A Phase II, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of an Endomyocardial Injection of hSDF-1 Plasmid to Ischemic Heart Failure Patients, the STOP-HF Trial

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Background & Purpose

- A non-viral DNA plasmid encodes the humans for SDF-1 has demonstrated safety and bioactivity in a Phase I clinical trial treating symptomatic heart failure patients (Penn et al. Circ Res 112:816, 2013)
- 8 kDa chemokine
- Receptor is CXCR4
- Mobilizes/recruits hematopoietic stem cells to injured tissue

Figure 1. SDF-1 plasmid map

- The Phase I results served as the basis for the design of the 93 patient Phase II randomized trial, STOP-HF

Hypothesis: Re-introducing SDF-1 expression in a chronically damaged heart using plasmid DNA may increase cardiac function.

Methods

STOP-HF Trial Design (NCT 01643590):
- Phase II randomized placebo-controlled trial
- 5 Cohorts (1:1:1): Placebo : 15 mg : 30 mg
- IP delivered as 15 distinct 1 ml injections to the peri-MI region via LV endomyocardial injection
- 4 & 12 month follow-up (12 month pending)

Primary Inclusion Criteria:
Symptomatic Ischemic Cardiomyopathy
- MI at least 6 months ago
- LVEF ≤ 40%
- 6 Minute Walk Distance ≤ 400 meters
- QoL Score ≥ 20 as assessed by MLWHFQ
- Optimal Pharmacological Therapy

Primary Exclusion Criteria:
- Ventricular wall thickness < 4mm
- Revascularization in next 30 days
- Moderate to severe valvular heart disease
- Active cancer
- NYHA class IV

Endpoints:
6MWD, QoL score, NYHA class, functional echo parameters (LVEF, LVESV & LVEDV) & additional mortality and morbidity endpoints

Figure 2. Changes in clinical & structural parameters: 30 mg vs placebo

Change parameter at baseline to 4 months relative to placebo

Based on these results, a further analysis of high-risk subjects defined as baseline LVESV > the median (151 ml) was performed.

Figure 3. Changes in LVEF from baseline vs 4 months

Change in LVEF shows dose dependent improvement in cardiac volume from baseline

Figure 4. Changes in EF from baseline vs 4 months

Absolute change in EF shows improvement in both treatment groups

Results

Efficacy
- Initial results of blinded 4 month data in 93 subjects
- 8 of 9 clinical & structural parameters demonstrated improvement at 4 months in 30 mg dose group
- High risk subjects defined as having baseline LVESV > median 151 ml, demonstrated significant improvement at 4 months

Figure 5. Change in NTproBNP from baseline vs 4 months

Change NTproBNP biomarker shows dose dependent improvement in both treatment groups compared to placebo

Conclusions

- SDF-1 over-expression induces greater degree of LV remodeling as a function of baseline LVESV in a dose dependent manner
- 30 mg of SDF-1 plasmid demonstrates clinically meaningful improvements in objective parameters: NTproBNP, LVESV, LVEDV, and LVEF in patients with highest risk ischemic cardiomyopathy
- The degree of LV volume reduction at 4 months in response to SDF-1 plasmid correlates high probability of a significant mortality benefit at 2 years (Kramer DG et. al. JACC. 2010; 56(5):392)

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Abbreviations
SDF-1 = stromal cell-derived factor-1; MI = myocardial infarction; IP = investigational product; QoL = quality of life, MLWHFQ = Minnesota living with heart failure questionnaire; LVEF = left ventricular ejection fraction; LV = left ventricle; ml = milliliter; NYHA = New York heart association