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Subcutaneous delivery of NPA7, first-in-class novel bispecific designer peptide: enhances cardiorenal function and suppresses renin and aldosterone in vivo and in vitro

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Introduction: The rapid increase of patients of heart failure (HF) is a major health burden worldwide. Most importantly is the need to develop innovative new drugs for treatment of HF, such as sacubitril/valsartan which in part functions by enhancing the natriuretic peptides (NPs). We engineered NPA7 as a novel 30 amino acid bispecific designer peptide which activates the particulate guanylyl cyclase A receptor (pGC-A)/cGMP and for which the NPs both ANP and BNP are ligands and the Mas-receptor (MasR)/cAMP pathways for Angiotensin 1-7 (Ang1-7) is the endogenous ligand. We previously reported that acute intravenous (IV) administration of NPA7 shows cardiorenal protective and renin-aldosterone suppressing actions that go beyond the native peptides, BNP or Ang 1-7, which may have therapeutic potential for HF.

Purpose: To support the clinical development of NPA7 as a potential therapy in HF which promotes NP and MasR pathways, we investigated the actions and stability of subcutaneous (SQ) administration of NPA7 in normal canines. We also defined NPA7’s peptide stability and metabolites in canine plasma.

Methods: Plasma and urinary cGMP, cardiorenal and renin-aldosterone responses to SQ injection (10µg/kg) were determined over 4 hours in normal canines (n=5) in vivo. Ex vivo, we established stability of NPA7 and key metabolites in canine serum using liquid chromatography-mass spectrometry (LC-MS). Data are expressed as mean ± SEM. * P<0.05 vs. BL.

Results: In vivo, SQ NPA7 resulted in a sustained increase at 2 hours in plasma (BL:10±3; 120 min:30±6* pmol/ml) and urinary (BL:1033±198; 120 min:5792±857* pmol/min) cGMP, GFR (BL: 29±6; 120 min:70±12* ml/min) and sodium excretion (BL:18±10; 120 min: 144±33* ueq/min). We observed a gradual reduction in BP at 60 min (BL:109±4; 60 min: 99±7* mmHg) with a sustained decrease in PCWP at 4 hours (BL:5±0.9; 240 min:3.1±0.6* mmHg). SQ NPA7 also suppressed plasma renin and aldosterone up to 3 hours after SQ injection. LC-MS revealed that NPA7 was highly stable with both the pGC-A and MasR activating moieties intact ex vivo in canine serum with a disappearance time of 2 hours. We also identified 2 major NPA7 metabolites NPA71-27 and NPA71-28.

Conclusions: SQ NPA7 possesses cGMP activating, cardiac unloading, diuretic, natriuretic, and renin-aldosterone suppressing actions in normal canines. NPA7 is also highly stable in serum. These studies support SQ administration as an effective delivery strategy for NPA7, a first-in-class innovative bispecific dual pGC-A/MasR activator now in preclinical development for HF.