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## Heart Failure

### INITIAL EXPERIENCE WITH SUBCUTANEOUS INFUSION OF CENDERITIDE IN PATIENTS WITH CHRONIC HEART FAILURE

ACC Moderated Poster Contributions  
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**Background:** Subcutaneous (SQ) infusion of Cenderitide (C), a chimeric natriuretic peptide (NP) with agonism for NP receptors A and B, is being developed as a maintenance therapy to improve clinical outcomes in post-acute heart failure (HF) patients.

**Methods:** This multi-centered Phase 1 dose escalating study evaluated the pharmacokinetic (PK) and pharmacodynamic responses to various SQ boluses and infusion regimens in HF patients. Systolic HF patients with an ejection fraction  $\leq 40\%$ , on stable HF medications, and systolic blood pressure (SBP)  $\geq 105$  mmHg were enrolled. Subjects were initially dosed with SQ boluses of C to evaluate bioavailability. Based on these results, additional cohorts were randomized to 24-hour continuous subcutaneous infusions of C or matching placebo using a Medtronic SQ pump to achieve targeted steady-state plasma levels of C. Direct glomerular filtration rate (GFR), renal biomarkers, and urine output (UO) were measured in the SQ infusion cohorts.

**Results:** 58 subjects were dosed (45 with C and 13 with placebo). The infusions were well tolerated. The results of escalating SQ boluses of C in 12 subjects confirmed good bioavailability and were used to determine the doses for the 24-h SQ infusions. SQ infusion regimens were 18  $\mu\text{g/hr}$  (n=12), 24  $\mu\text{g/hr}$  (n=10), 36  $\mu\text{g/hr}$  (n=2), and a weight-based dosing regimen (n=9), or matching placebo (n=13). The demographics of the subjects receiving placebo and C were similar. Targeted plasma levels of C were achieved. A dose-dependent reduction in SBP occurred. The mean maximum SBP reductions for the 18  $\mu\text{g/hr}$ , 24  $\mu\text{g/hr}$ , 36  $\mu\text{g/hr}$ , weight-based, and placebo of  $-16\pm 12$ ,  $-22\pm 8$ ,  $-28\pm 1$ ,  $-19\pm 7$ , and  $-12\pm 10$  mmHg, respectively. The PK variability of the weight-based cohort was less relative to the fixed dose regimens. No difference in GFR, creatinine, cystatin-C or UO between the placebo and the C dosed groups was detected.

**Conclusion:** SQ infusion of Cenderitide was well-tolerated, achieved and maintained targeted plasma levels, and produced a consistent dose-dependent reduction in SBP. This study supports a novel strategy for chronic administration with cenderitide for human HF.