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COMPOUND NUMBER: PHA-794428

PROTOCOL NO.: A6391002

PROTOCOL TITLE: An Open Label, Two Period Crossover Study to Explore the Safety, Pharmacokinetics and Pharmacodynamics of PHA-794428 After Single Subcutaneous Injections in Adult Male Patients With Growth Hormone Deficiency

Study Center: One (1) center in Belgium took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 16 June 2005 to 07 September 2005

Phase of Development: Phase 2

Study Objectives:

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

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

METHODS

Study Design: This was a randomized, open-label, 2-period, single dose cross over study in male AGHD subjects. Subjects were randomized into 2 groups and each group received 2 single doses of PHA-794428. There was a 3-week washout between doses. The study planned to recruit 8 subjects, 4 subjects to each group, to ensure that complete data were collected for at least 6 subjects. Subjects receiving current treatment with growth hormone therapy stopped their treatment at least 2 weeks before the first dose of PHA-794428. The timing of testosterone replacement therapy was controlled and other hypopituitarism treatments were maintained without change. For each subject the study consisted of:

- A screening visit up to 5 weeks before the start of dosing.

- Two (2) treatment periods (1 and 2) of 15 days, each consisting of an open label injection of PHA-794428.

- A wash-out period of 3 weeks between dosing in Period 1 and 2.

- A follow-up visit 3-4 weeks after the last dose of PHA-794428.

The planned duration per subjects was 15 weeks. Study procedures for the screening visit, Periods 1 and 2 and the final visit are shown in Table 1.

Table 1. Schedule of Study Activities

Period	Screen	Period 1								Washout	Period 2	FU
Days		**D 0**	**D 1**	**D 2**	**D 3**	**D5**	**D 8**	**D 11**	**D 15**		**Same as Period 1**	**3-4 Weeks Post Last Dose**
Hours			**0-24**	**24**	**48**	**96**	**168**	**240**	**336**	Three (3) weeks washout between injections of PHA-794428		
Informed consent	X											
Randomization		X[a]										
Stop GH treatment	X											
Medical history	X											
Physical examination[b]	X	X			X				X			X
Weight	X	X	X	X	X	X	X	X	X			X
Height	X											
Laboratory tests												
Hematology	X	X										X
Blood chemistry	X	X			X		X		X			X
Urinalysis	X	X			X		X		X			X
Glucose and insulin	X		X		X		X		X			X
T3 and T4	X		X				X					X
Free testosterone and oestradiol	X		X				X					X
Assessments												
BP and pulse rate	X		X[c]	X	X	X	X	X	X			X
ECG	X		X[d]		X		X		X			X
Adverse events			X	X	X	X	X	X	X			X
Investigational treatment			X[e]									
PD blood sampling for IGF-1	X	X	X[f]	X[g]	X	X	X	X	X			X
PHA-794428 PK blood sampling			X	X	X	X	X	X	X			
Blood sampling for PHA-794428 antibodies		X										X
Retained blood sample			X[a]									
HIV-Hepatitis B and C	X											
Urine drug screen	X	X										
Breath alcohol test		X										
Draize Score		X	X[h]	X	X	X	X	X	X			
Gracely Box Scale		X	X[i]	X	X							
Temperature	X	X	X	X	X	X	X	X	X			X

Table 1. Schedule of Study Activities

Period	Screen	Period 1								Washout	Period 2	FU
Days		**D 0**	**D 1**	**D 2**	**D 3**	**D5**	**D 8**	**D 11**	**D 15**		**Same as Period 1**	**3-4 Weeks Post Last Dose**
Hours			**0-24**	**24**	**48**	**96**	**168**	**240**	**336**	[a]		
Ring size			X	X	X	X	X	X	X			

BP = blood pressure; D = day; ECG = electrocardiogram; FU = follow-up; GH = growth hormone; HIV = human immunodeficiency virus; IGF-1 = insulin-like growth factor 1; PD = pharmacodynamics; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxin; Screen = screening.

a. Period 1 only.
b. Full physical examination at Screening and FU. Abbreviated examination at admission on Days 0, 3 and 15.
c. BP and pulse rate at predose and 6 and 12h postdose.
d. ECG at predose and 12h postdose.
e. PD blood sampling for IGF-1 on Day 1 at predose, 4 and 12h postdose.
f. PHA-794428 PK blood sampling on Day 1 at predose, 1, 2, 4, 6, 12h postdose.
g. PHA-794428 PK blood sampling on Day 2: 24 and 36h post-dosing.
h. Draize Score 1, 6 and 12h post dose.
i. Gracely Box Score 0.5, 1, 3, 6 and 12h postdose.

Number of Subjects (Planned and Analyzed): It was planned to randomize a total of 8 subjects with the intention that at least 6 subjects would complete the study. Clinical trial simulations using 6, 8 and 12 subjects indicated that this sample size would be sufficient to provide relevant PK and PD information to support the study objectives. Seven (7) subjects: 3 subjects received 20µg/kg PHA-794428 followed by 60µg/kg PHA-794428 and 4 subjects 60µg/kg PHA-794428 followed by 20µg/kg PHA-794428 were screened, randomized, treated and included in PK, PD and safety analysis.

Diagnosis and Main Criteria for Inclusion: Adult male subjects with severe growth hormone deficiency (GHD) aged 25 to 60 years with a weight of 60 to 100 kg and body mass index (BMI) of 18 to 30 kg/m^2 were included in the study.

Exclusion Criteria: Subjects with history or evidence of clinically significant disease other than hypopituitarism, hepatic disease, allergies especially drug hypersensitivity, drug abuse, uncontrolled pituitary tumour growth within 3 mm of the optic chiasm, other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have been increased the risk associated with trial participation or investigational product administration, received any experimental drug within the past 4 months (prior to the first dosing day of the study), donated blood during the previous 2 months or intend to donate blood or blood products during the study or for 2 months following the completion of the study, positive result from human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb) screening tests or anti-hepatitis C virus serology were excluded.

Study Treatment: Subjects received a single dose of PHA-794428 on Day 1 of each treatment period. One (1) group received a single subcutaneous injection of 20 µg/kg PHA-794428 in the first period followed by a single injection of 60 µg/kg in the second period. The second group received the higher dose in the first period followed by the lower dose in the second period.

Treatment was supplied as a lyophilized solid and after reconstitution with water administered as subcutaneous injections in the morning (ie between 08:00 am and 10:00 am) while the subject was sitting in their bed. Subjects remained semi-recumbent for at least 1 hour after dosing. Subcutaneous injections were administered through the same procedure at the same site of injection for all subjects: the right thigh on a site devoid of any current skin alteration/erythema/spot. In each period study treatment was administered for 15 days each and there was 3-weeks washout period between 2 periods.

Pharmacokinetic and Safety Endpoints:

Primary Endpoints:

- Safety and tolerance of a single subcutaneous injection of PHA-794428: Monitoring of adverse events (AEs), safety laboratory parameters, vital signs, physical examination, body temperature, electrocardiogram (ECG), signs of fluid retention (body weight, ring size measurement), reactions at the injection site (Draize Scoring and Gracely Box Scale).

- PD effects of PHA-794428 on insulin-like growth factor 1 (IGF-1).

- PHA-794428 PK (area under the concentration time curve extrapolated to infinity [AUC], maximum observed concentration [C_{max}], time to C_{max} [T_{max}], terminal half life [$t_{½}$]) after single subcutaneous injection.

Secondary Endpoints:

- Analysis of any antibody reaction, based on the titers of anti-human growth hormone and anti PHA-794428 antibodies taken before each dosing and 3-4 weeks following the second dose.

No efficacy evaluations were performed for this study.

Safety Evaluations: Evaluations included recording of AEs, physical examinations, laboratory tests, vitals signs and ECGs that were performed at Screening and at intervals up to 336 hours postdose and at Follow-up. The following were also recorded: body weight, ring size, oral temperature and reactions at injection site measured by Gracely Box and Draize scores.

Statistical Methods: All subjects were included in data presentations of PK and PD summaries provided they received at least 1 dose of PHA-794428 and did not violate any major inclusion/exclusion criteria.

The safety set consisted of all subjects who received at least 1 dose of PHA-794428.

No statistical hypotheses were tested. Descriptive statistics for serum PK parameters C_{max}, T_{max}, AUC, AUC_{last} and $t_{½}$ were presented for each dose group. Descriptive statistics for PD parameters maximum PD effect (E_{max}), E_{max} percentage change from Baseline, T_{max}, average PD effect (E_{av}) and E_{av} change were also presented for each dose group. AEs, clinical laboratory test results, vital signs, body weight, ring size, oral temperature and reactions at injection site (Gracely Box and Draize scores) were enlisted and changes from Baseline were summarized.

RESULTS

Subject Disposition and Demography: Seven (7) subjects were screened, randomized, entered and completed both periods of the study. No subjects withdrew from the study. Three (3) subjects were randomized to receive 20 µg/kg PHA-794428 followed by 60 µg/kg PHA-794428 and 4 subjects were randomized to receive 60 µg/kg PHA-794428 followed by 20 µg/kg PHA-794428. All 7 subjects were included in PK and PD evaluations. One (1) subject did not attend the clinic on Days 11 and 15 of Period 1. PD and safety data are therefore missing for this subject on these days. Subject's disposition and data set analyzed are summarized in Table 2.

Table 2. Subject Evaluation Group

Number of Subjects	PHA-794428	
	20 µg/kg	60 µg/kg
Assigned to study treatment = 7		
Treated	7	7
Completed	7	7
Discontinued	0	0
Analyzed for PK		
PK	7	7
Analyzed for PD		
PD	7	7
Analyzed for safety		
AEs	7	7
Laboratory data	7	7
Vital signs	7	7
ECG	7	7

AE = adverse events; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetics.

All subjects were White males with severe AGHD. Demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics (All Subjects)

	All Treatment Male
Number of subjects	7
Age (years)	
<18	0
18-25	1
26-35	1
36-45	2
>45	3
Mean	46.3
SD	16.2
Range	25-64
Weight (kg)	
Mean	83.4
SD	10.5
Range	72-103
Body mass index (kg/m^2)	
Mean	27.0
SD	2.8
Range	23-31

SD = standard deviation.

Pharmacokinetic and Pharmacodynamic Results:

Pharmacodynamic Result: The PD parameters for IGF-1 following each dose of PHA-794428 are summarised in Table 4. Serum concentrations of IGF-1 were raised for >168 hours (7 days) in both dose groups.

Table 4. Mean (and Range) Pharmacodynamic Parameters for IGF-1

Parameters (N=7/group)	20 µg/kg PHA-794428		60 µg/kg PHA-794428	
E_{max} (ng/ml)	153.3	(85, 315)	286.5	(193, 417)
E_{max} (% change)	128.5[a]	(38, 233)	302.0[b]	(183, 584)
E_{av} (ng/ml)	121.1	(69, 266)	207.4	(100, 307)
T_{max} (h)	75.4	(48, 96)	61.7	(48, 96)

Geometric means are presented for Eav , Emax and Emax (% change) and arithmetic means for Tmax..
Eav = average PD effect; Emax = maximum PD effect; IGF-1 = Insulin-like growth factor 1; N = number of subjects; PD = pharmacodynamics; Tmax = time to maximum observed concentration.
a. N=5 as Emax baseline was below the limit of quantification for 2 subjects.
b. N=6 as Emax baseline was below the limit of quantification for 1 subject.

Pharmacokinetic Result: The PK parameters of PHA-794428 following each dose are summarised in Table 5. The coefficients of variation (CV%) for AUC and C_{max} were 38.3% and 54.9%, respectively, in the 20 µg/kg group and 69.3% and 79.3%, respectively, in the 60 µg/kg group.

Table 5. Mean (and Range) Pharmacokinetic Parameters for PHA-794428

Parameters (N=7/group)	20 µg/kg PHA-794428		60 µg/kg PHA-794428	
C_{max} (ng/ml)	12.38	(4.3, 27.4)	56.34	(35.2, 185.0)
T_{max} (h)	23.1	(6, 48)	27.6	(1, 36)
AUC (ng.h/ml)	864	(537, 1550)	3642[a]	(2070, 9640)
AUC_{last} (ng.h/ml)	823	(480, 1540)	3303	(1980, 9600)
$t_{½}$ (h)	43.29	(30.1, 69.1)	43.32[a]	(24.0, 65.9)

Geometric means are presented for AUC_{last}, AUC and C_{max}, and arithmetic means for T_{max} and $t_{½}$.
AUC = area under the concentration time curve extrapolated to infinity; AUC_{last} = area under the concentration time curve until the last measurable concentration timepoint; C_{max} = maximum observed concentration; N = number of subjects; $t_{½}$ = terminal half life; T_{max} = time to C_{max}.
a. N=6 as $t_{½}$ was not recorded for 1 subject.

Antibody Results: There was no evidence of a humoral response to PHA-794428 as no immunoglobulin G (IgG) antibodies were detected after either dose.

No efficacy evaluations were performed for this study.

Safety Results: One (1) subject experienced a treatment-emergent AE (TEAE). This AE was considered treatment-related. This subject had mild diarrhea that occurred on the day he was administered 60 µg/kg PHA-794428. The event resolved on the same day. Others were reported, but were not treatment-emergent. The TEAE all causality and treatment-related was summarized in Table 6 and Table 7.

Table 6. Treatment-Emergent Adverse Events (All Causalities)

Number (%) of Subjects Evaluable for AEs System Organ Class MedDRA (v8.0) Preferred Term	20 µg/kg PHA-794428 (n=7)	60 µg/kg PHA-794428 (n=7)
Gastrointestinal disorders	0	1
Diarrhoea	0	1
Total preferred term	0	1

Subjects were only counted once per treatment for each row.
Includes data up to 14 days after last dose of study drug.
MedDRA (v8.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Table 7. Treatment-Emergent Adverse Events (Treatment-Related)

Number (%) of Subjects Evaluable for AEs System Organ Class MedDRA (v8.0) Preferred Term	20 µg/kg PHA-794428 (n=7)	60 µg/kg PHA-794428 (n=7)
Gastrointestinal disorders	0	1
Diarrhoea	0	1
Total preferred term	0	1

Subjects were only counted once per treatment for each row.
Includes data up to 14 days after last dose of study drug.
MedDRA (v8.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Serious Adverse Events (SAEs): There were no SAEs occurred during the study.

Permanent or Temporary Discontinuations or Dose Reduction due to Adverse Events: No subject discontinued the study due to an AE and no subject had a dose reduced or temporary discontinuation of study drug due to AEs.

Deaths: No deaths were reported in this study.

Laboratory Test Results: Single doses of PHA-794428 did not affect aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, fasting glucose, creatinine, insulin and blood urea nitrogen in these adults with severe GHD. Urine blood and insulin values below the lower limit of normal were the most commonly reported laboratory test abnormalities. Six (6) subjects had abnormal insulin levels and urine blood was reported in 5 subjects. In addition, 2 subjects with normal baseline values had raised potassium 3 days after dosing (1 subject after 20 µg/kg and 1 subject after 60 µg/kg). These values returned to normal by Day 15 for 1 subject and Day 24 for 1 subject. There was no evidence of a relationship between either dose of PHA-794428 and any laboratory parameter change. The incidence of laboratory test abnormalities at Normal Baseline and Abnormal Baseline is presented in Table 8 and Table 9, respectively.

Table 8. Incidence of Laboratory Test Abnormalities (Normal Baseline)

				PHA-794428 20 µg/kg		PHA-794428 60 µg/kg	
Number of Subjects Evaluable for Laboratory Abnormalities				**7**		**7**	
Number (%) With Laboratory Abnormalities				**4**		**4**	
Group	**Parameter**	**Units**	**Criteria**	**N**	**n**	**N**	**n**
Liver function	Total bilirubin	MG/DL	>1.5 × ULN	5	0	6	0
	Direct bilirubin	MG/DL	>1.5 × ULN	6	0	6	0
	Indirect bilirubin	MG/DL	>1.5 × ULN	5	0	6	0
	AST (SGOT)	IU/L	>3.0 × ULN	6	0	7	0
	ALT (SGPT)	IU/L	>3.0 × ULN	6	0	6	0
	GGT	IU/L	>3.0 × ULN	6	0	6	0
	Alkaline phosphatase	IU/L	>3.0 × ULN	7	0	7	0
	Total protein	G/DL	<0.8 × LLN	7	0	7	0
			>1.2 × ULN	7	0	7	0
	Albumin	G/DL	<0.8 × LLN	7	0	7	0
			>1.2 × ULN	7	0	7	0
Renal function	BUN	MG/DL	>1.3 × ULN	7	0	6	0
	Creatinine	MG/DL	>1.3 × ULN	7	0	7	0
	Uric acid	MG/DL	>1.2 × ULN	7	0	7	0
Electrolytes	Sodium	MEQ/L	<0.95 × LLN	6	0	6	0
			>1.05 × ULN	6	0	6	0
	Potassium	MEQ/L	<0.9 × LLN	6	0	6	0
			>1.1 × ULN	6	1	6	1
	Chloride	MEQ/L	<0.9 × LLN	7	0	6	0
			>1.1 × ULN	7	0	6	0
	Calcium	MG/DL	<0.9 × LLN	7	0	6	0
			>1.1 × ULN	7	0	6	0
	Bicarbonate	MEQ/L	<0.9 × LLN	6	0	5	0
			>1.1 × ULN	6	0	5	0
Clinical chemistry	Glucose (fasting)	MG/DL	>1.5 × ULN	6	0	6	0
(Other)			<0.6 × LLN	6	0	6	0
Urinalysis	Urine specific		<1.003	1	0		
(dipstick)	Gravity		>1.030	1	0		
	Urine pH		<4.5	7	0	7	0
			>8	7	0	7	0
	Urine glucose (Qual)		≥1	7	0	7	0
	Urine ketones (Qual)		≥1	7	0	7	0

Table 8. Incidence of Laboratory Test Abnormalities (Normal Baseline)

				PHA-794428 20 µg/kg		PHA-794428 60 µg/kg	
Number of Subjects Evaluable for Laboratory Abnormalities				**7**		**7**	
Number (%) With Laboratory Abnormalities				**4**		**4**	
Group	**Parameter**	**Units**	**Criteria**	**N**	**n**	**N**	**n**
	Urine protein (Qual)		≥1	7	0	7	0
Urinalysis (dipstick)	Urine blood/Hgb (Qual)		≥1	4	1	5	3
	Urine bilirubin (Qual)		≥1	1	0		
Miscellaneous	Insulin	IU/L	<LLN	1	3	6	2
			>ULN	6	1	6	0

Percentages are displayed for the laboratory tests having a category ≥50 evaluable subjects.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; Hgb = hemoglobin; LLN = lower limit of normal; N = total number of subjects with normal or missing baseline with at least 1 observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with normal or missing baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; Qual = qualitative; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

Table 9. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

					PHA-794428 20 µg/kg		PHA-794428 60 µg/kg	
Number of Subjects Evaluable for Laboratory Abnormalities					**5**		**6**	
Number (%) With Laboratory Abnormalities					**3**		**2**	
Group	**Parameter**	**Units**	**Primary Criteria**	**Secondary Criteria**	**N**	**n**	**N**	**n**
Liver function	Total bilirubin	MG/DL	>1.5 × ULN	>1.5 × baseline	2	0	1	0
	Direct bilirubin	MG/DL	>1.5 × ULN	>1.5 × baseline	1	0	1	0
	Indirect bilirubin	MG/DL	>1.5 × ULN	>1.5 × baseline	2	0	1	0
	AST (SGOT)	IU/L	>3.0 × ULN	>1.5 × baseline	1	0		
	ALT (SGPT)	IU/L	>3.0 × ULN	>1.5 × baseline	1	0	1	0
	Gamma GT	IU/L	>3.0 × ULN	>1.5 × baseline	1	0	1	0
Renal function	BUN	MG/DL	>1.3 × ULN	>1.3 × baseline			1	0
Electrolytes	Sodium	MEQ/L	<0.95 × LLN	<0.95 × baseline	1	0	1	0
			>1.05 × ULN	>1.05 × baseline	1	0	1	0
	Potassium	MEQ/L	<0.9 × LLN	<0.9 × baseline	1	0	1	0
			>1.1 × ULN	>1.1 × baseline	1	0	1	0
	Chloride	MEQ/L	<0.9 × LLN	<0.9 × baseline			1	0
			>1.1 × ULN	>1.1 × baseline			1	0
	Calcium	MG/DL	<0.9 × LLN	<0.9 × baseline			1	0
			>1.1 × ULN	>1.1 × baseline			1	0
	Bicarbonate	MEQ/L	<0.9 × LLN	<0.75 × baseline	1	0	2	0
			>1.1 × ULN	>1.25 × baseline	1	0	2	0
Clinical chemistry (Other)	Glucose (Fasting)	MG/DL	>1.5 × ULN	>1.25 × baseline	1	0	1	0
			<0.6 × LLN	<0.75 × baseline	1	0	1	0
Urinalysis (dipstick)	Urine blood/Hgb (Qual)		≥1	≥1	3	2	2	2
Miscellaneous	Insulin	IU/L	<LLN	<LLN	1	1	1	0
			>ULN	>ULN	1	0	1	0

Percentages are displayed for the laboratory tests having a category ≥50 evaluable subjects.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; Hgb = hemoglobin; LLN = lower limit of normal; N = total number of subjects with abnormal baseline with at least 1observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with abnormal baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; Qual = qualitative; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

Vital Signs: Mean changes from Baseline in BP and pulse rate were small and were not regarded as clinically significant (Table 10).

Table 10. Vital Signs: Mean Baseline and Mean Changes From Baseline

Measurement Day	Time Postdose (Hours)	PHA-794428 20 µg/kg Mean	SD	N	PHA-794428 60 µg/kg Mean	SD	N
Supine Systolic BP (mmHg)							
1	Baseline	118.6	23.9	7	118.1	20.2	7
	6	-3.0	8.0	7	-0.9	8.5	7
	12	3.3	16.0	7	3.0	6.2	7
2	24	-4.3	4.2	7	-0.4	9.7	7
3	48	1.9	7.9	7	2.6	10.4	7
5	96	3.0	6.4	7	4.3	8.3	7
8	168	4.1	8.5	7	3.0	7.3	7
11	240	2.6	7.2	7	7.0	9.5	6
15	336	0.4	7.1	7	0.8	6.8	6
Supine Diastolic BP (mmHg)							
1	Baseline	72.3	14.8	7	69.7	10.2	7
	6	-4.0	7.1	7	-3.9	5.6	7
	12	-2.7	10.2	7	1.0	3.4	7
2	24	-3.1	4.0	7	0.3	4.3	7
3	48	2.0	4.8	7	3.6	4.1	7
5	96	4.0	3.3	7	6.7	6.4	7
8	168	2.4	5.7	7	5.0	6.2	7
11	240	3.4	4.3	7	5.3	6.7	6
15	336	1.1	5.1	7	3.0	4.8	6
Supine Pulse Rate (bpm)							
1	Baseline	53.6	7.2	7	52.3	10.7	7
	6	1.0	6.0	7	3.0	7.5	7
	12	1.3	5.3	7	2.1	5.1	7
2	24	1.1	8.1	7	1.7	5.0	7
3	48	3.0	5.0	7	7.1	6.1	7
5	96	5.0	9.4	7	9.9	9.9	7
8	168	4.3	8.3	7	4.9	8.1	7
11	240	3.1	7.7	7	5.5	7.2	6
15	336	2.9	10.0	7	7.8	5.1	6

The means listed are the changes from treatment Baseline for all times postdose after baseline.
Baseline is the last pre-treatment measurement prior to treatment of Day 1.
Day was relative to first day of each treatment period. First day of each treatment period = Day 1.
BP = blood pressure; N = number of subjects; SD = standard deviation.

Physical Examination: The results of subjects' physical examinations did not change after study drug administration.

Body Temperature: Mean oral temperature is presented in Table 11. Mean changes from Baseline in oral body temperature were not clinically significant (Table 12).

Table 11. Summary of Oral Temperature (Degree C)

Time Postdose (Hours)	PHA-794428 20 µg/kg			PHA-794428 60 µg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	36.4	0.53	7	36.6	0.53
24	7	36.3	0.49	7	36.3	0.49
48	7	36.7	0.49	7	36.7	0.49
96	7	36.4	0.53	7	36.6	0.53
168	7	36.3	0.76	7	36.3	0.49
240	7	36.4	0.53	6	36.2	0.75
336	7	36.4	0.53	6	36.2	0.41

The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

Table 12. Summary of Oral Temperature (Degree C): Baseline and Mean Changes From Baseline

Time Postdose (Hours)	PHA-794428 20 µg/kg			PHA-794428 60 µg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	36.4	0.53	7	36.6	0.53
24	7	-0.1	0.38	7	-0.3	0.49
48	7	0.3	0.49	7	0.1	0.69
96	7	0.0	0.82	7	0.0	0.58
168	7	-0.1	1.07	7	-0.3	0.76
240	7	0.0	0.58	6	-0.3	0.52
336	7	0.0	0.82	6	-0.3	0.52

Baseline is the predose measurement in each period.
The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

ECG: Mean baseline and mean changes from Baseline in ECG parameters (heart rate, PR interval, QRS width, QT interval and QT interval corrected using Bazett's formula (QTc) interval are shown in Table 13. One (1) subject had a >30 msec increase in QT interval corrected using Fridericia's formula (QTcF) interval (1 subject: change in QTcF from Baseline +57 msec, 12 hours after a 60µg/kg PHA-794428 dose).

Table 13. ECG: Mean Baseline and Mean Changes From Baseline

ECG Parameter Day[a]	Time Postdose (Hours)	PHA-794428 20 μg/kg N	Mean	SD	PHA-794428 60 μg/kg N	Mean	SD
Heart Rate (bpm)							
Baseline	0	7	54.4	6.4	7	53.7	11.0
1	12	7	2.9	4.0	7	4.4	5.0
3	48	7	2.0	6.3	7	7.3	9.3
8	168	7	2.6	5.6	7	2.6	8.4
15	336	7	3.3	5.2	6	6.3	4.8
PR Interval (msec)							
Baseline	0	7	176.3	17.4	7	175.7	21.5
1	12	7	-1.3	9.3	7	-6.1	10.6
3	48	7	-1.7	9.0	7	-3.4	10.5
8	168	7	-2.4	13.5	7	-2.9	11.4
15	336	7	-5.6	12.2	6	-0.3	12.0
QRS Width (msec)							
Baseline	0	7	95.7	5.0	7	95.3	6.1
1	12	7	1.6	3.0	7	2.0	2.4
3	48	7	0.4	3.2	7	0.0	2.9
8	168	7	-1.7	3.3	7	2.7	3.5
15	336	7	0.7	3.6	6	-0.2	1.9
QT Interval (msec)							
Baseline	0	7	387.9	18.4	7	391.4	26.6
1	12	7	-2.0	15.8	7	3.1	21.9
3	48	7	-5.3	10.2	7	-23.4	21.0
8	168	7	-2.4	17.9	7	-7.4	19.8
15	336	7	0.6	14.2	6	-13.7	19.0
QTc (Fridericias) Interval (msec)							
Baseline	0	7	374.3	9.6	7	374.5	15.8
1	12	7	3.8	15.0	7	14.5	19.7
3	48	7	-2.1	11.8	7	-5.3	12.8
8	168	7	3.4	14.5	7	0.3	9.7
15	336	7	7.4	11.6	6	3.1	13.4
QTc Interval (msec)							
Baseline	0	7	367.4	13.6	7	366.4	23.1
1	12	7	6.9	16.9	7	19.7	21.3
3	48	7	-0.1	17.1	7	3.0	21.2
8	168	7	6.3	16.3	7	3.9	14.0
15	336	7	11.1	13.6	6	10.7	14.6

Baseline has been taken as the last non-missing value prior to dosing.
The mean listed was the change from Baseline for all times postdose after baseline.
ECG = electrocardiogram; N = number of subjects; QTc = QT corrected for heart rate using the Bazetts formula; SD = standard deviation.
a. Day relative to start of study treatment (Day 1).

Sign of Fluid Retention:

Ring Size: Mean ring size is presented in Table 14. Mean changes from Baseline in were small (Table 15). Fourteen (14) days after injection the mean change from Baseline in ring size was -0.7 in the 20 µg/kg PHA-794428 dose group and -1.2 in the 60 µg/kg PHA-794428 dose group.

Table 14. Summary of Ring Size

Time Postdose (Hours)	PHA-794428 20 µg/kg			PHA-794428 60 µg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	40.7	4.99	7	40.7	4.89
24	7	40.6	5.06	7	40.3	5.12
48	7	40.9	4.81	7	41.0	5.35
96	7	40.7	4.89	7	40.7	4.82
168	7	40.6	4.86	7	40.7	4.61
240	7	41.0	4.62	6	40.5	5.43
336	7	40.0	4.20	6	39.7	5.82

The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

Table 15. Summary of Ring Size: Baseline and Mean Changes From Baseline

Time Postdose (Hours)	PHA-794428 20 µg/kg			PHA-794428 60 µg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	40.7	4.99	7	40.7	4.89
24	7	-0.1	0.90	7	-0.4	1.13
48	7	0.1	1.07	7	0.3	1.11
96	7	0.0	1.00	7	0.0	0.82
168	7	-0.1	0.90	7	0.0	1.29
240	7	0.3	0.95	6	-0.3	1.21
336	7	-0.7	1.70	6	-1.2	1.72

Baseline is the predose measurement in each period.
The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

Body Weight: Small increases in mean body weight from Baseline were recorded (1.3 kg and 1.5 kg 14 days postdose in the 20 µg/kg and 60 µg/kg PHA-794428 dose groups, respectively; Table 17). Mean body weight is presented in Table 16. Maximum changes in body weight for individual subjects were not clinically significant.

Table 16. Summary of Body Weight

Time Postdose (Hours)	PHA-794428 20 μg/kg			PHA-794428 60 μg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	82.0	11.14	7	82.0	11.52
24	7	82.1	11.45	7	82.3	11.83
48	7	82.1	11.55	7	82.4	11.47
96	7	82.4	11.13	7	83.3	11.34
168	7	83.0	11.27	7	83.1	11.48
240	7	83.0	11.34	6	83.8	12.73
336	7	83.3	11.41	6	84.0	12.98

The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

Table 17. Summary of Body Weight: Baseline and Mean Changes From Baseline

Time Postdose (Hours)	PHA-794428 20 μg/kg			PHA-794428 60 μg/kg		
	N	Mean	SD	N	Mean	SD
Baseline	7	82.0	11.14	7	82.0	11.52
24	7	0.1	0.38	7	0.3	0.76
48	7	0.1	0.69	7	0.4	0.53
96	7	0.4	0.79	7	1.3	1.11
168	7	1.0	0.58	7	1.1	1.07
240	7	1.0	0.58	6	1.3	1.21
336	7	1.3	0.49	6	1.5	0.84

Baseline is the predose measurement in each period.
The means listed were for planned times postdose.
N = number of subjects; SD = standard deviation.

Gracely Box Scale: Subjects recorded no pain at the injection site at most timepoints after either dose of PHA-794428. The maximum Gracely Box score recorded was 2. The Gracely Box scale has a score of 0 for no pain and 20 for intense pain.

Draize Score: Two (2) subjects recorded Draize scores of 1 at single timepoints after dosing. One (1) subject recorded Draize scores of 1 at 2 consecutive timepoints after dosing. Most subjects experienced no erythema, eschar or edema following injections of PHA-794428. The Draize score ranges from 0 (none) to 4 (severe).

CONCLUSIONS:

- Mean C_{max} of PHA-794428 were 12.38 and 56.34 ng/ml in the 20 μg/kg and 60 μg/kg dose groups, respectively. The mean AUC was 864 ng.h/ml in the 20 μg/kg group and 3642 ng.h/ml in the 60 μg/kg group. $t_{½}$ was similar with both doses (43.3 hours).

- Mean E_{max} of IGF-1 were 153.3 ng/ml and 286.5 ng/ml in the 20 μg/kg and 60 μg/kg dose groups, respectively. Mean percentage changes from Baseline in IGF-1 were 128.5% and 302.0% in the 2 dose groups. Serum IGF-1 concentrations were raised for >168 hours (7 days) in both treatment groups.

- Single 20 μg/kg and 60 μg/kg doses of PHA-794428 were well tolerated by AGHD subjects in this study. There were no serious or severe AEs and no subjects withdrew from the study. One (1) AE was recorded as treatment-emergent (mild treatment-related diarrhea). There were no notable laboratory test abnormalities or changes in vital signs. Few subjects experienced any pain, erythema, eschar or edema at the injection site and there were no signs of fluid retention assessed by changes in ring size.

- There was no evidence of a humoral response to PHA-794428 as no IgG antibodies were detected after either dose.