TRV027, A BETA-ARRESTIN BIASED LIGAND AT THE ANGIOTENSIN 2 TYPE 1 RECEPTOR, PRODUCES RAPID, REVERSIBLE CHANGES IN HEMODYNAMICS IN PATIENTS WITH STABLE SYSTOLIC HEART FAILURE

Poster Contributions
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Background: TRV027 is a β-arrestin biased ligand at the angiotensin 2 type 1 receptor (AT1R); it antagonizes G-protein coupling while stimulating β-arrestin-mediated signaling. TRV027 inhibits ang2-mediated systemic and renal vasoconstriction while, via β-arrestin, it increases cardiac contractility and anti-apoptotic signaling. TRV027’s novel pharmacology at a precededent target suggests that TRV027 may be an effective and safe new therapy for heart failure (HF).

Methods: This was a randomized, double-blind, placebo-controlled, titration study to evaluate the safety and pharmacology of TRV027 in patients with stable HF. Inclusion criteria: ≥3-month history of systolic HF, systolic blood pressure ≥100 mmHg, average pulmonary capillary wedge pressure (PCWP) ≥20 mmHg. Other HF medications were withheld for 6 hrs.

Results: Four cohorts of 8 patients were enrolled. Subjects were randomized 1:3 to receive either placebo (PBO) or a dose regimen of TRV027. Study drug was administered by i.v. infusion for 14 hrs: a 5 hr dose escalation phase and a 9 hr maintenance phase, followed by a 4 hr washout phase. Maintenance doses in each cohort were 1 mcg/kg/min (cohort 1), 3 mcg/kg/min (cohorts 2 and 4), and 10 mcg/kg/min (cohort 3). Mean arterial pressure (MAP) decreased during dose escalation in patients with high plasma renin activity exposed to TRV027 (high-PRA), but not in the normal PRA TRV027 group (normal-PRA) or in PBO. This decreased MAP was sustained during the maintenance phase and reversed in the washout phase. PCWP declined during dose escalation in patients with high plasma renin activity exposed to TRV027 (high-PRA) and PBO. PCWP increased back to baseline during washout in high-PRA, suggesting reversible pharmacology, while PCWP was unchanged in PBO and normal-PRA during washout. Cardiac index did not change in subjects with either high or normal PRA in this small sample size.

Conclusions: TRV027 a β-arrestin biased AT1R ligand produced reversible improvements in hemodynamics and was well-tolerated in patients with advanced stable HF. As expected, pharmacologic effects of TRV027 were dependent on PRA elevation, a common feature of acute HF. Studies are planned to evaluate TRV027’s efficacy and safety in patients hospitalized for HF.