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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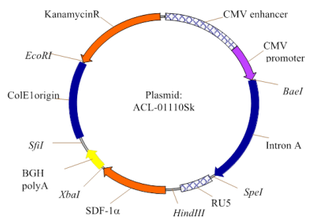
Background & Purpose

- A non-viral DNA plasmid the encodes for human 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
- 3 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

Methods

Endpoints:

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

STOP-HF Patient Profiles: Full Population

Parameter	Placebo	15 mg	30 mg	All JVS-100
N	31	32	30	62
NYHA I/II	29%	37%	30%	34%
NYHA Class III/IV*	71%	63%	70%	66%
6 Min. Walk (m)	284±98	295±96	308±72	301±84
QoL Score	56±17	49±18	47±22	48±20
LVESV (ml)**	159±62	158±61	174±73	165±67
LVEDV (ml)**	226±72	216±65	238±84	226±75
LVEF (%)**	30±7	28±8	28±7	28±8
NTpro	1260±1373	1144±1005	952±802	1051±910
GAL-3	12.5±5.5	13.0±7.2	13.3±5.3	13.1±6.3

* Note only 1 patient in study was class IV at baseline. Subject not identified to maintain blinding
** Only echoes with contrast reported. Placebo (n=30) 15 mg (n=29) 30 mg (n=25) All JVS-100 (n= 54)

Results

- 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

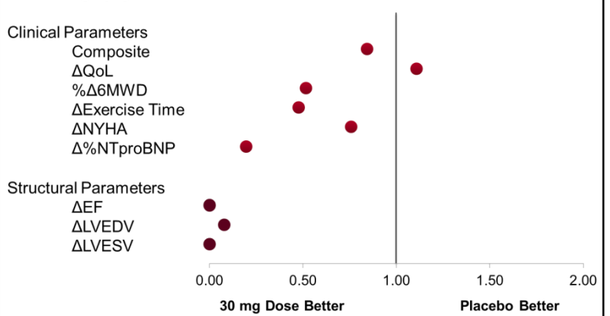


Figure 2. Changes in clinical & structural parameters 30 mg vs placebo
Change in parameter at baseline to 4 months relative to placebo

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

Results

STOP-HF Patient Profiles: High Risk Population

	Below median LVESV (< 151 ml)		Above median LVESV (> 151 ml)	
Parameter	Placebo	30 mg	Placebo	30 mg
N	14	11	14	14
6 Min. Walk (m)	314	298	263	324
QoL Score	58	46	55	40
LVESV (ml)	117	117	208	223
LVEDV (ml)	176	174	283	291
LVEF (%)	33	32	27	24
NTpro	580	877	1849	1031
GAL-3	12	11	12	16

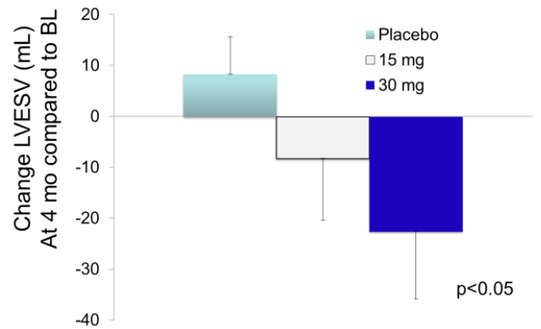


Figure 3. Changes in LVESV from baseline vs. 4 months
Change in LVESV shows dose dependent improvement in cardiac volume from baseline

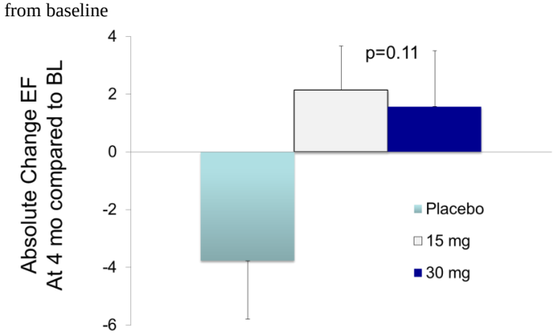


Figure 4. Changes in EF from baseline vs. 4 months
Absolute change in EF shows improvement in both treatment groups

Results

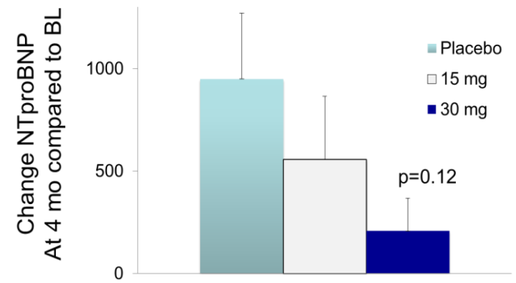


Figure 5. Change in NTproBNP from baseline vs. 4 months
Change NTproBNP biomarker shows dose dependent improvement in both treatment groups compared to placebo

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 derived factor -1, MI – myocardial infarction, IP – investigational product, QoL – quality of life, MLWHFQ – Minnesota living with heart failure questionnaire, LVESV – left ventricular end systolic volume, LVEF – left ventricular ejection fraction, NYHA – New York heart association