

Safety and Preliminary Efficacy of Intravenous Allogeneic Mesenchymal Stem Cells in Patients With Non-ischemic Heart Failure

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Sponsor: CardioCell, LLC



Declaration of Interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amgen
- Bayer
- Boehringer Ingelheim
- Cardiocell
- Gilead
- Janssen
- Merck
- Novartis
- Trevena
- Relypsa
- Z Pharma.)



Introduction

- Direct myocardial injections of mesenchymal stem cells (MSCs) in patients with HFrEF have shown safety with potential efficacy.
- MSCs secrete a broad array of molecules with potential therapeutic benefit, including anti-inflammatory and immunomodulatory activities
 - May be effective with intravenous delivery
 - Ischemia-tolerant bone marrow derived allogeneic MSCs (itMSC, CardioCell LLC.) are grown under hypoxic conditions
 - Enhanced paracrine properties



Aims and Eligibility

- Aim: To assess the safety and preliminary efficacy of intravenous itMSC injection in patients with non-ischemic HF
- Eligibility
 - Non-ischemic cardiomyopathy
 - Ejection fraction $\leq 40\%$
 - NYHA class II-III symptoms
 - No evidence hyper-enhancement on MRI
 - Stable on evidence based medical therapy for at least 3 months.



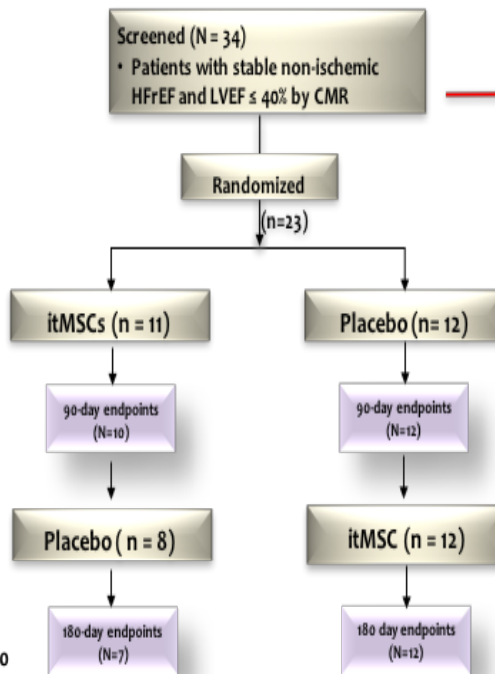
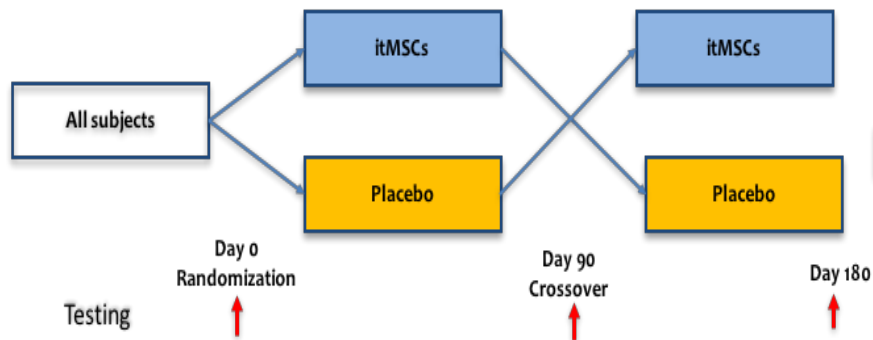
Study Design

Design: Phase IIa, single-blind, placebo-controlled, crossover, multi-center, RCT

Subjects: 23 patients

Randomization: 1:1 itMSC or placebo injection with 90 day crossover

Intervention: itMSC group: Single dose 1.5 million cells/kg iv. Placebo group: 1 mL/kg Lactate Ringer's solution iv.



Enrollment

Screen Failure (n=11)

Did not undergo infusion (n=1)

Did not undergo 180 day assessments

- 1 withdrawal after 90 day evaluation, before cross-over infusion
- 1 Protocol violation after 90 day evaluation, before cross-over infusion
- 1 Protocol violation after cross-over infusion – no show for Day 180 tests. Tests performed on Day 240 visit.



Safety

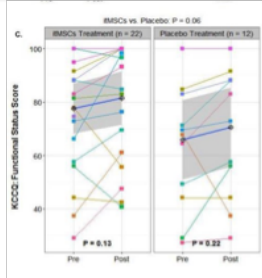
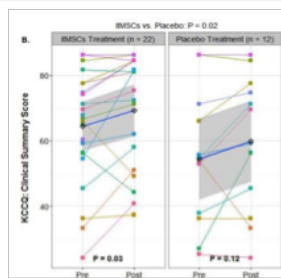
	Placebo	itMSC
Adverse events	34	35
Serious adverse events	0	0
Cell related AE *	0	1
Hospitalizations	1	0
Death	0	0

*bruising at iv site

No significant changes in

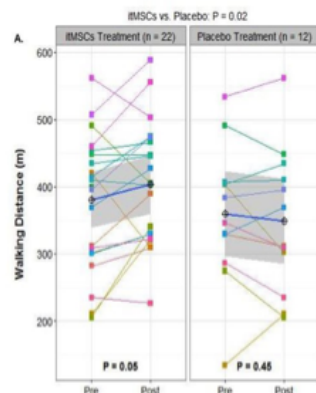
1. Holter monitor
2. Liver function (ALT, AST, Alk Phos, bilirubin, and albumin)
3. Renal function (creatinine, eGFR)
4. Pulmonary function (FVC, FEV1, FEV1/FVC, DLCO)

Kansas City Cardiomyopathy Questionnaire



KCCQ	Differences between groups, itMSC minus placebo (95% CI)	P value
Functional Status Score	5.65 (-0.11-11.41)	0.06
Clinical Summary Score	5.22 (0.70-9.74)	0.02

Six Minute Walk Distance



6 Minute Walk Test	Differences between groups, itMSC minus placebo (95% CI)	P value
Distance (m)	36.47 (5.98-66.97)	0.02
Distance (% change from baseline)	15.94 (1.63-30.24)	0.03

Left Ventricular Function

Initial Injection: itMSC (N=10)

Variable	Diff	95% CI		P
LVEF (%)	2.31	-0.09	4.71	0.06
LVEDV (ml)	-17.86	-35.03	-0.69	0.04
LVESV (ml)	-16.60	-33.22	0.02	0.05

Initial Injection: Placebo (N=12)

Variable	Diff	95% CI		P
LVEF (%)	1.62	-0.82	4.05	0.17
LVEDV (ml)	-10.56	-30.54	9.43	0.27
LVESV (ml)	-8.90	-27.40	9.60	0.31

Initial Injection: difference itMSC - placebo

Variable	Diff	95% CI		P
LVEF (%)	-0.69	-3.93	2.54	0.66
LVEDV (ml)	7.30	-18.02	32.61	0.55
LVESV (ml)	7.70	-16.09	31.49	0.50

Post crossover - 22 itMSC, 12 placebo

Variable	Diff	95% CI		P
LVEF (%)	0.01	-1.50	1.54	0.99
LVEDV (ml)	1.67	-8.60	11.93	0.75
LVESV (ml)	0.67	-7.28	8.62	0.87



Summary

Single administration of IV itMSCs in patients with non-ischemic HFrEF was

- Safe (clinical, PFT, LFT, arrhythmias)
- Improved 6-minute walk test
- Improved KCCQ Clinical Summary score and trend for Functional Status score
- No significant change in LV function

Future studies

- Confirm findings in larger non-ischemic cohort with clinical endpoints
- Explore effectiveness in ischemic cardiomyopathy
- Explore whether multiple injections lead to further improvement, including changes in cardiac function

