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Rationale and Design of the SENECA (StEm cell iNjECTION in cAncer survivors) Trial★

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Abstract

Objectives: SENECA (StEm cell iNjECTION in cAncer survivors) is a phase I, randomized, double-blind, placebo-controlled study to evaluate the safety and feasibility of delivering allogeneic mesenchymal stromal cells (allo-MSCs) transendocardially in subjects with anthracycline-induced cardiomyopathy (AIC).

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Background: AIC is an incurable and often fatal syndrome, with a prognosis worse than that of ischemic or nonischemic cardiomyopathy. Recently, cell therapy with MSCs has emerged as a promising new approach to repair damaged myocardium.

Methods: The study population is 36 cancer survivors with a diagnosis of AIC, left ventricular (LV) ejection fraction <40%, and symptoms of heart failure (NYHA class II-III) on optimally-tolerated medical therapy. Subjects must be clinically free of cancer for at least two years with a 30% estimated five-year risk of recurrence. The first six subjects participated in an open-label, lead-in phase and received 100 million allo-MSCs; the remaining 30 will be randomized 1:1 to receive allo-MSCs or vehicle via 20 transendocardial injections. Efficacy measures (obtained at baseline, 6 months, and 12 months) include MRI evaluation of LV function, LV volumes, fibrosis, and scar burden; assessment of exercise tolerance (six-minute walk test) and quality of life (Minnesota Living with Heart Failure Questionnaire); clinical outcomes (MACE and cumulative days alive and out of hospital); and biomarkers of heart failure (NT-proBNP).

Conclusions: This is the first clinical trial using direct cardiac injection of cells for the treatment of AIC. If administration of allo-MSCs is found feasible and safe, SENECA will pave the way for larger phase II/III studies with therapeutic efficacy as the primary outcome.

Anthracycline-based chemotherapies remain common and effective treatments for breast cancer, lymphomas, leukemias, and sarcomas. Unfortunately, use of anthracyclines is limited by cardiotoxicity, which may manifest as late as 20 years after initial exposure.¹ The risk of anthracycline-induced cardiomyopathy (AIC) is primarily related to the lifetime cumulative dose of anthracyclines, but even at low cumulative doses (such as standard-dose therapy for breast cancer), some patients will have evidence of AIC as demonstrated by endomyocardial biopsy or clinically-significant decline in left ventricular (LV) ejection fraction (EF).²⁻⁴ Thus, every exposure to an anthracycline carries some risk of inducing cardiac dysfunction. AIC often is irreversible and carries a prognosis that is worse than that of ischemic or nonischemic cardiomyopathy, with a ~3.5 higher relative risk of dying within five years.⁵ Many patients with AIC are relatively young, and ~70% are women.⁶ Several strategies have been tested to decrease the incidence of AIC, with little or no success.⁷ Other than heart transplant or mechanical support device, current therapies are palliative, and AIC remains an incurable and often fatal disease for which no effective treatment is available.

Given the limited availability of donor hearts and the bleak prognosis of AIC, new treatment strategies are sorely needed; this is an important unmet need in contemporary cardiovascular medicine. Recently, cell-based therapies with bone marrow-derived mesenchymal stromal cells (MSCs) have emerged as a novel approach to regenerate and/or repair damaged myocardium.^{8,9} Since cell therapy appears to be a safe and promising treatment for regenerating/repairing myocardium and improving cardiac function in both ischemic cardiomyopathy⁸⁻¹¹ and dilated nonischemic cardiomyopathy,^{12,13} we postulated that it may be beneficial in AIC as well; in all of these conditions, the underlying cause of heart failure is the loss of viable myocytes with replacement fibrosis. We selected allogeneic MSCs (allo-MSCs) to obviate the risk of disseminating the original malignancy and because mounting evidence supports the potential therapeutic utility of these cells in augmenting LV function both in a preclinical model of AIC¹⁴ and in patients with ischemic or nonischemic cardiomyopathy.¹¹⁻¹³ Accordingly, we designed the SENECA trial (StEm cell iNjECTION in

cancer survivors) to test the safety and feasibility of administering allo-MSCs in subjects with AIC.

Methods

Study design

SENECA is a phase I, randomized, double-blind, placebo-controlled study to evaluate the safety and feasibility of delivering allo-MSCs by the transendocardial route in subjects with LV dysfunction secondary to AIC ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02509156) Identifier: [NCT02509156](https://clinicaltrials.gov/ct2/show/study/NCT02509156)). This first-in-human trial, funded by the National Heart, Lung, and Blood Institute (NHLBI) and sponsored by the Cardiovascular Cell Therapy Research Network (CCTRn), will also collect preliminary evidence for the therapeutic efficacy of allo-MSCs in this population. The primary hypotheses are: (i) that allo-MSCs are well-tolerated (safety) and (ii) that they can be delivered as planned and the outcome measures can be collected (feasibility). The secondary hypothesis is that allo-MSCs promote myocardial repair, thereby reducing scar burden and improving cardiac performance, functional capacity, and quality of life (efficacy). The design of the study was determined in consultation with the Food and Drug Administration, while the drafting and editing of this paper was the sole responsibility of the authors. While the independent safety profiles of both allogeneic MSCs and transendocardial injection are well known, introduction of the study product for the first time in subjects with AIC warranted an additional safety assessment prior to initiating a placebo arm. The lead-in evaluation assuaged any concerns of acute complications related to the performance of 20 transendocardial injections of 0.4 ml each throughout the left ventricle in a diffusely fibrotic heart.

Study population

Inclusion and exclusion criteria are summarized in Tables I and II, respectively. Candidates for enrollment include men and women, aged 18 to 79, who are cancer survivors with a diagnosis of AIC. Subjects must have LV systolic dysfunction (LVEF <40%) and symptoms of heart failure (NYHA class II-III), and must be receiving stable, optimally-tolerated heart failure therapy (e.g., beta blockers, ACE inhibitors/ARBs, and/or aldosterone antagonists), unless contraindicated. Subjects must be clinically free of cancer (except carcinoma in situ and fully resected basal and squamous cell cancer of the skin) for at least two years and must have an estimated five-year risk of recurrence <30%. Ongoing antiestrogen, HER2, or rituximab maintenance are not considered chemotherapy for the purposes of this definition, and therefore are permissible during study participation. Following preliminary review of their medical records to determine eligibility, potential subjects will meet with the research staff to review the protocol, the informed consent document, and possible risks of participation. To exclude heart failure secondary to ischemic cardiomyopathy, available imaging obtained within five years of enrollment will be reviewed. Acceptable imaging for detection of CAD includes a coronary arteriogram, a rest/stress SPECT/PET/CT scan, a stress echocardiogram, a stress MRI, or cardiac computed tomography angiography (CCTA). Any of these tests is acceptable provided there have been no symptoms or evidence of CAD since the test. If none of these tests is available within the past five years, the subject will

have one of them performed before entry into the study to confirm absence of obstructive CAD or ischemia.

A total of 36 subjects will be enrolled. The first six subjects participated in an open-label, lead-in phase; all of them received active treatment (100 million allo-MSCs via transendocardial injection). After a 1-month safety review of these first six subjects by an NHLBI-sponsored Data and Safety Monitoring Board (DSMB), approval was granted to enroll the remaining 30 subjects, who will be randomized 1:1 to receive either 100 million allo-MSCs (n = 15) or cell-free Buminate solution (n = 15) via transendocardial injections.

Baseline testing and randomization

Following informed consent, subjects begin baseline testing. The period from consent to treatment will not exceed 45 days (Figure 1). After successful completion of the baseline evaluation (Table III), subjects are randomized via an online access database created and maintained by the Data Coordinating Center (DCC).

Cell manufacturing

Allo-MSCs were manufactured by the Center for Cell and Gene Therapy (CAGT; Baylor College of Medicine, Houston, TX) using donor marrow from a healthy, young female volunteer meeting federal eligibility requirements for donors of human cell and tissue products (including infectious disease testing, risk behavior assessment, and clinical examination).¹⁵ The cell product was grown and expanded using a functionally-closed computer-controlled bioreactor (Terumo Quantum Cell Expansion System). Cells are cryopreserved at the CAGT and transported to each clinical site, via validated liquid nitrogen dry shipper, within one week prior to scheduled injection. Placebo product consists of cell-free Buminate solution. Local cell processors receive and prepare all products for administration. Both study products (allo-MSCs and placebo) are provided to treatment teams in packaging with identical appearance.

Study product delivery

Each subject receives 20 transendocardial, electromechanically-guided injections performed with the NOGA MyoStar injection catheter (Biologic Delivery Systems) (Figure 2). The intervention group receives a total of 100 million allo-MSCs in 8 ml of Buminate solution; the placebo group receives 8 ml of cell-free Buminate solution. Electromechanical mapping is used to identify target areas for injection based on viability according to unipolar voltage. Priority for injection is given to areas of relative fibrosis demonstrating intermediate levels of unipolar voltage (4–8 mV); however, areas with unipolar voltage up to 12 mV can be included to treat the entire left ventricle. In addition, injection sites should satisfy the following two criteria: (i) perpendicular position of the catheter to the LV wall and (ii) loop stability ≤ 4 mm. After proper placement of the catheter is confirmed, subjects in the treatment group receive transendocardial injections of 0.4 ml of solution (approximately 5 million allo-MSCs per injection). Those in the placebo group receive vehicle (0.4 ml of Buminate solution per injection). All subjects are monitored overnight. After the procedure, a transthoracic 2-D echo without contrast is performed to evaluate subjects for pericardial effusion, and serial blood samples for troponin measurements are collected for 24 hours.

Outcomes

The primary endpoints are safety and feasibility. All adverse events grade 2 and higher, based on the Common Terminology Criteria for Adverse Events (CTCAE), are captured. These events include major adverse cardiac events (MACE) and other significant clinical events (Table IV). The feasibility of preparing and delivering the study product, as well as collecting cardiac MRI variables in subjects with cardiac devices, is assessed.

Efficacy measures of interest are obtained at baseline, 6 months, and 12 months, permitting an assessment of their trajectory over time and whether that trajectory is modified by therapy. MRI evaluations of LV function, structure (including LV volumes), fibrosis, and scar burden provide a comprehensive assessment of myocardial performance and morphology. All MRI analyses are performed in a core laboratory by investigators masked to treatment assignment and other subject data. Functional capacity encompasses exercise tolerance (six-minute walk test)¹⁶ and quality of life assessment (Minnesota Living with Heart Failure Questionnaire). We also assess clinical outcomes (measured by MACE and cumulative days alive and out of the hospital) and biomarkers of heart failure (NT-proBNP).

Statistical methods

The principal analysis will be based on “intention-to-treat”. The reasons for non-treatment of the anticipated small number of subjects who are randomized but do not receive treatment will be tabulated. All analyses will be performed on two cohorts: first, on the 30-subject randomized cohort and then on the total cohort (randomized plus the six open label therapy subjects). Descriptive statistics for baseline characteristics, known or suspected to be associated with outcomes, will be prepared for the treatment groups, including, but not limited to, demographic characteristics, medical history, physical examination, laboratory data, and quality of life and psychosocial data. Exact testing for categorical variables and Wilcoxon two-sample rank sum test for continuous variables will be used to evaluate the differences in baseline variables between treatment groups. There are two prospectively declared follow up durations: 6 months and 12 months after injection. For each of these periods, the change in every efficacy measure of interest will be computed. The difference in these changes between the two treatment groups will be described and evaluated using Wilcoxon two-sample procedures, with regression modeling to adjust for a small number of treatment confounders. No adjustment for multiplicity is anticipated for this feasibility trial.

Follow-up visits and surveillance

In both the lead-in and the main trial, subjects are followed for 12 months for safety and efficacy. Follow-up initiates on the day of injection and subsequent visits occur at day 1, 1 week, 1 month, 6 months (primary endpoint assessment), and 12 months (primary endpoint assessment). All available standard-of-care medical records for cancer surveillance are reviewed for cancer recurrence at 12 months. A telephone contact takes place at 24 months to assess the subject’s current medications, as well as morbidity and mortality.

Safety monitoring

The DCC employs a comprehensive and data driven safety monitoring program that provides ongoing capture and analysis of safety data, and generates timely notifications and

reports of safety issues to appropriate study personnel (for local institutional review board reporting) to the NHLBI DSMB and to the Food and Drug Administration (FDA). All SENECA subjects are closely monitored for adverse events with trans-mission of information to these relevant oversight groups. The DSMB meets at least twice annually to review performance of participating centers, assess recruitment, evaluate study progress, and report recommendations to the NHLBI. The DCC monitors regulatory and safety compliance at each clinical center and conducts regular visits to each site to ensure protocol adherence.

Biorepository

A central biorepository is utilized. The goals are to provide: i) storage of critical biomaterials (i.e., subject peripheral blood and donor allo-MS-C product), ii) long-term integrity (up to 10 years) of these biospecimens and products, and iii) management of immunologic, immunohistochemical, cellular, and molecular analyses of donor allo-MS-C product and subject serum samples, as well as phenotypic and functional analyses of cells and plasma samples. The overall aim of this central biorepository is to gain insights into the diagnostic accuracy of disease progression and prognostic information into successful intervention.

Discussion

SENECA is the first clinical trial to utilize direct cardiac injection of cells for the treatment of AIC – an incurable and often fatal syndrome that disproportionately affects women and young adults, and for which no effective treatment currently exists.^{5,7} This first-in-human study has the potential to herald a novel approach to the management of AIC.

Despite attempts at improving therapy, the prognosis of AIC is grim, worse than that of ischemic or idiopathic cardiomyopathy.^{5,7} Anthracyclines induce cell death and fibrosis via free radical production, DNA damage, and altered intracellular signaling.¹⁷ The biological hypothesis underlying SENECA is that allo-MS-Cs may promote replacement of lost cardiomyocytes, repair of injured cardiomyocytes, decrease in interstitial myocardial fibrosis, and/or reduction of chronic inflammation, all of which may promote restoration of cardiac tissue and function. As noted earlier, the primary endpoints are safety and feasibility. If administration of allo-MS-Cs is found to be feasible and safe, SENECA will pave the way for larger phase II/III studies whose primary endpoint will be therapeutic efficacy. Clearly, the results of SENECA (e.g., changes in LV function and functional status) will be crucial to inform the design of such studies and ensure that they are adequately powered.

Preclinical studies of cell therapy in AIC

The concept that cell therapy is beneficial in AIC is supported by preclinical observations. De Angelis et al. induced AIC in rats with a three-week doxorubicin treatment; subsequent treatment with syngeneic c-kit⁺ cardiac stem cells resulted in a 66% decrease in mortality at 6 weeks and a significant improvement in multiple parameters of LV function compared with control rats treated with vehicle.¹⁸

Psaltis et al. examined the safety and utility of allo-MSCs delivered transendocardially in a sheep model of AIC.¹⁴ In this study, allo-MSCs were prepared from ovine bone marrow by immunoselection using the tissue nonspecific alkaline phosphatase, or STRO-3, monoclonal antibody. Fifteen sheep with AIC were assigned to catheter-based, transendocardial injections of ovine allo-MSCs (n = 7) or placebo (n = 8) under electromechanical mapping guidance. Ten weeks after the first exposure to doxorubicin, animals received 20 injections of placebo or allo-MSCs distributed throughout the left ventricle. At 8 weeks after treatment, LV end-diastolic volume (LVEDV) increased similarly in both cohorts; however, allo-MSC therapy attenuated the increase in LV end-systolic volume (LVESV) compared with the control group (P b .01). LV ejection fraction (LVEF) increased from $37.3 \pm 2.8\%$ before cell therapy to $39.2 \pm 1.4\%$ at 8 weeks after cell therapy (P=NS) in treated sheep, whereas in control animals it decreased from $38.8 \pm 4.4\%$ to $32.5 \pm 4.9\%$ (P b .05) at corresponding time points. Histological analysis showed that allo-MSC therapy was associated with less fibrosis than in the control group and increased density of karyoki-netic cardiomyocytes and arterioles (P b .05 for each), although the engraftment of cells after transplantation was modest. This study, conducted in a large animal model of AIC, provides evidence for the therapeutic utility of allo-MSCs in the treatment of AIC, and thus supports the rationale for SENECA.

Rationale for performing SENECA in the CCTRN

Because the prevalence of AIC is lower than that of ischemic or idiopathic cardiomyopathy,^{5,19–21} conducting a phase I trial of AIC in one center would be difficult, if not impossible. On the other hand, by virtue of its multicenter structure, the CCTRN is an ideal resource for such a study. The lead-in phase (with six subjects) began on September 22, 2016 and its 1-month follow-up ended on January 24, 2017. The main trial began on March 2, 2017; based on a conservative projection, we expect that the infrastructure of the CCTRN (consisting of seven clinical centers) will enable us to enroll 30 subjects within 12 months, highlighting the advantages of a network infrastructure for clinical trials of cell therapy.

SENECA is an example of the benefits that accrue from an interdisciplinary cooperation. Indeed, this trial requires a close partnership among cardiologists, oncologists, and primary care physicians in addressing a common problem that represents a major cause of morbidity and mortality in this specific patient population. Several aspects of SENECA were designed in collaboration with oncologists and cancer researchers (Kathy Miller, Indiana University; Tan Ince, University of Miami; Carrie Lenneman, University of Louisville).

Selection of endpoints

Because the effects of allo-MSCs in AIC are unknown, SENECA is designed as a phase I, hypothesis-generating study. We will assess not only changes in LV volumes, LV function, and myocardial structure (e.g., fibrosis), but also changes in functional capacity (measured by the six-minute walk test and the MLHF questionnaire), clinical outcomes (measured by MACE and cumulative days alive and out of the hospital), and biomarkers of heart failure (NT-proBNP). This broad set of endpoints will ensure that beneficial actions of allo-MSCs are not overlooked and will provide information essential for selecting the most appropriate endpoint and sample size for a subsequent phase II trial.²² As outlined in Table IV, cMRI

will be used to evaluate myocardial function and structure. cMRI was selected over other imaging modalities, such as cardiac CT and echocardiography, because it enables accurate, high-resolution assessment of myocardial injury (e.g., fibrosis, inflammation, edema),^{23–25} is considered to be more reproducible for measuring LV function and volumes,^{26,27} and does not require additional radiation exposure. In addition, cMRI enables assessment of myocardial strain, which may have greater sensitivity than LVEF in predicting clinical outcome,²⁸ particularly in chemotherapy-induced cardiomyopathy.²⁹ Accordingly, use of cMRI may allow for an improved assessment of the benefits of cell therapy. While not all subjects will require a cardiac device, it is anticipated that 60–65% of participants in the study population will have one. The presence of most pacemakers or implanted defibrillator devices is not a contraindication to MRI scanning in SENECA^{30,31} (Table II).

Safety of allo-MSCs in cancer patients

The experience obtained thus far with administration of adult progenitor cells for heart disease indicates that this therapy is safe; in particular, there has been no evidence of tumor formation.³² Nevertheless, based on evidence from cell lines, case reports, and clinical studies, concerns have been raised that some cell-based therapies, particularly those involving cells that augment angiogenesis and repress apoptosis, may stimulate growth of active, high-grade tumors^{33–38}; in contrast, cancer in remission does not appear to be activated by cell therapy.³⁹ To address such concerns, subjects enrolled in SENECA must have firmly established cancer remission (i.e., be in remission for at least two years) and low risk of recurrence (i.e., estimated five-year risk of recurrence < 30%) to be eligible for the study. Clearly, the outcome of this trial will be of utmost importance in elucidating whether administration of MSCs is safe in this population.

Rationale for using allo-MSCs

The choice of MSCs is motivated by the fact that this is a particularly promising cell type for cardiac regenerative therapy, due to availability, immunologic properties, and record of safety and efficacy.^{40–42} Studies in rodent and swine models of myocardial infarction have shown that MSC administration results in improved recovery of LV function after MI, neo-angiogenesis at the infarct site, and decreased collagen deposition in the scar region.^{43,44} Differentiation of MSCs into mature cardiomyocytes has not been observed,^{43,44} although MSC-derived cells expressing contractile and sarcomeric proteins but lacking true sarcomeric functional organization have been reported.^{45,46} A potentially important mechanism of action of MSCs is stimulation of endogenous cardiac progenitor cells.⁴⁷ Complementary mechanisms that have been shown to play key, perhaps dominant, roles in the salutary cardiac effects of MSCs involve the secretion of paracrine factors.^{41,48} With respect to AIC in particular, recent work has shown that the cell-free secretome produced by human bone marrow or iPSC-derived MSCs as well as by human MSCs cultured from amniotic fluid is sufficient to attenuate anthracycline toxicity in cardiomyocytes *in vitro* and AIC *in vivo*.^{49,50}

MSCs are thought to be ideal candidate cells for allogeneic transplantation because they show minimal expression of major histocompatibility complex (MHC) class II antigens and intercellular adhesion molecules (ICAM), and they lack B-7 co-stimulatory molecules

necessary to trigger T-cell-mediated immune response.^{51,52} In addition, they exert anti-proliferative and anti-inflammatory effects, exhibit immunosuppressive properties, and suppress proliferation of T cells activated by allogeneic cells or mitogens.⁵³ In this regard, human MSCs fail to induce proliferation of allogeneic lymphocytes in vitro.⁵⁴ Finally, recent trials suggest safety and efficacy of allo-MSCs in patients with nonischemic dilated cardiomyopathy.^{11–13} Taken together, these considerations support the concept that MSCs represent a promising cell type for allogeneic cell therapy.⁴¹

The rationale for administering allo-MSCs (rather than autologous MSCs) in SENECA is multifarious. Use of allogeneic cells obviates any concern that autologous cells may lead to dissemination of the original malignancy for which patients were treated with anthracyclines. Clearly, recurrence or dissemination of the original neoplasm would be a catastrophic outcome that prohibits use of autologous cell therapy. Administration of allogeneic cells also avoids the challenge of harvesting potentially compromised progenitor cells from a subject with severe co-morbidities or advanced age, both of which are known to alter the phenotype of autologous MSCs.⁵⁵ Allo-MSCs have been used in several recent FDA-approved trials with encouraging results,^{11,13} and one trial suggests that they may be more effective than autologous MSCs.¹² The cumulative experience from these studies has demonstrated not only an outstanding safety margin but also a considerable potential for allo-MSCs to exert beneficial effects in heart failure patients.^{11–13}

Rationale for using the dosage of 100 million allo-MSCs

Our dosing strategy is based upon three major considerations: i) safety data, ii) cell concentration, and iii) total number of injections. By dividing 100 million MSCs into 20 injections of 0.4 ml each, the treatment regimen balances the desire for broad distribution of cells throughout the ventricle with the maintenance of an optimally low concentration of cells (12.5 million/ml). The experience accumulated with clinical trials of MSCs^{11–13,56,57} provides substantial evidence of safety with doses up to 200 million MSCs, as well as preliminary evidence of efficacy. In SENECA, subjects receive a total of 100 million allo-MSCs, divided into 20 injections of 5 million cells each. A dose of 100 million MSCs, delivered transendocardially, has been used in several clinical trials, such as POSEIDON,¹¹ TAC-HFT,⁵⁶ POSEIDON-DCM,¹² and a study by Perin et al.¹³ and has proven to be safe. The rationale for selecting 100 million cells, rather than a greater dose, is that in the POSEIDON trial,¹¹ there was an inverse dose–response relationship, leading the authors to speculate that higher doses may be less efficacious due to deleterious effects on cell retention, survival, or performance. The 100-million dose appeared to give an efficacy signal in POSEIDON-DCM.¹²

Data from preclinical investigations also are consistent with an inverse dose–response relationship. In an ovine model of acute MI treated with transendocardial injection of 25, 75, 225, or 450×10^6 STRO-3 MSCs, Hamamoto et al. demonstrated that, compared with control animals, low doses (25 and 75×10^6 cells) of MSCs significantly attenuated the increase in LVEDV and LVESV; the 225×10^6 dose improved only the LVESV over control, whereas the 450×10^6 dose did not produce any salutary remodeling effect relative to controls.⁵⁸ In addition, infarct expansion was attenuated only in the 25, 75, and to some

extent the 225×10^6 groups, although LVEF improved at all cell doses. CD31 and smooth muscle actin (SMA) immunohisto-chemical staining demonstrated increased vascular density in the border zone only at the two lower cell doses.⁵⁸ Another ovine study used a protocol and allo-MSC doses similar to the above study and arrived at similar conclusions: the LVEDV increase was significantly attenuated only in the 25 and 75×10^6 groups compared with controls, although LVEF improved with all doses of allo-MSCs in comparison with the control animals ($P < .05$).⁵⁹ In summary, both preclinical and clinical data suggest that the beneficial effects of transendocardially administered MSCs may decrease as the dose approaches $200\text{--}225 \times 10^6$.

Rationale for using the transendocardial route of administration

In AIC patients, myocardial fibrosis is diffuse, with a unique cardiac MRI profile.^{20,60} Injections of study product in SENECA targets areas of diffuse fibrosis using the NOGA technology, which can assess in real time and 3-D space underlying myocardial viability based on unipolar voltage. The choice of transendocardial delivery is based on both preclinical and clinical data. The aforementioned study by Psaltis et al. in an ovine model demonstrated that MSC therapy delivered by the NOGA device is safe and effective in the treatment of doxorubicin-induced cardiomyopathy.¹⁴ Several studies in porcine models of ischemic cardiomyopathy have shown therapeutic efficacy of transendocardially delivered MSCs.^{43,61–63} Moreover, there is substantial clinical experience with the transendocardial delivery of autologous bone marrow-derived mono nuclear cells as well as autologous MSCs and allo-MSCs in the setting of chronic LV dysfunction. Many studies^{11,13,56,57,64–67} confirm the safety of NOGA-mediated injections in patients with cardiomyopathy, including studies that have used up to 20 transendocardial injections.^{11,14,67} In addition, lower cell concentrations have been reported to be associated with greater efficacy.^{13,59} Based on these considerations, we have chosen a volume of 0.4 ml, which is in keeping with previous trials demonstrating safety of volumes of 0.2–0.5 ml (FOCUS, TAC-HFT, RENEW, POSEIDON DCM, etc.).^{11,56,64,65,68,69} On the other hand, intracoronary delivery of MSCs is thought to be potentially hazardous because of the possibility of producing microvascular obstruction with resultant dose-dependent myocardial damage, as suggested by preclinical studies.^{70,71} In addition, no published clinical trial supports the efficacy of intracoronary MSC delivery, in contrast to copious literature supporting the efficacy of transendocardial MSC delivery, as discussed above. Finally, unlike in ischemic cardiomyopathy in which cell injections are provided in a relatively small area of myocardium surrounding a scar, the diffuse nature of the disease requires that in the SENECA protocol the injections be dispersed through the entire left ventricle.

In summary, SENECA is the first clinical trial using direct cardiac injection of a cell product for the treatment of anthracycline-induced cardiomyopathy. This phase I trial will evaluate the safety and feasibility of delivering allo-MSCs transendocardially in a patient population that has limited therapeutic options and a grim prognosis. If the results are encouraging, SENECA will inform future larger studies of this new therapeutic modality.

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Figure 1.
Flowchart of subject participation timepoints.

Figure 2.

The polar map displayed shows unipolar voltage (UniV) values present on the endocardial surface of the left ventricle. The UniV is displayed according to the color spectrum shown (color legend) with lower values in red and higher values displayed in yellow, green and blue. The data points that constitute the map are depicted by white dots (n=75) and the sites of transendocardial injection are depicted by black dots (n=20). Characteristically, voltage maps in nonischemic cardiomyopathy are heterogeneous suggesting that the fibrotic process that takes place secondary to the underlying pathology is not uniform. A large area of fibrosis (lower UniV) is noted throughout the septum and relatively higher UniV is present in the inferior wall. UniV values serve as the basis for selection of the target injection areas. The overriding cell injection strategy for the SENECA trial is to distribute injections broadly throughout the myocardium and deliver product to areas that demonstrate intermediate level UniV (4 to 8mV). This range can be expanded to include areas with UniV of up to 12mV, if necessary. Each of the 20 injections contains either 0.4 ml of cell suspension with 5 million

allo-MSCs per injection site for the active cell treatment arm or 0.4 ml of cell-free Buminate solution for the placebo group.

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Table I**Inclusion Criteria**

To participate, a subject **MUST**:

- Be 18–79 years of age
- Be a cancer survivor with diagnosis of anthracycline-induced cardiomyopathy
- Have an LVEF $\geq$ 40% by cardiac magnetic resonance imaging
- Be in New York Heart Association class II—III
- Have received the initial diagnosis of anthracycline-induced cardiomyopathy at least six months earlier and be on stable, optimally-tolerated therapy with beta-blockers, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers, and/or aldosterone antagonists for 1 month, unless contraindicated
- Have a period of at least two years of clinical cancer-free state* and low likelihood of recurrence (a five-year risk of recurrence estimated at 30% or less), as determined by an oncologist, based on tumor type, response to therapy, and negative metastatic work-up at the time of diagnosis

**exceptions to this are carcinoma in situ or fully resected basal and squamous cell cancer of the skin.*

- Be a candidate for cardiac catheterization
-

Table II**Exclusion Criteria (abbreviated list)**

To participate, a subject **MUST NOT HAVE**:

- A life expectancy <12 months
 - A computed tomography scan or baseline cardiac magnetic resonance imaging showing new tumor or suspicious lymphadenopathy raising concern of malignancy
 - Presence of coronary artery disease as determined by imaging test within 5 years prior to study enrollment, provided there have been no symptoms or evidence of coronary artery disease since the test
 - Had a previous myocardial infarction
 - A history of radiation therapy AND evidence of constrictive physiology and/or evidence of other patterns of non-ischemic cardiomyopathy on cardiac magnetic resonance imaging (e.g., amyloidosis, sarcoidosis, hemochromatosis, pure radiation-induced cardiomyopathy, etc.) not consistent with anthracycline-induced cardiomyopathy being the dominant etiology of heart failure
 - Valvular heart disease including 1) mechanical or bioprosthetic heart valve; or 2) severe valvular (any valve) insufficiency/regurgitation within 12 months of consent
 - A history of left ventricular reduction surgery or cardiomyoplasty
 - Evidence of cardiogenic shock
 - A history of ischemic or hemorrhagic stroke within 90 days of baseline testing
 - Diabetes with poorly controlled blood glucose levels (HbA1c > 8.5%)
 - A baseline estimate glomerular filtration rate <35 ml/min/1.73m²
 - A history of organ or cell transplantation, except for transplantation of bone, skin, ligament, tendon, or cornea
 - A hematologic abnormality during baseline testing as evidenced by hemoglobin < 9 g/dl; hematocrit < 30%; absolute neutrophil count < 2,000 or total white blood count count more than 2 times upper limit of normal; or platelet values < 100,000/ul
 - Coagulopathy (INR> 1.5) not due to a reversible cause (e.g., warfarin and/or Factor Xa inhibitors)
 - Presence of left ventricular thrombus
 - Presence of a pacemaker and/or implantable cardioverter-defibrillator generator with any of the following limitations/conditions; manufactured before the year 2000; leads implanted < 6 weeks prior to consent; non-transvenous epicardial or abandoned leads; subcutaneous ICDs; leadless pacemakers; any other condition that, in the judgment of device-trained staff, would deem an MRI contraindication
 - Pacemaker-dependence with an implantable cardioverter-defibrillator
 - A cardiac resynchronization therapy device implanted less than 3 months prior to consent
 - Ventricular tachycardia > 20 consecutive beats without an implantable cardioverter-defibrillator within 3 months of consent, or symptomatic Mobitz 11 or higher degree atrioventricular block without a functioning pacemaker within 3 months of consent
 - Pregnancy, lactation, plans to become pregnant in the next 12 months, or is unwilling to use acceptable forms of birth control during study participation
-

Table III**Baseline Evaluation**

•	Laboratory tests, including: complete metabolic panel, complete blood count, liver function testing, NT-proBNP, Troponin I/T, HbA1c, PT/INR/PTT, and panel reactive antibodies
•	Infectious disease panel (HBc, HBsAg, HBV, HCV, HIV-1 groups M&O RNA, and Anti-HIV)
•	Comprehensive review of medical, oncological, and radiation history, vital signs, and physical examination
•	New York Heart Association (NYHA) classification
•	Current prescription and over-the-counter medications
•	Pregnancy test (for women of childbearing potential)
•	12-lead electrocardiogram
•	Minnesota Living with Heart Failure Questionnaire (MLHFQ.)
•	Six-minute walk test (6MWT)
•	Cardiac magnetic resonance imaging (cMRI)
•	Implantable cardioverter defibrillator interrogation (if applicable)

NT-Pro BNP= N-Terminal pro-Brain Natriuretic Peptide; HbA1c= Glycated Haemoglobin (A1c); PT/INR/PTT= Prothrombin Time/International Normalized Ratio/ Partial Thromboplastin Time; HBc=Hepatitis B Core Total Antibodies; HBsAg=Hepatitis B Surface Antigen Test; HBV=Hepatitis B Virus Testing; HCV= Hepatitis C Virus Testing; HIV-1 groups M&O RNA= Human Immunodeficiency Virus)

Table IV**Study Endpoints.**

Primary endpoint: Safety (assessed from baseline to 6-months and from baseline to 12- months)	
Major Adverse Cardiac Events (MACE)	
<ul style="list-style-type: none"> • Death • Hospitalization for worsening heart failure • Other exacerbation of heart failure (not requiring hospitalization) 	
Other Significant Clinical Events	
<ul style="list-style-type: none"> • Non-fatal stroke • Non-fatal myocardial 	<ul style="list-style-type: none"> • Infectious myocarditis • Hypersensitivity reaction
Infarction	
<ul style="list-style-type: none"> • Coronary artery 	<ul style="list-style-type: none"> • Neoplasm
Revascularization	
<ul style="list-style-type: none"> • Ventricular tachycardia/fibrillation • Pericardial tamponade 	<ul style="list-style-type: none"> • Any other potential deleterious late effects detected and corroborated by clinical presentation, laboratory investigations, image analysis, and when necessary, biopsy from suspected target sites
All adverse events at least grade 2 in severity (Common Terminology Criteria for Adverse Events)	
Primary endpoint: Feasibility	
Number and percent of subjects who	
<ul style="list-style-type: none"> • Have events between randomization and study product injection (SPI) that preclude the procedure • Receive less than 20 injections during the SPI procedure • Do not receive the intended dose of cells (100 million), reason, and actual dose delivered • Have at least one cardiac MRI endpoint measure that is uninterpretable due to issues related to the device, including, but not limited to, inability to undergo the procedure • Fail to complete follow-up 	
Secondary endpoint: Efficacy (assessed from baseline to 6 months and from baseline to 12 months)	
Myocardial Function and Structure (cardiac MRI)	
<ul style="list-style-type: none"> • Function: Change in LV ejection fraction, global strain, and regional strain • Structure: Change in LV end-diastolic and end-systolic volume indices and LV sphericity index • Morphology: Change in area of delayed contrast enhancement (e.g., inflammation, edema, fibrosis) 	
Functional Capacity	
<ul style="list-style-type: none"> • Change in exercise tolerance (six minute walk test) • Change in MLHF Questionnaire 	
Clinical Outcomes	
<ul style="list-style-type: none"> • MACE • Cumulative days alive and out of hospital 	
Bio markers	
<ul style="list-style-type: none"> • Change in NT-proBNP 	