events

There were no deaths, dose reductions or temporary discontinuations due to AEs during the study. Table S7 summarizes the total all causality and treatment-related AEs by period and treatment group. The highest incidence of AEs occurred during Treatment C Period 2 (8 mg [n = 30]) followed by Treatment B Period 1 (3 mg [n = 28]). The highest number of treatment-related AEs occurred during Treatment A Period 2 (2 mg [n = 20). The incidence of AEs did not increase with increasing dose of PHA-794428.

Table S7.Summary of Adverse Events

	PHA-794428																			
	A				B				C				D				E			
	Period 1 1 mg		Period 2 2 mg		Period 1 3 mg		Period 2 6 mg		Period 1 4 mg		Period 2 8 mg		Period 1 4 mg		Period 2 4 mg		Period 1 PBO		Period 2 PBO	
N	29		25		26		20		26		23		13		9		11		9	
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Number of AEs	22	9	29	20	28	16	17	9	23	8	30	12	13	5	13	5	11	5	5	1
Subjects with AEs	13	7	10	9	14	11	11	6	13	6	15	7	8	5	6	5	7	4	4	1
Subjects with SAEs	0	0	1	1	0	0	0	0	1[a]	0	3[a]	2	0	0	1	1	0	0	0	0
Subjects with Severe AEs	1	0	0	0	0	0	0	0	3	2	2	1	1	0	0	0	0	0	0	0
Subjects Discontinued due to AEs	1	1	2	2	0	0	1	1	0	0	1	1	0	0	1	1	0	0	0	0

PBO = placebo, AE = adverse event, SAE = serious AE, AC = all causality AEs, TR = treatment-related AEs
[a] SAEs of ankle fracture and fall were recorded in 2 dosing periods

AEs occurring in ≥2 subjects are summarized in Table S8. The most common body system associated with treatment emergent AEs was general disorders and administration site conditions (all causality [n = 33] and treatment-related [n = 29]). Headache was the most frequently reported all causality AE across all periods and doses. Injection site pain was the most frequently reported treatment-related AE. At least 1 injection site pain AE occurred for all doses except placebo.

Table S8.Summary of Adverse Events Occurring in ≥2 Subjects

	PHA-794428																			
	A				B				C				D				E			
	Period 1 1 mg		Period 2 2 mg		Period 1 3 mg		Period 2 6 mg		Period 1 4 mg		Period 2 8 mg		Period 1 4 mg		Period 2 4 mg		Period 1 PBO		Period 2 PBO	
N	29		25		26		20		26		23		13		9		11		9	
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Headache	3	1	0	0	3	1	2	0	3	2	3	1	2	1	0	0	3	2	2	1
Injection Site Pain	2	2	3	3	5	5	2	2	0	0	1	1	1	1	1	1	0	0	0	0
Lipoatrophy	0	0	2	2	2	2	1	1	0	0	1	1	0	0	2	2	0	0	0	0
Nasopharyngitis	1	0	2	0	1	0	1	0	2	0	1	0	0	0	0	0	0	0	0	0
Arthralgia	2	0	1	0	1	1	1	1	1	0	0	0	2	1	0	0	0	0	0	0
Myalgia	1	1	1	1	2	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0
Back Pain	0	0	0	0	0	0	0	0	1	0	2	1	0	0	0	0	1	0	1	0
Pain in Extremity	2	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	1	0

PBO = placebo, AE = adverse event, SAE = serious AE, AC = all causality AEs, TR = treatment-related AEs

The majority of AEs were mild to moderate in severity; 7 severe events occurred of which 3 were considered treatment-related.

This study was suspended on 23 November 2006 due to lipoatrophy AEs; an injection site rotation plan was implemented and the study restarted. The total number of injection site AEs pre and post study suspension are summarized in Table S9. The number of injection site reactions decreased after study suspension and the introduction of the injection rotation plan.

Table S9.Total Number of all Causality Injection Site Adverse Events Pre and Post Study Suspension

Preferred Term	Pre-Suspension		Post-Suspension	
	AC	TR	AC	TR
Injection Site Pain	11	11	4	4
Lipoatrophy	5	5	3	3
Injection Site Atrophy	2	2	1	1
Lipohypertrophy	2	2	0	0
Injection Site Hematoma	2	2	0	0
Injection Site Swelling	1	1	0	0
Injection Site Edema	1	1	0	0
Injection Site Erythema	0	0	1	1
Injection Site Warmth	0	0	1	1
Injection Site Irritation	0	0	1	1
Injection Site Injury	1	0	0	0
Total	25	24	11	11

AC = all causality, TR = treatment related

All AEs associated with the injection site are summarized in Table S10. In total 43 injection site reactions were recorded during the study; the majority (26/43) occurred during Period 2; 4 were recorded as SAEs, and 6 resulted in discontinuation from the study. Table S11 summarizes the IGF-1 concentrations associated with the 13 lipoatrophy events.

Table S10. Adverse Events Associated With Injection Site

T[a]	Period	PHA-794428 Dose (mg)	Preferred Term[b]	Severity	Relatedness	Outcome	SAE
A	1	1	Injection Site Pain	Mild	Related	Resolved	No
	2	2	Injection Site Atrophy	Moderate	Related	Ongoing	No
	2	2	Injection Site Pain	Mild	Related	Resolved	No
	2	2	Muscle Atrophy	Mild	Related	Resolved	No
A	2	2	Injection Site Irritation	Mild	Related	Resolved	No
A	1	1	Injection Site Warmth	Mild	Related	Resolved	No
A	2	2	Injection Site Erythema	Mild	Related	Ongoing	No
A	2	2	Lipohypertrophy	Moderate	Related	Ongoing	No
A	2	2	Injection Site Haematoma	Mild	Related	Ongoing	No
	2	2	Lipoatrophy	Moderate	Related	Ongoing	No
A	1	1	Injection Site Pain	Moderate	Related	Resolved	No
	2	2	Injection Site Pain	Moderate	Related	Resolved	No
	2	2	Lipoatrophy	Moderate	Related	Ongoing	Yes
A	2	2	Injection Site Pain	Moderate	Related	Ongoing	No
	2	2	Injection Site Swelling	Moderate	Related	Ongoing	No
B	1	3	Injection Site Pain	Moderate	Related	Resolved	No
	1	3	Injection Site Pain	Mild	Related	Ongoing	No
B	1	3	Injection Site Pain	Mild	Related	Resolved	No
	1	3	Injection Site Pain	Mild	Related	Ongoing	No
B	1	3	Injection Site Pain	Mild	Related	Resolved	No
B	1	3	Injection Site Injury	Mild	Other (subject hit injection site)	Resolved	No
B	1	3	Injection Site Pain	Mild	Related	Ongoing	No
	2	6	Injection Site Atrophy	Mild	Related	Ongoing	No
	2	6	Injection Site Pain	Mild	Related	Ongoing	No
B	1	3	Myalgia	Mild	Related	Ongoing	No
	2	6	Myalgia	Mild	Related	Ongoing	No
B	1	3	Injection Site Pain	Moderate	Related	Resolved	No
	2	6	Injection Site Pain	Moderate	Related	Resolved	No
B	1	3	Lipoatrophy	Moderate	Related	Ongoing	No
	2	6	Lipoatrophy	Moderate	Related	Ongoing	No
C	2	8	Lipohypertrophy	Moderate	Related	Ongoing	No
C	2	8	Injection Site Haematoma	Moderate	Related	Ongoing	No
	2	8	Muscle Hypertrophy	Moderate	Related	Ongoing	Yes
	2	8	Lipoatrophy	Moderate	Related	Resolved	Yes
C	2	8	Injection Site Atrophy	Mild	Related	Ongoing	No
C	2	8	Injection Site Pain	Mild	Related	Resolved	No
D	1	4	Injection Site Pain	Mild	Related	Resolved	No
	1	4	Injection Site Pain	Mild	Related	Resolved	No
D	1	4	Lipoatrophy	Moderate	Related	Ongoing	Yes
D	2	4	Lipoatrophy	Mild	Related	Ongoing	No
D	2	4	Injection Site Pain	Moderate	Related	Resolved	No
E	1	Placebo	Injection Site Edema	Mild	Related	Resolved	No
B	1	3	Lipoatrophy	Moderate	Related	Ongoing	No

[a]Each treatment consisted of two 3 week periods. Doses for each period were: Treatment: A (1/2 mg), B (3/6 mg), C (4/8 mg), D (4 mg), and E (placebo).
[b]MedDRA (v10.1) coding dictionary applied.

Table S11.Subjects with Lipoatrophy

Subject[a]	Sex	Age	BMI	T[b]	PHA-794428 Dose (mg)	Treatment Start	Injection Number	IGF-1 (ng/ml)	
								Maximum	Reference Range
10051001	F	58	28.7	B	3	16 OCT 06	5	139	81-225
					3	23 OCT 06			
					3	30 OCT 06			
					6	06 NOV 06			
					6	13 NOV 06			
10051002	F	26	22.6	A	1	16 OCT 06	5	121	117-329
					1	23 OCT 06			
					1	30 OCT 06			
					2	06 NOV 06			
					2	13 NOV 06			
10151001	F	41	24.1	C	4	09 OCT 06	6	177	101-267
					4	16 OCT 06			
					4	23 OCT 06			
					8	30 OCT 06			
					8	06 NOV 06			
					8	13 NOV 06			
10151002	M	38	25.1	A	1	09 OCT 06	6	143	109-284
					1	16 OCT 06			
					1	23 OCT 06			
					2	30 OCT 06			
					2	06 NOV 06			
					2	13 NOV 06			
10191002	F	26	19.9	A	1	10 OCT 06	6	103	117-329
					1	16 OCT 06			
					1	23 OCT 06			
					2	30 OCT 06			
					2	06 NOV 06			
					2	13 NOV 06			
10221004	M	53	30	B	3	01 NOV 06	4	231	87-238
					3	08 NOV 06			
					3	15 NOV 06			
					6	22 NOV 06			
10301002	F	47	26.5	B	3	02 NOV 07	4	85	94-252
					3	09 NOV 07			
					3	19 NOV 07			
					6	23 NOV 07			
10331001	F	30	20.6	A	1	25 SEP 06	4	74	117-329
					1	02 OCT 06			
					1	09 OCT 06			
					2	16 OCT 06			
10331002	F	29	21.1	C	4	27 SEP 06	5	216	117-329
					4	04 OCT 06			
					4	11 OCT 06			
					8	18 OCT 06			
					8	25 OCT 06			
10331003	F	54	23.7	D	4	18 OCT 06	5	221	87-238
					4	25 OCT 06			
					4	01 NOV 06			
					4	07 NOV 06			
					4	15 NOV 06			

10461010	F	63	24.3	D	4	17 OCT 07	6	110	75-212
					4	24 OCT 07			
					4	31 OCT 07			
					4	07 NOV 07			
					4	14 NOV 07			
					4	21 NOV 07			
10481003	M	49	36.5	B	3	07 NOV 06	3	596	94-252
					3	14 NOV 06			
					3	21 NOV 06			
10561004[c]	F	55	21.9	C	4	23 OCT 07	6	822	87-238
					4	30 OCT 07			
					4	06 NOV 07			
					8	13 NOV 07			
					8	20 NOV 07			
					8	27 NOV 07			

Source: Appendix A14.1

BMI = body mass index, F = female, M = male

[a]All subjects were white.
[b]Each treatment consisted of two 3 week periods. Doses for each period were: Treatment: A (1/2 mg), B (3/6 mg), C (4/8 mg), D (4 mg), and E (placebo).
[c]Subject was treatment naïve.

Table S12 summarizes the discontinuations due to AEs. A total of 6 subjects discontinued due to 9 AEs: 8 of these AEs were considered related to study drug. The majority (5/6) of subjects discontinued during Period 2, and the most common cause of discontinuation was injection site reactions.

Table S12.Discontinuations Due to Adverse Events

T[a]	Period	PHA-794428 Dose (mg)	Preferred Term[b]	Severity	Relatedness	Outcome	SAE
A	1	1	Angina pectoris	Moderate	Related	Ongoing	No
A	2	2	Chills	Moderate	Unrelated	Resolved	No
			Lipoatrophy	Moderate	Related	Ongoing	Yes
			Hematoma	Moderate	Related	Resolved	No
B	2	2	Injection site atrophy	Moderate	Related	Ongoing	No
D	2	4	Lipoatrophy	Moderate	Related	Ongoing	Yes
B	2	6	Injection site atrophy	Mild	Related	Ongoing	No
C	2	8	Muscle hypertrophy	Moderate	Related	Ongoing	Yes
			Lipoatrophy	Moderate	Related	Resolved	Yes

[a]Each treatment consisted of two 3 week periods. Doses for each period were: Treatment: A (1/2 mg), B (3/6 mg), C (4/8 mg), D (4 mg), and E (placebo).
[b]MedDRA (v10.1) coding dictionary applied.

Five subjects experienced 7 SAEs of these 5 events were considered related to study drug, and 3 subjects discontinued due to a SAE (Table S13).

Table S13.Serious Adverse Events

T[a]	Period	PHA-794428 Dose (mg)	Serious Adverse Event
C	1	4	Fall
			Ankle fracture
A	2	2	Injection site atrophy[b,c]
C	2	8	Injection site atrophy[b,c]
			Muscle hypertrophy[b,c]
D	2	4	Injection site atrophy[b,c]
C	2	8	Transaminases increased[c]

[a]Each treatment consisted of two 3 week periods. Doses for each period were: Treatment: A (1/2 mg), B (3/6 mg), C (4/8 mg), D (4 mg), and E (placebo).
[b]Permanently discontinued
[c]Related to study drug as evaluated by the investigator
[d] SAEs of ankle fracture and fall were recorded in 2 dosing periods

Mean changes from baseline in weight, pulse rate and blood pressure were small and not significant. Gracely and Draize scores showed no trend toward pain or edema formation with increasing dose. There were no clinically significant laboratory abnormalities.

CONCLUSIONS:

Following the further cases of injection-site lipoatrophy reported in this Phase 2 study after implementation of an injection site rotation plan the sponsor took the decision to suspend the study and terminate the program based on the fact that:

- These lipoatrophies were observed effectively after "first dose" at the injection site.
- The increased frequency (>10% overall and around 20% in females) and size (up to 30 x 10 cm and 20 mm depth) of the lipoatrophy lesions observed compared to daily GH.
- Based on the data, this effect was not minimized by rotation of the injection site.
- It was not readily predictable in which patients this effect of PHA-794428 might occur.