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 which would not be expected to produce in healthy volunteers.

OBJECTIVES

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

METHODS

- Placebo-controlled, randomized, double-blind, ascending-dose phase 1 study.

RESULTS

- Men meeting entry criteria during screening period (0-3 days) were randomized to receive either a single, subcutaneous dose of PL-3994 or placebo.

- All randomized subjects received a control 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 cohort was given in the clinic and subjects were monitored for 1.5 hours and returning to baseline 8 hours after drug administration.

- Adverse events observed were pain at injection site, dizziness, tiredness, flu-like symptoms, 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 decompenated congestive heart failure and acute hyperension are planned.

INTRODUCTION

New therapies are required for acute and chronic heart failure. PL-3994 is a novel A-type natriuretic peptide receptor agonist being developed for the treatment of congestive heart failure and acute hyperension.

Hypothesis:

PL-3994 is expected to reduce blood pressure in a dose-related manner after a single subcutaneous injection. It is being developed for the treatment of acutely decompenated congestive heart failure and acute hyperension.

Methods:

1. Two volunteers experienced the pre-specified 15% reduction in systolic blood pressure at the 0.7 mcg/kg dose level, and 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.

2. The decreases in left ventricular blood pressure were greater than 1.0 mmHg and met in the 1.0 mcg/kg dose group.

3. Adverse events observed were pain at injection site, dizziness, tiredness, flu-like symptoms, and headache. All adverse events were mild and resolved.

4. No volunteer experienced a serious adverse event related to PL-3994 administration.

5. PL-3994 is expected to reduce blood pressure in a dose-related manner after a single subcutaneous injection.

- The decreases in left ventricular blood pressure were greater than 1.0 mmHg and met in the 1.0 mcg/kg dose group.

6. Increases in 24-hour urine volumes and sodium excretion compared to the day before dosing were seen, particularly at the highest dose level.

7. Sodium excretion increased by approximately 40% compared to placebo-treated subjects in the highest dose group.

8. There were no obvious trends toward change from baseline following increasing doses of PL-3994 for aldosterone, epinephrine, and dopamine.

9. Catecholamines, BNP or renin. (Table 2).

10. The mean values for the 0.7 and 1.0 mcg/kg groups were 3.03 and 2.98, respectively.

11. There were no obvious trends toward change from baseline following increasing doses of PL-3994 for aldosterone, epinephrine, and dopamine.

12. Catecholamines, BNP or renin. (Table 2).

13. 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 later time points as a 24-hour post dose sample may have missed potential changes.

DISCUSSION AND CONCLUSIONS

- 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 maximal tolerated dose, the decreases were seen as early as 15 minutes after injection.

- At the 0.25 mg/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 (beat/min) show, between the placebo subjects and any of the PL-3994 dose level.