Coronary Sinus Delivery of SDF-1 Plasmid for the Treatment of Heart Failure

Juliana Woda, PhD 1, Scott J. Fisher, PhD 1, Joseph Pastore, PhD 1, Amit Patel, MD, MS 2, Rahul Aras, PhD 1, Marc Penn, MD, PhD 1,3

1Juventas Therapeutics, Cleveland, Ohio; 2University of Utah, Salt Lake City, UT; 3Summa Health, Akron OH

**Background**
- SDF-1 is an 8 kDa chemokine that promotes tissue repair through recruiting stem cells, promoting angiogenesis and preventing apoptosis
- Preclinical and clinical studies (Phase I and II) have demonstrated transendocardial delivery of a SDF-1 expressing non-viral DNA plasmid (pSDF-1) is safe and may result in myocardial repair following ischemic injury
- Retrograde infusion through the coronary sinus provides an alternative route to transendocardial delivery

**Methods**
- **Induce myocardial infarction**: 90 minute LAD balloon occlusion
  - **Treatment**
    - Placebo: (5%) Dextrose
    - pSDF-1 (15 mg) in 5% Dextrose
    - pSDF-1 (45 mg) in 5% Dextrose
  - Delivered via retrograde coronary sinus infusion

  - **Procedure**: Retrograde Coronary Sinus Infusion
    - CS access (jugular vein access)
    - Insert balloon catheter
    - Inflate balloon to occlude CS, confirm occlusion with contrast agent
    - Inflate 40 ml of pSDF-1 or vehicle over 2 minutes
    - Maintain occlusion for 15 minutes: Deflate balloon

  - **SDF-1 (CXCL12)**

**Results**

**Safety**
- Administration of the pSDF-1 via retrograde coronary sinus perfusion was not associated with any adverse effects including any mortality, clinical findings, changes in body weights, adverse electrocardiographic findings, changes in clinical pathology endpoints or adverse macroscopic or microscopic findings.

**Biodistribution: Day 3**
- Quantitative qPCR was used to examine the biodistribution of plasmid 3 and 60 days following retrograde delivery. The highest level of copies was found in the heart.
- Plasmid was also detected in the kidney. Low levels of plasmid were detected in other non-target organs.
- Plasmid was cleared from all other organs except the heart by day 60 (data not shown). This biodistribution pattern is the same as previously observed following endomyocardial delivery

**Endpoints**
- **Structural (echoes):** LVF1, LVESV, LVEDV, WMSI
- **Functional:** 6MWD, MLWHFQ, NYHA Class
- **Clinical:** HF rehospitalizations, MACE, hospitalizations
- **Biomarkers:** NT-proBNP, Galectin-3

**Major Inclusion Criteria**
- Symptomatic Ischemic Cardiomyopathy
  - MI at least 6 months ago
  - EF<35%, 3 contiguous LV with abnormal WMSI
- 6 Minute Walk Distance (6MWD) ≤ 400 m
- Optimal Pharmacological Therapy
  - Beta blockers
  - Diuretics
  - ACE inhibitors or ARB
- Stable unless contraindicated

**Major Exclusion Criteria**
- Active cancer other than non-melanoma skin cancer
- Scheduled for revascularization in next 30 days
- Scheduled for mitral valve repair or replacement
- IIV pacemaker (lead in CS) or previous CS trauma

**Recruitment Dates**
- The study began enrolling in November 2013 and plans to end recruitment in August 2014 (NCT01961726)

**Conclusions**
- Retrograde coronary sinus infusion of plasmid into the heart results in protein expression in the myocardium within two to three days following delivery.
- SDF-1 is primarily delivered to the heart following retrograde CS infusion with some distribution to the kidneys. Plasmid was cleared from all organs except the heart by day 60. The biodistribution pattern of plasmid following retrograde coronary sinus infusion is similar to the pattern seen following endomyocardial injection of the plasmid.
- Delivery of pSDF-1 via retrograde CS infusion in a porcine model of heart failure was safe and did not result in any adverse effects.
- In a porcine model of heart failure, delivery of pSDF-1 via retrograde CS infusion resulted in a trend towards improvement in cardiac function and remodeling as measured by LVF1, LVESV, LVEDV. Wall motion score index was significantly improved in treated animals compared to placebo.
- Based on these results, we initiated a 72 patient Clinical Phase I/II trial to test safety and efficacy of delivery pSDF-1 plasmid via retrograde CS infusion to treat ischemic heart failure.