A PHASE 1 STUDY OF THE SAFETY AND PHARMACOKINETICS OF THE INTRAVENOUS NITROXYL PRODRUG, CXL-1427

Poster Contributions
Poster Hall B1
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Background: CXL-1427 is a 2nd generation intravenous prodrug that delivers nitroxy (HNO). HNO has been shown to have multiple cardiovascular effects, including inotropy, lusitropy and peripheral vasodilation, suggesting benefit in the treatment of acute heart failure patients.

Methods: The objectives of this phase 1 dose escalation study were to determine the MTD of 24-48 hour IV infusions in healthy volunteers (HV) and to estimate a dose range for evaluation in future studies. Seven cohorts of 10 HVs received escalating doses of CXL-1427 or placebo (6:4 ratio) for 24 hours. Subsequently, the 24hr MTD of CXL-1427 was administered as a continuous infusion for 48hrs in an additional cohort to determine safety with a longer exposure. Safety was assessed by adverse events, clinical laboratory tests, physical exams and ECGs.

Results: A total of 70 HV participated in the escalation phase at doses of 0.1-15 mcg/kg/min for 24 hours. Dose-dependent changes in hemodynamic parameters were observed. The MTD at 24 hours was determined to be 10 mcg/kg/min based on robust blood pressure reductions observed at 15 mcg/kg/min. Subsequently, an additional 10 HVs were administered 10 mcg/kg/min for 48 hours. Pharmacokinetic analyses demonstrated dose-dependent exposure to CXL-1427; the half-life of CXL-1427 was ~40-144 mins. Likely drug-related adverse events included headaches (42.9%, vs 25% in PBO), consistent with the known vasodilatory activity of HNO. Headaches, which were predominantly mild-to-moderate (91%), were occasionally accompanied by nausea (19% vs 10.7% in PBO) and vomiting (4.8% vs 3.6% in PBO). No effect on ECG parameters was noted.

Conclusion: CXL-1427, a nitroxy prodrug, was generally well-tolerated up to a dose of 10 mcg/kg/min, with dose-dependent pharmacokinetics and preliminary evidence for dose-dependent pharmacodynamic activity.