PHASE IIa STUDY OF THE NPR-AGONIST, PL-3994, IN HEALTHY ADULT VOLUNTEERS WITH CONTROLLED HYPERTENSION

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ABSTRACT

Introduction: PL-3994 is a novel natriuretic peptide-A receptor (NPR-A) agonist which is being developed for the treatment of heart failure. It has a half life of approximately 3 hours and a subcutaneous route of administration may make it suitable for chronic self-administration.

Hypothesis: PL-3994 is expected to lead to an increase in plasma cGMP concentration and to decrease blood pressure as doses increase. Subjects taking certain antihypertensive medications may demonstrate an additive effect on blood pressure as PL-3994 doses increase.

Methods: 21 subjects were enrolled in cohorts where 6 patients received active treatment and 1 received placebo. The patients were selected to have a diagnosis of essential hypertension, meet criteria for adequate control and be taking 1-3 antihypertensive medications. The prespecified definition of maximum tolerated dose (MTD) was the development in 2 patients per cohort of symptomatic hypotension or a 20% decrease in systolic or diastolic blood pressure. The first cohort was treated at 0.3 µg/kg as a single, subcutaneous injection. As the criteria for MTD were met, the next cohort received 0.1 µg/kg and another cohort received 0.3 µg/kg.

Results: The mean age of the patients was 53.3 years; 52.4% were male; 76.2% were Caucasian and 23.8% African-American. Of 21 patients, 12 were taking 1 antihypertensive, 3 were taking 2, and 6 were taking 3. Nine patients were taking an ACE inhibitor (5 in the 0.3 µg/kg cohorts), 6 an ARB, 9 a diuretic, 7 a calcium channel blocker, 1 an α-blocker and 2 a β-blocker. Patients receiving placebo or 0.1 µg/kg of PL-3994 showed no change in blood pressure, pulse, or plasma cGMP levels. At 0.3 µg/kg, all subjects showed an increase in plasma cGMP levels with a mean peak change of 1.7 ng/mL. The mean systolic blood pressure decrease in this group was 12%. The peak blood pressure effect was seen at 6 hours, was still seen at 16 hours and returned to baseline by 24 hours. Three patients met the criteria for MTD. All were taking concomitant lisinopril, an ACE inhibitor. There were no serious adverse events noted.

Conclusions: PL-3994 was well tolerated in subjects with controlled hypertension. Consistent with a prior study in healthy volunteers, PL-3994 increased plasma cGMP levels at a similar dose. However, 3 of 5 patients taking ACE inhibitors reached MTD at 0.3 µg/kg, but no patients taking other classes of antihypertensives. This interaction should be incorporated in dosing for subsequent Phase II studies.

INTRODUCTION

- Natriuretic peptides are neurohormonal substances involved in the maintenance of cardiovascular homeostasis.
  - The class of compounds has multiple effects including arterial and venous vasodilatation, suppression of the renin-angiotensin-aldosterone system (RAAS), suppression of ventricular hypertrophy and effects on the kidney leading to increased clearance of water and salt. In addition, some natriuretic peptides have non-cardiovascular effects such as the regulation of bone formation.
  - When given at pharmacologic doses as an intravenous infusion, natriuretic peptides can be useful treatments for acute heart failure. Recombinant forms of ANP (atrial natriuretic peptide, carperitide) and BNP (brain-type natriuretic peptide, nesiritide) are approved for sale in Japan and the United States, respectively.
- A number of modified natriuretic peptides are in clinical trial for the treatment of heart failure.
- PL-3994 is an agonist at the NPR-A (natriuretic peptide receptor-A).
  - It has been designed to have a longer half-life than the natural natriuretic peptides and high potency.
  - It is well absorbed by subcutaneous administration.
  - Thus, it is suitable for self-administration and can be investigated for clinical problems where medium-term and long-term use could be appropriate.
- A Phase 1 study in healthy volunteers showed that a single subcutaneous injection of PL-3994 was associated with a dose-related increase in plasma cGMP and a decrease in systemic blood pressure. A diuretic effect was noted as well.
  - Based on a prespecified criterion of a maximum allowable decrease in systolic blood pressure of 15%, the maximum tolerated dose was determined to be 1.0 µg/kg.
  - The half-life of PL-3994 was found to be 3 hours and the duration of the effect on blood pressure was 8 to 12 hours.
- Patients with heart failure are often managed with the chronic administration of oral agents that themselves can lower blood pressure, such as ACE inhibitors, angiotensin receptor blockers (ARBs) and β blockers.
  - There is a potential for interactions between these medications and newer agents which could be added to the regimen. For example, the nesiritide package insert refers to a 6% incidence of hypotension in patients given nesiritide who are taking concomitant ACE inhibitors.
  - Thus, dosing in such patients for PL-3994 might be different than in healthy volunteers not taking concomitant medications.
  - To assess this possibility before initiating trials in heart failure patients, a Phase 2a study was conducted with volunteers with controlled essential hypertension who are on stable doses of medications from classes often prescribed to heart failure patients.

OBJECTIVES

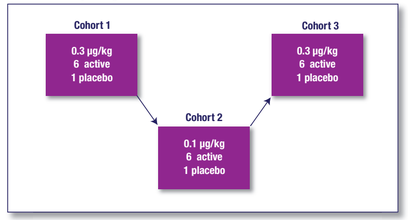
- Evaluate the safety, tolerability, and pharmacodynamics of subcutaneously administered PL-3994 relative to placebo in subjects with controlled hypertension.

METHODS

Study Design

- Placebo-controlled, randomized, double-blind, ascending dose-group Phase 2a study (Figure 1).

FIGURE 1. Study Design



- Cohorts of 7 subjects were enrolled at each planned dose level. Within each cohort, 6 patients were randomized to receive PL-3994 and one to receive placebo.
  - The first cohort received 0.1 µg/kg of PL-3994 and the second cohort received 0.3 µg/kg of PL-3994. The latter cohort was repeated to confirm that this level is the maximum tolerated dose.
- The maximum tolerated dose was defined as the dose where 2 subjects out of the 6 who received PL-3994 met at least one of the following criteria:
  - Symptomatic hypotension, regardless of duration.
  - A 20% decrease in systolic blood pressure from baseline in 2 consecutive systolic blood pressure readings taken 15 minutes apart.
- The test medication was supplied in vials containing 0.5 mg of vehicle with (active) or without (placebo) 1 mg of PL-3994.
- Subjects reported to the clinic the afternoon of the first day and were put on a standardized diet.
  - The next morning, they began blood pressure monitoring, urine collection and blood sampling. These measurements were the study baseline.
  - On the following morning, the final baseline blood pressure measurement was taken and patients were given a subcutaneous injection of either PL-3994 or placebo. Blood pressure measurements, urine output and blood samples were again collected for 24 hours.
  - On the following morning, patients underwent a safety check, final vital sign and blood sample collections and were discharged.
  - They returned at 30 days for safety checks and blood sampling for immunogenicity.
- 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.

Major Inclusion Criteria

- Males and females, 18 to 65 years of age.
- Diagnosis of essential hypertension for ≥1 year and have been on a stable dose of not more than 3 antihypertensive medications for ≥3 months.
- Systolic BP must be between 120 and 150 mm Hg, and diastolic BP must not exceed 105 mm Hg at screening, check-in and baseline.

Major Exclusion Criteria

- As ascertained by verbal history, current tobacco use (within last 6 months), uncontrolled endocrine disease, cardiovascular disease (including history of angina, valvular heart disease, MI or abnormal echocardiogram), significant neurological disease, current or history of any cancer (except non-melanomatous skin cancer) diagnosed less than 5 years prior to screening, clinically significant renal disease (defined as GFR criteria <40 by Modification of Diet in Renal Disease [MDRD] study equation), acute or chronic disease requiring frequent changes in medications or changes in dosages of chronic therapy, orthostatic hypotension, history of alcohol abuse or drug abuse within the last 5 years, weight >100 kg or <50 kg.
- Any significant medical condition or abnormal safety laboratory results which, in the judgement of the Investigator would place the subject at significant risk.

RESULTS

Patient Disposition

- A total of 21 subjects (mean age 53.3 years) with essential hypertension 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.
- The number and type of concomitant blood pressure medications the subjects were taking are listed in Table 1.

TABLE 1. Demographics

	PL-3994 Dose Groups (µg/kg)		
	Placebo (n=3)	0.1 (n=6)	0.3 (n=12)
Age (y)	59.3 ± 5.13	53.5 ± 5.24	53.3 ± 5.72
Males (%)	33.3	50.0	58.3
Race (%)			
Caucasian	66.7	83.3	75.0
Black	33.3	16.7	25.0
Blood pressure (mm Hg)			
Systolic	128.7 ± 3.5	136.7 ± 12.4	131.2 ± 14.5
Diastolic	75.7 ± 5.1	85.3 ± 7.0	82.3 ± 9.4
Concomitant blood pressure medications (number of patients)			
By total number taking			
1	1	3	8
2	1	1	1
3	1	2	3
By drug class			
ACE inhibitor	2	2	5
ARB	1	2	3
Diuretic	2	2	5
CCB	1	2	4
α blocker	0	1	0
β blocker	0	2	0

ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor blockers, CCB=calcium channel blocker.

Blood Pressure Results

- The mean change in systolic blood pressure from baseline was -13.2, -17.2, and -22.1 mm Hg for placebo, PL-3994 0.1 µg/kg, and PL-3994 0.3 µg/kg groups, respectively (Figure 2).
- The mean change in diastolic blood pressure from baseline was -3.5, -6.4, and -11.3 mm Hg for placebo, PL-3994 0.1 µg/kg, and PL-3994 0.3 µg/kg groups, respectively (Figure 3).
- The median time to maximum reduction in systolic and diastolic pressure ranged from 2 to 3 hours.
- There were no clinically relevant changes in pulse rate for any treatment group (Figure 4).

FIGURE 2. PL-3994: Change From Baseline In Systolic Blood Pressure

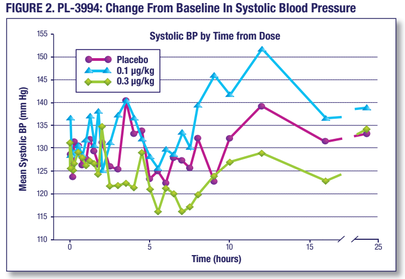


FIGURE 3. PL-3994: Change From Baseline In Diastolic Blood Pressure

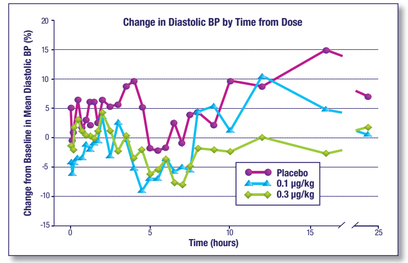
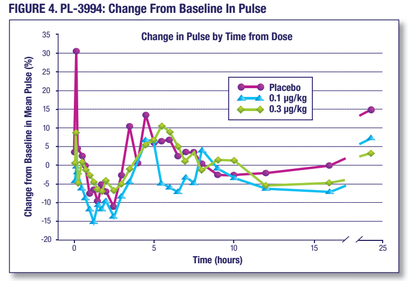


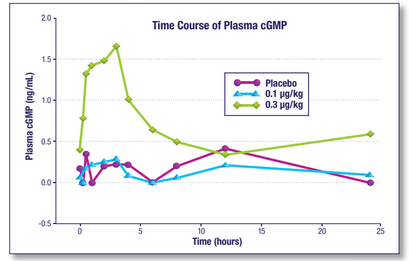
FIGURE 4. PL-3994: Change From Baseline In Pulse



Pharmacodynamic Results

- The mean plasma cGMP E_{max} and $AUEC_{(0\text{-}t)}$ values tended to increase with increasing subcutaneous doses of PL-3994 (Figure 5).
  - The half-life of PL-3994 was 3 hours.
  - Elevations in plasma cGMP returned to baseline by approximately 8 hours after PL-3994 administration.

FIGURE 5. PL-3994: Change From Baseline In Plasma cGMP



- 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).

TABLE 2. Change From Baseline In Neurohormone Levels 8 Hours Post-Dose

	PL-3994 Dose Groups (µg/kg)		
	Placebo (n=3)	0.1 (n=6)	0.3 (n=12)
Aldosterone (ng/dL)	-1.5	0.33	3.65*
Catecholamine (pg/mL)	71.1	-7.7	-28.2†
Endothelin (pg/mL)	-0.16	0.39	0.36†
Renin (ng/mL/hr)	0.4	-0.78	-0.38*
BNP (pg/mL)	-4.0	-7.8	-3.18†

*n=10; †n=11.

- Three patients met the MTD criteria, each were taking concomitant lisinopril (Figure 6, Table 3).

FIGURE 6. Patients Meeting Maximum Tolerated Dose Criteria

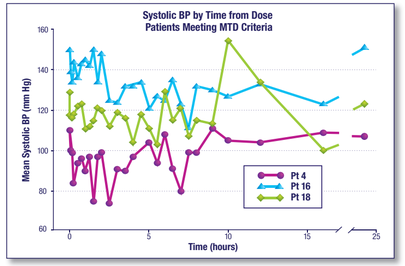


TABLE 3. Patients Meeting MTD Criteria (PL-3994 0.3 µg/kg)

		Blood Pressure (mm Hg)			
Patient Number	Concomitant Medications	Baseline	Lowest	Symptoms	Comments
4	Triamterene 37.5 mg HCTZ 25 mg Lisinopril 20 mg	110/70	74/48	Lightheaded at 15 minutes Trendelenberg Saline infusion	Started with systolic blood pressure 108 mm Hg. Systolic blood pressure still low 1 week later. Blood pressure criteria revised.
16	Lisinopril 10 mg	150/81	111/77	Asymptomatic	Spontaneously resolved
18	Lisinopril 20 mg	129/61	96/61	Lightheaded at 4 hours	Spontaneously resolved

Safety

- The most frequent drug-related treatment-emergent adverse event was dizziness, which occurred at a similar frequency in the placebo and PL-3994 groups.
- All adverse events were mild in severity and resolved spontaneously.
- There were no serious adverse events.

DISCUSSION AND CONCLUSIONS

- PL-3994 was well tolerated in subjects with controlled hypertension.
- PL-3994 increased plasma cGMP levels at the 0.3 µg/kg dose.
- No changes in neurohormone or urine output seen.
- 3 of 5 patients taking ACE inhibitors reached MTD at 0.3 µg/kg.
  - This MTD is a half log lower than in the healthy volunteers not taking ACE inhibitors.
  - No patients taking other classes of antihypertensives met the criteria for MTD at 0.3 µg/kg.
  - This interaction should be incorporated in dosing for subsequent Phase II studies.
- Given its long half-life and subcutaneous administration, PL-3994 may also offer an opportunity for treatment of resistant hypertension.