PHASE 1 STUDY OF THE NOVEL A-TYPE NATRIURETIC RECEPTOR AGONIST, PL-3994, IN HEALTHY VOLUNTEERS

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ABSTRACT

Introduction: PL-3994 is a novel A-type natriuretic receptor agonist with an extended half life attributed to reduced binding to the NPR-C receptor and reduced cleavage by neutral endopeptidase. It is being developed for the treatment of acutely decompensated congestive heart failure and acute hypertension.

Hypothesis: PL-3994 is expected to reduce blood pressure in a dose-related manner after a single subcutaneous injection. It is also expected to increase plasma cGMP levels and increase 24-hour urine volumes and sodium excretion.

Methods: Cohorts of 7 healthy male volunteers were confined to a Phase I unit. After 24 hours of a controlled sodium and fluid diet, they randomly received either PL-3994 or placebo as a single subcutaneous injection. The doses used were 0.1 mcg/kg (6 active, 2 placebo), 0.3 mcg/kg (3 active, 1 placebo), 0.7 mcg/kg (6 active, 1 placebo), and 1.0 mcg/kg (7 active). Dose escalation was to be stopped when 2 volunteers experienced a 15% decrease in blood pressure compared to pre-dose baseline in any cohort.

Results: Two volunteers experienced the pre-specified 15% reduction in systolic blood pressure at the 1.0 mcg/kg dose level; neither was symptomatic. The decreases in blood pressure lasted at least 8 hours and returned to baseline by 24 hours. One of 6 volunteers showed an increase in cGMP levels at the 0.3 mcg/kg dose level. All showed an increase in cGMP levels at the 0.7 and 1.0 mcg/kg dose levels with the increases greatest at the 1.0 mcg/kg dose level. The elevations in plasma cGMP returned to baseline by approximately 8 hours after PL-3994 administration. Increases in 24-hour urine volumes and sodium excretion compared to the day before dosing were seen in a dose-related manner. PL-3994 levels in the plasma were below the level of quantification (0.25 ng/mL) at all time points. No changes in neurohormone levels between baseline and the 24 hour time point were seen. Adverse events observed were: pain at injection site, dizziness, tiredness, blurry vision, and headache. All adverse events were mild and resolved. No volunteer experienced a serious adverse event related to PL-3994 administration.

Conclusions: PL-3994 appears safe to administer in a clinical trial setting. As expected for an A-type natriuretic peptide receptor agonist, it led to dose-related decreases in blood pressure, increases in plasma cGMP, and increases in urine volume and sodium excretion. Phase II studies in acutely decompensated congestive heart failure and acute hypertension are planned.

INTRODUCTION

- New therapies are required for acute and chronic heart failure. PL-3994 is a novel A-type natriuretic receptor agonist being developed for the treatment of congestive heart failure and resistant hypertension.
  - It was designed to have an extended half life compared to native ANP and BNP so as to have the potential for chronic, self-administered, subcutaneous administration.
  - The extended half life of PL-3994 results from reduced binding to the natriuretic peptide receptor-C and reduced cleavage by neutral endopeptidase.
  - The mechanism of its action is likely mediated through the cyclic guanosine monophosphate (cGMP) second messenger system causing systemic vasodilation and multiple effects in the kidney.
- In preclinical animal models, subcutaneous administration of PL-3994 causes a rapid decrease in blood pressure and an increase in urine output in rats and dogs.
  - These effects are dose related, although a plateau in the extent of blood pressure decrease can be demonstrated.
  - The plasma concentration of PL-3994 tracks closely with plasma cGMP concentrations which in turn follows closely the decrease in blood pressure.
- The current study is the first in which humans are exposed to PL-3994.
  - The purposes of the study are to see if PL-3994 is safe to administer to humans, what are its pharmacokinetics, if it produces the expected pharmacologic effects predicted from animal studies and at what doses these effects occur.
  - Cohorts of healthy volunteers were exposed to increasing doses of PL-3994 or placebo until 2 patients in that cohort demonstrated a 15% decrease in blood pressure, a decrease judged safe to produce in healthy volunteers.

OBJECTIVES

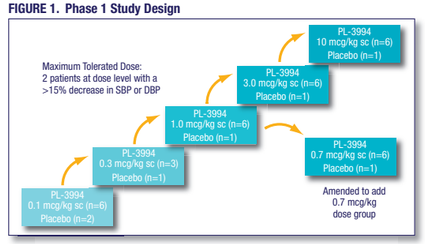
- Evaluate the safety, tolerability, and pharmacokinetics/pharmacodynamics of subcutaneously administered PL-3994 in healthy male subjects.

METHODS

Study Design

- Placebo-controlled, randomized, double-blind, ascending dose-group phase 1 study (Figure 1).

FIGURE 1. Phase 1 Study Design



- Men meeting entry criteria during screening period (1 day) were randomized to receive either a single, subcutaneous dose of PL-3994 or placebo.
  - All randomized subjects received a controlled sodium and fluid diet 24-hours prior to dosing.
  - Subjects participating in the study only received one dose and were not eligible to receive subsequent (ascending) doses.
- The randomized PL-3994 dose groups included 0.1, 0.3, 0.7, and 1.0 mcg/kg.
  - The lowest dose was the first dose group administered. The 0.7 mcg/kg dose group was added after the maximal tolerated dose (MTD) criteria (see top of next column) was met in the 1.0 mcg/kg dose group.
  - Each dose group was given in the clinic and subjects remained in the clinic overnight for assessments.
  - Safety data were evaluated by the sponsor and investigator to determine whether to proceed to the next (ascending) dose group.
    - A decrease in sitting systolic blood pressure *greater than 15% from baseline or symptomatic hypotension* in 1 subject in either of the first 2 dose groups will cause a subsequent group (three active and one placebo) of subjects to be enrolled at the same dose level before proceeding to the next higher dose level.
    - Decreases in sitting systolic blood pressure *greater than 15% from baseline or symptomatic hypotension* in 2 subjects or more in any dose group will constitute MTD and will halt progression of the study to the next dose.
  - Subjects returned to the clinic approximately 30 days after study drug administration and underwent an echocardiogram and provided laboratory samples for analysis for potential anti-PL-3994 antibody formation.
- This study was conducted with Good Clinical Practice requirements described in the current revision of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines and all applicable regulations, including current United States Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164.

Inclusion/Exclusion Criteria

- The major inclusion criteria were:
  - Healthy men 18 to 45 years of age with a body mass index between 18 to 29 kg/m^2.
- Patients were not eligible for study participation if they had any of the following:
  - Orthostatic hypotension, current diagnosis of hypertension, systolic blood pressure <100 mm Hg, diastolic blood pressure <60 mm Hg.
  - Significant concomitant illness or disease.
  - Cardiovascular disease (including history of angina, any valvular pathology or myocardial infarction).
  - Weight >100 kg or <50 kg.
  - History of alcohol and/or drug abuse.

RESULTS

Patient Disposition

- A total of 26 healthy male subjects entered the study, were randomized to study treatment, completed the study, and included in the pharmacokinetic/pharmacodynamic and safety analyses. No subjects were dropped or withdrew from the study.

TABLE 1. Demographics

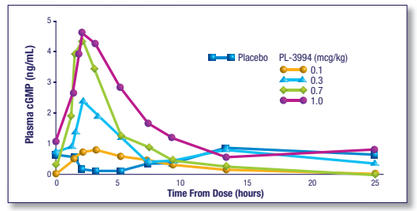
		PL-3994 Dose Groups (mcg/kg)			
	Placebo (n=4)	0.1 (n=6)	0.3 (n=3)	0.7 (n=6)	1.0 (n=7)
Age (y)	29.3 ± 9.8	30.3 ± 3.2	30.3 ± 10.5	29.2 ± 7.0	32.7 ± 7.5
Height (in)	175.3 ± 4.9	175.5 ± 7.1	175.7 ± 8.1	175.8 ± 9.8	176.1 ± 4.1
Weight (kg)	72.8 ± 3.5	78.5 ± 12.2	79.4 ± 16.9	74.3 ± 6.8	81.5 ± 10.4
Race (%)					
Caucasian	75	0	33	83	29
Black	25	100	33	0	71
Asian	0	0	33	17	0

Pharmacokinetic Results

- A single, subcutaneous administration of 0.1 and 0.3 mcg/kg did not result in quantifiable plasma concentrations of PL-3994.
- A single, subcutaneous administration of 0.7 and 1.0 mcg/kg resulted in:
  - Mean C_{max} values: 0.68 ± 0.22 and 0.71 ± 0.25 ng/mL, respectively.
  - Mean t_{max} values: 0.376 (0.249, 0.503) and 0.524 (0.251, 1.99), respectively.
  - As these values are close to the lower limit of quantification of the assay (0.25 ng/mL), half life, clearance and AUC could not be reliably calculated.

Pharmacodynamic Results

FIGURE 2. Plasma cGMP Time Course



- The mean plasma cGMP E_{max} and $AUEC_{(0\text{-}t)}$ values tended to increase with increasing subcutaneous doses of PL-3994.
  - Elevations in plasma cGMP returned to baseline by approximately 8 hours after PL-3994 administration.
- Calculated $t_{1/2}$ values for the 0.7 and 1.0 mcg/kg groups was 3.03 and 2.98 hours, respectively.
- There were no obvious trends toward change from baseline following increasing doses of PL-3994 for aldosterone, epinephrine, endothelin, catecholamines, BNP or renin. (Table 2).
  - Given the peak of cGMP plasma levels occurring at 1.0 to 1.5 hours and returning to baseline 8 hours after drug administration, future studies should include sampling for neurohormones at earlier time points as a 24 hour post-dose sample may have missed potential changes.

TABLE 2. Change From Baseline in Neurohormone Levels 24 hours Post-Dose

		PL-3994 Dose Groups (mcg/kg)			
	Placebo (n=4)	0.1 (n=6)	0.3 (n=3)	0.7 (n=6)	1.0 (n=7)
Aldosterone (ng/dL)	1.2	-0.03	2.00	1.75	1.76
Epinephrine (pg/mL)	9.00	17.5	3.33	-7.50	8.00
Endothelin (pg/mL)	-0.93	1.02	0.47	0.05	-0.29
Renin (ng/mL/hr)	0.13	0.15	-0.43	0.22	0.29
BNP (pg/mL)	-1.75	9.50	-3.00	-1.83	-5.71
Dopamine (pg/mL)	14.5	24.2	7.33	4.17	0.00
Norepinephrine (pg/mL)	67.5	171.3	39.7	2.67	59.4

FIGURE 3. Change in Systolic Blood Pressure

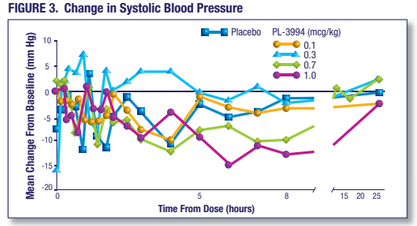


FIGURE 4. PL-3994 0.7 and 1.0 mcg/kg: Change in Systolic Blood Pressure

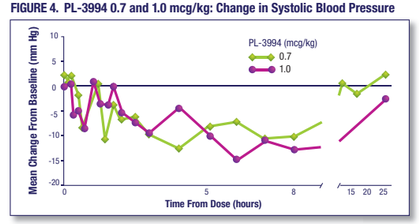


FIGURE 5. Systolic Blood Pressure in Patients Meeting MTD Criteria in the 1.0 mcg/kg Group

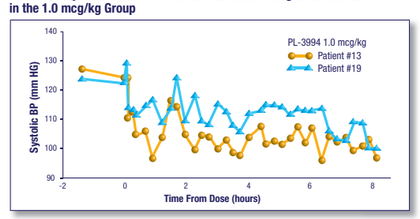


FIGURE 6. PL-3994 1.0 mcg/kg Group: Change in Systolic Blood Pressure at 1 Hour

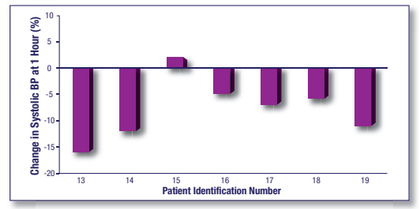
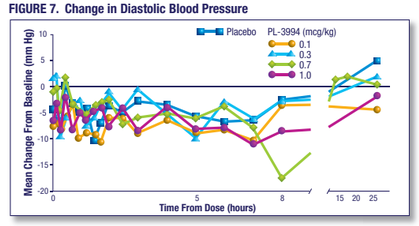
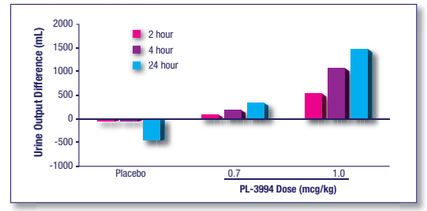


FIGURE 7. Change in Diastolic Blood Pressure



- Two volunteers experienced the pre-specified 15% reduction in systolic blood pressure at the 1.0 mcg/kg dose level; neither was symptomatic.
  - The decreases in blood pressure lasted at least 8 hours and returned to baseline by 24 hours.
- Systolic blood pressure decreases of approximately 10 mm Hg were seen in the 0.7 and 1.0 mcg/kg dose groups.
  - The decreases lasted at least 8 hours and returned to baseline by 16 to 24 hours.
- In the patients with blood pressure decreases meeting the definition of maximum tolerated dose, the decreases were seen as early as 15 minutes after injection.
- At the 1.0 mcg/kg dose level, 6 of 7 subjects had a blood pressure decrease of at least 5 mm Hg.
- There was no clear difference in the diastolic blood pressure or pulse (not shown), between the placebo subjects and any active PL-3994 dose level.

FIGURE 8. Effects on Urine Output



- Increases in 24-hour urine volumes and sodium excretion compared to the day before dosing were seen, particularly at the highest dose level.
  - Sodium excretion increased by approximately 40% compared with placebo-treated subjects in the highest dose group in the 0 to 2 and 2 to 4 hour collection fraction, but not in the overall 24-hour collection.

SAFETY

- Adverse events observed were: pain at injection site, dizziness, tiredness, blurry vision, and headache.
  - All adverse events were mild in severity and resolved spontaneously.
  - There were no serious adverse events.

DISCUSSION AND CONCLUSIONS

- The subcutaneous administration of PL-3994 appears safe for future clinical trials.
- The highest doses of PL-3994 (0.7 and 1.0 mcg/kg) resulted in quantifiable plasma concentrations.
  - The lowest dose levels did not exceed the lower limit of quantification (0.25 ng/mL).
- As expected for an A-type natriuretic peptide receptor agonist, PL-3994 produced dose-related decreases in blood pressure, increases in plasma cGMP, and increases in urine volume and sodium excretion.
  - Reductions in blood pressure had an onset of 15 minutes and a duration of at least 8 hours, but less than 16 to 24 hours.
  - Plasma cGMP levels increased after PL-3994 administration in a dose-related manner, particularly in the 0.7 and 1.0 mcg/kg dose levels. The time course of cGMP increase closely paralleled the decreases in blood pressure.
  - No neurohormone changes were documented from baseline, but the 24-hour time point may have missed changes if they occurred at a similar time point to changes in cGMP.
- Phase II studies in acutely decompensated congestive heart failure and acute hypertension are planned.