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 agonist (NPR-A) agonist which is being developed for the treatment of heart failure. It has a half-life of approximately 3 hours and a substantial route of administration may make it suitable for chronic oral administration.

Hypothesis: PL-3994 is expected to lead to an increase in plasma cGMP concentration and to decrease blood pressure as doses increase.

Methods: 21 subjects were enrolled in cohorts where 6 patients received active treatment and 5 patients served as controls. The patients were randomized to one of three cohorts (0.1 µg/kg, 0.3 µg/kg, 1.0 µg/kg) for adequate control and for taking 1-3 antihypertensive medications.

Results: The mean age of the patients was 53.3 years; 52.4% were Caucasian and 33.3% Black. As the criteria for MTD were met, the next cohort received 0.1 µg/kg of PL-3994. The latter cohort was continued at 0.3 µg/kg, as an increase in plasma cGMP levels with a mean peak change of 1.7 ng/mL.

PL-3994 is an agonist at the NPR-A of the natriuretic peptide receptor-A (NPR-A), which is coupled to a guanylyl cyclase-cGMP-dependent protein kinase system. As the criteria for MTD were met, the next cohort received 0.1 µg/kg of PL-3994. The latter cohort was continued at 0.3 µg/kg, as an increase in plasma cGMP levels with a mean peak change of 1.7 ng/mL.

PL-3994 was well tolerated in subjects with controlled hypertension. No serious adverse events were noted. 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 was well tolerated in subjects with controlled hypertension.

RESULTS

• The next criteria that was met was a 20% decrease in systolic blood pressure from baseline in any patient. Since this was met, the next cohort received 0.3 µg/kg of PL-3994. The latter cohort was continued at 0.3 µg/kg, as an increase in plasma cGMP levels with a mean peak change of 1.7 ng/mL.

• The most frequent drug-related treatment-emergent adverse events were nausea, lightheadedness, and headache.

• There were no serious adverse events.

• There was no clinically relevant change in pulse rate at any dose except for an increase in diastolic blood pressure.

DISCUSSION AND CONCLUSIONS

• PL-3994 was well tolerated in subjects with controlled hypertension.

• There were no serious adverse events.

• There were no obvious trends toward change from baseline following dosing with placebo, triamterene, and BNP (brain-type natriuretic peptide, nesiritide) are approved for sale in Japan and the United States, respectively.

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