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COMPOUND NUMBER: PHA-794428

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: 00314938

PROTOCOL NO.: A6391004

PROTOCOL TITLE: A Double Blind, Single Dose Study to Explore the Safety, Pharmacokinetics and Pharmacodynamics of PHA-794428 in Pediatric Patients with Growth Hormone Deficiency

Study Centers: 8 centers in total; 3 Belgium; 1 France, 1 Germany, 2 United Kingdom and 1 Israel

Study Initiation and Completion Dates: 17 July 2006 to 10 December 2007 (Early Termination)

Phase of Development: Phase 2a

Study Objectives:

- To explore the pharmacokinetics (PK) and pharmacodynamics (PD) of PHA-794428 after single subcutaneous injections in pediatric growth hormone deficiency (PGHD) subjects in order to support the development of a PK/PD model in the subject population.

- To explore the safety, tolerance and humoral response of PHA-794428 after single subcutaneous injections in PGHD subjects.

METHODS

Study Design: This was a double-blind, third-party open-label study in male and female children aged ≥6 years. The study consisted of a screening, treatment and follow-up phases. Subjects underwent a minimum 2 week recombinant human growth hormone (GH) washout period prior to starting study drug. There were 4 cohorts planned with 8 subjects each (3:1 ratio for PHA-794428: placebo). Cohort 1 was administered a low dose of 25 μg/kg PHA-794428 or placebo, Cohort 2 50 μg/kg PHA-794428 or placebo, Cohort 3 100 μg/kg PHA-794428 or placebo and Cohort 4 200 μg/kg or placebo. Dose escalation was based on

preliminary safety and PK/PD results from the previous cohort. Due to early termination of the study Cohort 3 was not started.

Studies A6391003 (an adult multiple dose study) and A6391004 were temporarily suspended on 23 November 2006 following the observation of injection site reactions in 5 adult subjects in study A6391003. Following this suspension, further cases of lipodystrophy were reported. The sponsor considered the reactions to be most likely related to the direct local lipolytic action of growth hormone itself, due to the same injection site (thigh) being used for each injection. The protocol for study A6391003 was subsequently amended to include an injection site rotation plan. The informed consent document for both studies was updated to indicate lipoatrophy as a potential adverse event (AE). No amendment to this study was considered necessary as it involved only a single dose in children. After the studies were restarted, further new cases of injection-site lipoatrophy were reported in A6391003 and A6391004, consequently both studies were terminated on 10 December 2007.

The study schedule is shown in Table S1.

Table S1.Schedule of Activities

Period	Screen	Study Treatment Phase						Follow-up
Visit	1[a]	2[a]	3	4	5[c]	6[c]	7	8[a]
Days	14 to 28 predose	1	2[b]	3	5[c]	8[c]	11 to 15	21 to 28 postdose
Hours		0	12 to 24	48	96	168	240 to 336	
Informed Consent	X							
Stop rhGH Treatment	X[d]							
Restart rhGH Treatment							X[e]	
Randomisation		X						
Medical History	X							
Physical Examination[f]	X	X						X
Weight	X	X	X	X	X	X	X	X
Height	X							
Body Temperature	X	X	X	X	X	X	X	X
Laboratory Assessments								
Haematology	X	X						X
Blood Chemistry	X	X		X		X	X	X
Urinalysis (dipstick)	X	X		X		X	X	X
TSH and free T4 (fT4)	X							
Other Assessments								
BP and Pulse Rate	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Investigational Treatment		X						
Blood Sampling for IGF-1 and IGFBP-3	X	X	X	X	X	X	X	X
Blood Sampling for PHA-794428		X	X	X	X	X	X	
Blood Sampling for PHA-794428 Ab		X						X
Draize Scores		X	X	X	X	X	X	
Gracely Box Scale		X	X	X				

rhGH = recombinant growth hormone, TSH = thyroid stimulating hormone, T4 = thyroxine, BP = blood pressure, IGF-1 = insulin like growth factor 1, IGFBP-3 = insulin like growth factor binding protein 3, Ab = antibody

[a] Screening visit, Visit 2 and follow-up visits were conducted at the clinic. Visits 3 to 7 could be conducted at either the clinic or by a research nurse or research physician at the subject's home.

[b] Visit 3 could take place at any time 12 to 24 hours after dosing.

[c] There was a minimum interval of 2 days between Visits 5 and 6. An allowance of ±24 hours around the timing of these visits was permitted.

[d] Subjects stopped their rhGH treatment at least 2 weeks before PHA-794428 dosing.

[e] Subjects were allowed to restart their rhGH treatment 2 weeks after PHA-79428 dosing.

[f] A full physical examination was performed at screening and follow-up. An abbreviated physical examination was performed at Visit 2.

Number of Subjects (Planned and Analyzed): 32 subjects were planned and 15 were treated and included in the PK and safety analyses.

Diagnosis and Main Criteria for Inclusion: Pre-pubertal (as defined by Tanner staging) males and females aged at least 6 years or more, with growth hormone deficiency and pretreatment with GH for at least 6 months prior to screening.

Study Treatment: Subjects received PHA-794428 or placebo as a subcutaneous injection.

Efficacy Evaluations: (None)

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Pharmacokinetic: Analysis of PHA-794428 in Serum

A blood sample (2 mL) was collected from baseline (Visit 2) to final visit (Visit 7). Samples were analyzed using a validated analytical method.

Pharmacodynamic: Analysis of ICF-1 and IGFBP-3 in Serum

A blood sample (2 mL) was collected at all visits. IGF-1 and IGFBP-3 were used as biomarkers for PHA-794428 activity. Samples were assayed using validated immunoassays.

Determination of anti PHA-794428/Anti hGH Antibodies

A blood sample (2 mL) was collected from baseline and follow-up visit. Samples were used to characterize any immunogenic response.

Safety Evaluations: Adverse events, laboratory assessments, blood pressure, weight and physical examinations were monitored throughout the study.

Pain at the site of injection was assessed using the Gracely Box scale at 1, 2 and 3 days postdose (Visits 2, 3 and 4).

Erythema/ eschar and oedema at the site of injection were assessed using the Draize scoring scale at all visits between baseline and the final (Visits 2 to 7). Where possible the Draize score was assessed by the same study personnel at each visit.

Statistical Methods: The PK, PD (IGF-1, IGFBP-3) and safety endpoints were tabulated and summarised by treatment. Where endpoints were collected on different days and at planned times postdose the summaries were also split by day/visit and/or time, as appropriate. Individual profile plots were produced for the serum PHA-794428, IGF-1 and IGFBP-3 concentrations over time.

RESULTS

Subject Disposition and Demography:

Eighteen subjects were screened, 15 subjects were treated and completed the study. Six subjects received 25 μg/kg, and 6 subjects received 50 μg/kg, 3 subjects received placebo. All subjects were included in the efficacy, PK, PD and safety analyses. Subjects were white

with a mean age of 8.7 years ranging from 6 to 12 years. Twelve (80.0%) subjects were male and 3 (20.0%) female; none of the females received placebo or 25 μg PHA-794428.

Thirteen (86.7%) subjects had a medical history of growth hormone deficiency and 5 (33.3%) had hypopituitarism; 1 (6.7%) subject had previously been diagnosed with hypothalamo-pituitary disorder.

The most common drug treatments prior to the start of the study were somatrophin (11 [73.3%]), levothyroxine sodium (5 [33.3%]), hydrocortisone (4 [26.7%]) and pituitary and hypothalamic hormones (4 [26.7%]) (Table 13.3.2.1). The most common concomitant medications were somatrophin (11 [73.3%]), levothyroxine sodium (5 [33.3%]) and hydrocortisone (4 [26.7%]) (Table 13.3.2.3). No prior non-drug treatments were recorded; concomitant non-drug treatments were of no clinical significance. All 15 subjects had previously taken GH, the mean dose 0.76 mg/kg ranged from 0.25 to 1.3 mg/kg. The average prior dose was similar for the 25 and 50 μg/kg PHA-794428 doses.

Efficacy Results: (None)

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

The PK parameters for serum PHA-794428 concentration are summarised in Table S2 and Figure S1. After dosing the time to peak serum concentration (T_{max}) was approximately 22 hours for both doses. The mean maximum serum concentrations of PHA-794428 (C_{max}) were 15.7 and 109.9 ng/mL for the 25 and 50 μg/kg doses, respectively.

Following single-dose administration of 25 and 50 μg/kg, serum exposure to PHA-794428 increased more than proportionally with increasing PHA-794428 dose. Of note, the highest AUC (about 4-fold higher than the mean value) was seen in the child who subsequently had lipoatrophy.

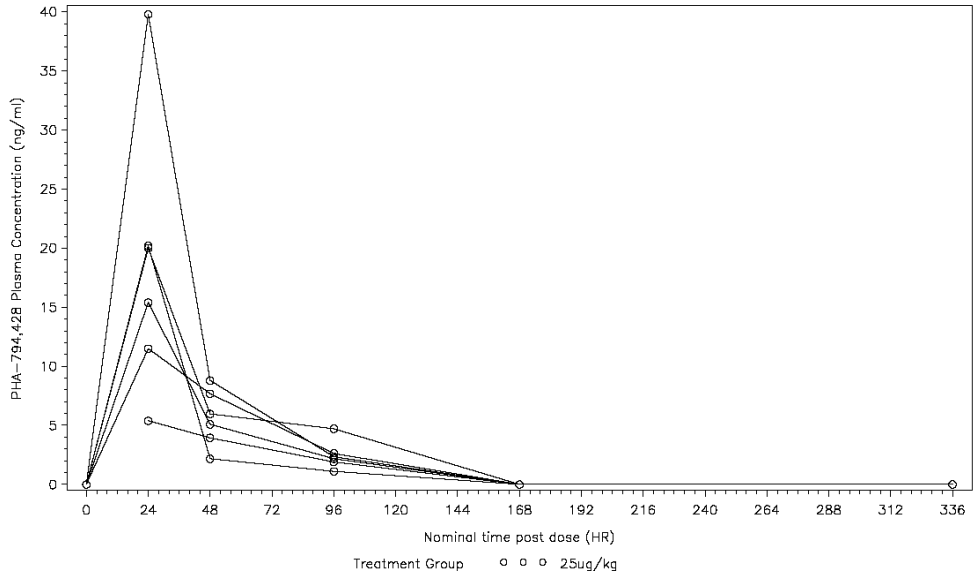
Serum concentrations exhibited a mean $t_{1/2}$ of approximately 20-33 hours. The terminal $t_{1/2}$ was not well estimated for some subjects because the data were so sparse.

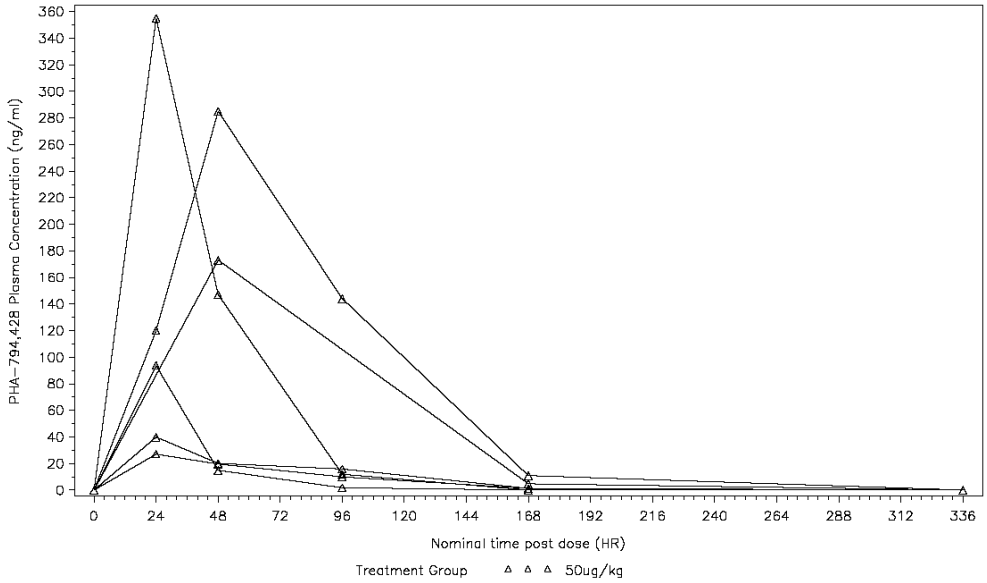
Table S2.PHA-794428 Pharmacokinetic Parameters

	25 µg/kg	50 µg/kg
N	6	6
AUC_{inf} (ng.h/mL)		
Mean[a] (CV%)	680.5 (44)	5200.1 (92)
Min, Max	433.0, 1340.0	1600.0, 20200.0
AUC_{last} (ng.h/mL)		
Mean[a] (CV%)	565.1 (52)	5103.8 (92)
Min, Max	303.0, 1240.0	1550.0, 19800.0
C_{max} (ng/mL)		
Mean[a] (CV%)	15.7 (63)	109.9 (83)
Min, Max	5.3, 39.8	27.1, 355.0
T_{max} (hours)		
Median (Min, Max)	21.9 (20.5, 24.0)	22.0 (20.5, 47.2)
$t_{1/2}$ (hours)		
Mean[b] (CV%)	33.1 (35)	20.0 (42)
Min, Max	23.0, 48.1	6.7, 28.0

CV=coefficient of variance
[a]Geometric mean
[b]Arithmetic mean

Figure S1. Individual PHA-794428 Concentrations Versus Time





The lower limit of quantification was 0.5 ng/mL

The mean percentage change from baseline IGF-1 increased from 24 hours after dosing with 25 and 50 µg/kg PHA-794428 reaching a peak at 48 hours for 25 µg/kg dose and 96 hours for both 50 µg/kg dose and placebo. The median times to maximum concentration (T_{max}) were 35, 48 and 92 hours for 3 treatment groups (Table S3).

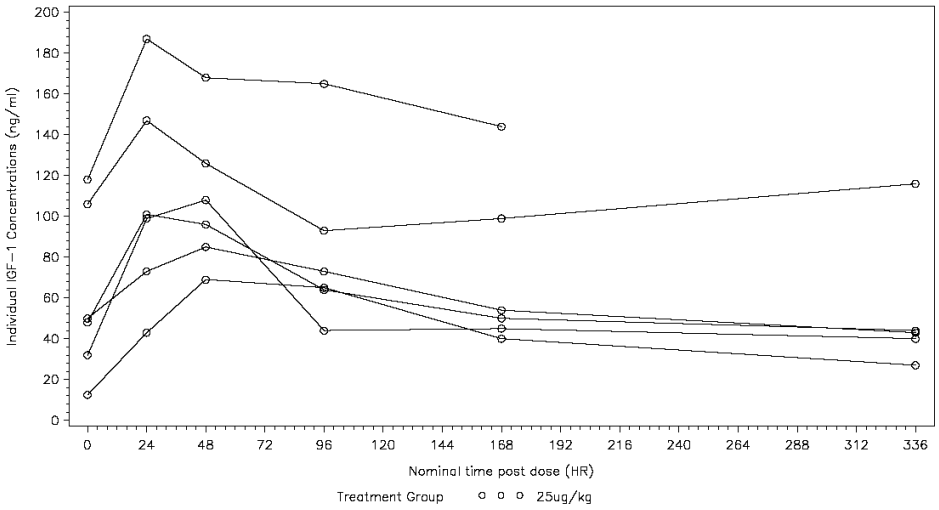
The PD parameters for IGF-1 are summarised in Table S3 and the individual IGF-1 concentration versus time profiles are shown in Figure S2. The IGF-1 concentrations after PHA-794428 administration increased over time. Mean maximum observed serum concentrations of IGF-1 (E_{max}) were 109.9 and 147.1 ng/mL for the 25 and 50 µg/kg doses, respectively. The mean E_{max} change from baseline in IGF-1 increased with increasing dose. The subject who developed lipoatrophy had the highest AUC values and E_{max} percentage change from baseline (836 ng/mL). The mean E_{max} changes from baseline for the 50 µg/kg dose were 88 and 56 ng/mL for the females (n=3) and males (n=3), respectively.

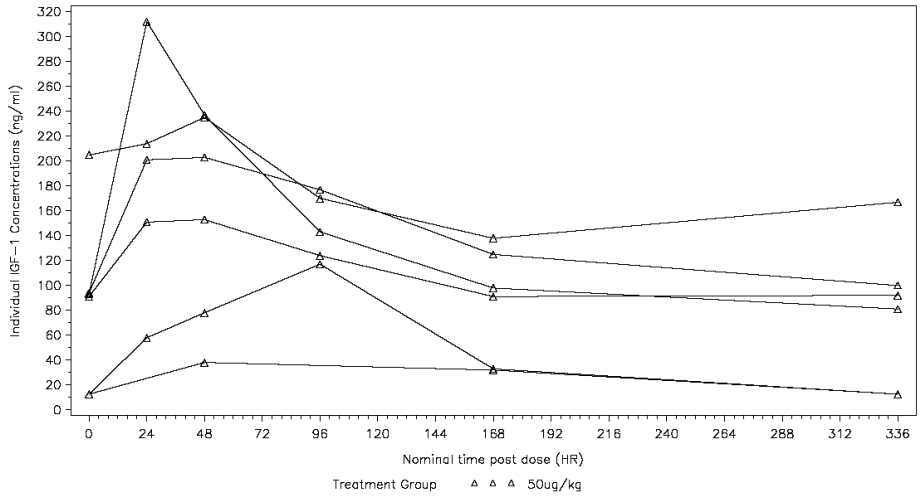
Table S3.Serum IGF-1 PD Parameters

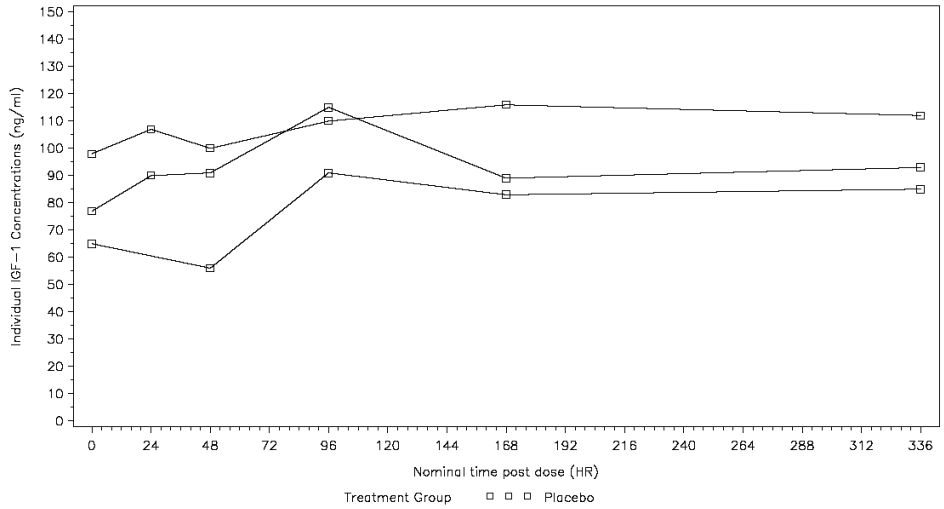
	25 µg/kg	50 µg/kg	Placebo
N	6	6	3
E_{max} (ng/mL)			
Mean[a] (CV%)	109.9 (37)	147.1 (54)	106.7 (13)
Min, Max	69.0, 187.0	38.0, 312.0	91.0, 116.0
E_{max} (change) (ng/mL)			
Mean[a] (CV%)	53.1 (30)	70.1 (99)	26.1 (39)
Min, Max	35.0, 76.0	25.5, 219.0	18.0, 38.0
E_{max} (% change) (ng/mL)			
Mean[a] (CV%)	111.0 (116)	129.1 (231)	33.1 (56)
Min, Max	39.0, 452.0	15.0, 836.0	18.0, 49.0
E_{av} (ng.h/mL)			
Mean[a] (CV%)	82.0 (45)	106.7 (48)	94.2 (17)
Min, Max	51.5, 160.1	32.2, 179.2	77.2, 110.0
T_{max} (hours)			
Median (Min, Max)	35 (21, 48)	48 (22, 94)	92 (60, 192)

CV=coefficient of variance
[a]Geometric mean

Figure S2. Individual IGF-1 Concentration Versus Time







The PD parameters for IGFBP-3 are summarised in Table S4. E_{max} and E_{av} values were similar for the 25, 50 µg/kg PHA-794428 and placebo doses.

Table S4.Serum IGFBP-3 PD Parameters

	25 µg/kg	50 µg/kg	Placebo
N	6	6	3
E_{max} (ng/mL)			
Mean (CV%)	3.9 (29)	4.0 (30)	3.6 (5)
Min, Max	2.5, 5.3	2.7, 6.1	3.4, 3.7
E_{av} (ng.h/mL)			
Mean (CV%)	3.3 (35)	3.8 (34)	3.4 (7)
Min, Max	2.0, 4.8	1.8, 5	3.1, 3.6
T_{max} (hours)			
Median (Min, Max)	48 (21,93)	48 (47, 94)	46 (44,92)

CV=coefficient of variance
[a] Geometric mean

Serum hGH Antibodies

Serum hGH antibodies were absent in 100% of subjects at baseline and follow-up.

Antibody Response

Serum antibody concentrations were absent in 100% of subjects at baseline and follow-up.

Safety Results:

Adverse Events

There were no SAEs, death, temporary discontinuations, dose reductions or discontinuations due to AEs during the study. Seventeen AEs were recorded for 9 subjects.

An overview of AEs is shown in Table S5. Nine (60.0%) subjects had at least 1 AE. A total of 17 AEs occurred during the study of which 10 were considered treatment related. The highest incidence for all causality and treatment-related AEs occurred in the in the 50 µg/kg treated subjects.

Table S5.Overview of all Adverse Events

	PHA-794428 25 µg/kg		PHA-794428 50 µg/kg		Placebo	
	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Subjects Evaluable for AEs	6	6	6	6	3	3
Number of AEs	6	1	9	8	2	1
Subjects with AEs	4	1	4	4	1	1
Subject with severe AE	0	0	1	1	0	0

Except for the number of AEs subjects were counted only once per treatment in each row.

Adverse events are summarised in Table S6. The most common treatment-emergent AE by body system was general disorders and administration site conditions (n=4). The most frequently reported all causality AEs were vertigo (n=2), headache (n=2) and injection site pain (n=2).

Table S6.Incidence of all Adverse Events

	PHA-794428 25 µg/kg		PHA-794428 50 µg/kg		Placebo	
Subjects Evaluable for AEs	6		6		3	
	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Vertigo	1	0	0	0	1	0
Injection Site Pain	0	0	2	2	0	0
Headache	1	0	1	1	0	0
Vomiting	0	0	1	0	0	0
Injection Site Erythema	1	1	0	0	0	0
Injection Site Haematomoa	0	0	1	1	0	0
Injections Site Induration	0	0	1	1	0	0
Influenza	1	0	0	0	0	0
Pain in Extremity	0	0	0	0	1	1
Depression	1	0	0	0	0	0
Cough	1	0	0	0	0	0
Epistaxis	0	0	1	1	0	0
Lipoatrophy	0	0	1	1	0	0
Skin Odour Abnormal	0	0	1	1	0	0

The majority of AEs were mild in severity, 1 severe event was recorded; a female aged 8 years, receiving 50 µg/kg PHA-794428, experienced severe injection site pain on Day 1 of dosing.

A total of 6 AEs associated with the injection site were recorded, all were considered treatment-related by the investigator and are summarised in Table S7.

Table S7.Treatment Related AEs Associated With Injection Site

	PHA-794428 25 µg/kg				PHA-794428 50 µg/kg				Placebo			
Preferred Term	N (%)	Mild	Moderate	Severe	N (%)	Mild	Moderate	Severe	N (%)	Mild	Moderate	Severe
Injection Site Erythema	1	1	0	0	0	0	0	0	0	0	0	0
Injection Site Haematomoa	0	0	0	0	1	1	0	0	0	0	0	0
Injection Site Induration	0	0	0	0	1	1	0	0	0	0	0	0
Injection Site Pain	0	0	0	0	2	1	0	1	0	0	0	0
Lipoatrophy	0	0	0	0	1	0	1	0	0	0	0	0

This study was suspended on 23 November 2006 due to reports of lipoatrophy AEs in the adult multiple dose study A6391003, before this suspension there had been no lipoatrophy events in this study; both studies were restarted, the following event occurred after this study had restarted.

One subject (white female aged 8 years, weight 25 kg, height 116.3 cm and BMI 18 kg/m^2), receiving 50 µg/kg PHA-794428, experienced lipoatrophy which was detected on Day 21, 488 hours postdose. The reaction was observed on the right thigh and measured 8 cm by 10 cm; there was no redness, pain or inflammation associated with the lipoatrophy. The

investigator considered this event to be of moderate severity. The lipoatrophy was considered resolved at the clinic visit on 09 April 2008.

Laboratory Abnormalities

Two subjects (25 µg/kg, n=1; 50 µg/kg, n=1) with normal baselines had abnormalities for eosinophil (absolute [>1.2xULN]) and eosinophil (% [>1.2xULN]). No subjects with abnormal baselines had laboratory abnormalities.

Vital Signs

Mean changes from baseline in blood pressure, temperature and pulse rate were small and were not regarded as clinically significant.

Body Weight

There were small increases in mean body weight across all treatment groups. There was no difference in change from baseline between the PHA-794428 treated subjects and placebo.

Gracely Score

The Gracely box scale was scored from 0 (no pain) to 20 (severe pain); the median scores recorded at 0, 12-24 and 48 hours postdose are summarised in Table S8. The highest scores recorded during this study were immediately post injection for subjects receiving 50 µg/kg PHA-794428 at 0 hours postdose. The scores for 25 µg/kg PHA-794428 were much lower. Subjects receiving placebo recorded 0 (no pain) for all time points.

Table S8. Gracely Box Scores

		Time Postdose (Hours)		
Dose (Median [Min, Max])	**N**	**0**	**12-24**	**48**
PHA-794428 25 µg/kg	6	0.5 (0, 2)	0 (0, 5)	0 (0, 0)
PHA-794428 50 µg/kg	5[a]	8 (0, 13)	0 (0, 0)	0 (0, 0)
Placebo	3	0 (0, 0)	0 (0, 0)	0 (0, 0)

[a] Due to an unplanned assessment Subject 10161002 was excluded from the median. At the unplanned assessment the Gracely score was recorded as 1.

The 2 highest scores recorded during the study were associated with the AE injection site pain; 1 subject experienced injection site pain, 0.5 hours postdose, which scored 10 (moderate) another subject experienced injection site pain, 0 hours postdose, which scored 13 (slightly intense). The subject who scored 8 (mild) 0 hours postdose did not have an associated AE.

Draize Score

The Draize score for erythema and eschar formation was assessed from 0 (no erythema) to 4 (severe erythema and eschar). There was no trend towards erythema and eschar formation with dose or time postdose. There were 6 reported cases of erythema and eschar formation

(score 1) at 0, 12-24 and 240-336 hours postdose for the 25 μg/kg PHA-794428 group and at 0, 12-24 and 96 hours for the 50 μg/kg PHA-794428 group.

The Draize score for oedema formation was assessed from 0 (no oedema) to 4 (severe oedema). There was no trend towards oedema formation with dose or time postdose. There were 2 reported cases of oedema formation (scores 1 and 3) in the 50 μg/kg PHA-794428 at 0 hours postdose.

CONCLUSIONS:

There was a non-linear, greater than proportional increase in concentration and exposure of PHA-794428 with dose. After dosing, the time (T_{max}) to reach maximum PHA-794428 serum concentration (C_{max}) was approximately 22 hours for both PHA-794428 doses. The mean maximum observed serum concentrations of PHA-794428 (C_{max}) were 15.7 and 109.9 ng/mL for the 25 and 50 μg/kg doses, respectively.

The pharmacodynamic response was shown by a dose related increase in IGF-1. Mean maximum observed serum concentrations of IGF-1 (E_{max}) were 109.9 and 147.1 ng/mL for the 25 and 50 μg/kg doses, respectively. E_{max} and E_{av} values for IGFBP-3 serum concentrations were similar for the 25, 50 μg/kg PHA-794428 and placebo doses.

Single 25 and 50 μg/kg doses of PHA-794428 were well tolerated; there were no deaths, SAEs or discontinuations due to AEs. There was 1 lipoatrophy AE. There were no clinically important laboratory test abnormalities or changes in vital signs. Few subjects experienced pain, erythema, eschar or oedema at the injection site. There was no evidence of a humoral response.