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Reply

# The C-CURE Randomized Clinical Trial (Cardiopoietic stem Cell therapy in heart failURE)

We appreciate the interest of Dr. Mielewczik and colleagues in the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial. As outlined in our paper (1), feasibility and safety were the primary endpoints in this first-in-man study that assessed cardiogenically-oriented, autologous bone marrow-derived mesenchymal stem cell therapy in chronic heart failure. The technology and study findings were reviewed in the scientific literature in the context of advances in regenerative medicine (2,3). We would like here to confirm that the C-CURE trial was designed, planned, executed, analyzed, and presented according to best standards in innovative clinical research. There are no inconsistencies in the C-CURE trial, as will be further illustrated in the following text. Following this initial study, a larger trial designed and powered to evaluate efficacy was approved and launched (the CHART-1 [Congestive Heart Failure CArdiopoietic Regenerative Therapy] trial) (4). Herein, we directly address the Letter to the Editor by Dr. Mielewczik and colleagues that noted interest in the C-CURE trial but raised a number of questions.

**How many patients were randomized? Counts range from 45 to 48.**

Informed consent was requested from a total of 48 patients. One patient refused participation, and of the remaining 47 randomized subjects, 2 patients were subsequently excluded based on criteria identified prior to bone marrow harvest (1 patient was diagnosed with a left ventricular aneurysm; a second patient developed a left ventricular thrombus). There was an imprecision in the text where 48 patients who entered the consent process are described as "randomized." It would have been more precise to state, "Consent was requested from 48 patients, and 47 were randomized…" Figure 1 in our paper (1) depicts the flow of the study, presenting its stepwise execution.

**The authors' corporate website currently states that randomization was 1:1 but Figure 1 in the paper (1) shows counts close to 1:2; conversely, at AHA 2011, the authors said that randomization was 2:1 but reported counts that were close to 1:1. Can the authors please clarify the randomization ratio?**

Randomization (2:1) was executed by a site-independent centralized process. Of note, the authors do not have a corporate website. The website of Cardio3 BioSciences, the sponsor of the study, indicated at 1 stage a 1:1 ratio. This error has been corrected.

**Once randomized to 1 arm, did any patient's data appear under the heading of the opposite arm? Were some patients allocated to arms by routes other than randomization to those arms? Are baseline characteristics and result data regarding the trial arms, as randomized, available?**

Protocol-defined analysis, in which all patients not receiving cell therapy were placed in the control arm (n = 24) and all those receiving cell therapy were placed in the cell therapy arm (n = 21), is presented in Online Figure 13 of our paper (1), with patient demographics shown in Table 1 (1). The paper also presents in main figures a complementary analysis, as advised in the peer-review process, that maintains the randomization schedule with analysis taking into account clinical inclusion/cell release criteria (n = 15 control arm; n = 21 cell therapy arm). We here include an updated demographics table with baseline characteristics pertinent to both analyses (Table 1). Neither the 15 of 21 nor the 24 of 21 baseline comparisons reveal significant differences in populations, nor do they change the outcome of efficacy signals. The revised table corrects for original typographical errors, which had no material impact on trial findings, interpretations, or conclusions (Table 1).

**The primary endpoint was pre-specified to be radionuclide ejection fraction, but its results do not appear in the paper. A new primary endpoint is described in the paper. Did all authors agree on this change, and when?**

Safety and feasibility are the primary endpoints of the C-CURE trial, as reported in the paper (1). The initial design of the C-CURE trial included a safety and feasibility phase (termed Stage A; n = 45 patients) to be potentially followed by an efficacy phase with a primary endpoint of radionuclide ejection fraction (EF) (termed Stage B; n = 195 patients). The Stage A part of the study had a built-in "go/no go" decision at the 3-month follow-up visit. Indeed, at the 3-month time point, the procedure was deemed feasible and safe. Yet, in line with advice received from regulatory authorities indicating that a properly powered study assessing efficacy in heart failure would require inclusion of outcome endpoints beyond a focus on cardiac function, the steering committee communicated to study sites the decision not to proceed with Stage B and limited the C-CURE trial to a safety/feasibility study, completing Stage A per protocol.

**Regarding the data presented in the paper (1), its Online Appendix, and the previous trial reports (see the Online Appendix for citations), which of these various conflicting versions are correct regarding ejection fraction, end-systolic volume, end-diastolic volume, New York Heart Association functional class, quality of life, and walk distance?**

Data reported in the paper are correct (1). Earlier abstracts or initial oral presentations are considered preliminary, providing reports of datasets not yet monitored for source data verification per good clinical practice guidelines, not yet sanctioned or adjudicated by the independent data safety monitoring board (DSMB), and not subject to peer review.

**Fewer of certain events, such as arrhythmias, are reported in the current narrative than in previous ones. Could the authors clarify how many stem cell recipients died?**

This is a request for clarification regarding the description of adverse events and patient deaths as it pertains to preliminary reports. Initial communications presented data in various forms, for example, the number of arrhythmic events versus the number of patients with arrhythmia. The paper reports those data adjudicated by the DSMB (1). For example, the number of episodes versus the number of patients suffering from arrhythmic events was distinguished in the paper (1). Furthermore, as stated in the paper (1), 1 patient died in the cell-treated group of the randomized C-CURE trial. This followed an elective cardiac transplantation and post-operative sepsis. In a separate nonrandomized pilot study, the Swiss Feasibility Study, which is distinct from the C-CURE trial, 1 patient died prior to being treated. The event is thus not reported in the paper, while this information may have been presented in earlier presentations to represent the totality of experience.

**Table 1** Patient Demographics, Cardiac History, and Medication Profile in Control and Cell Therapy Cohorts

| | Control (N = 15) | Control (N = 24) | Cell Therapy (N = 21) | p Value 15/21 | p Value 24/21 |
|---|---|---|---|---|---|
| Age, yrs | 58.7 ± 8.2 | 59.5 ± 8.0 | 55.3 ±10.4 | 0.424 | 0.234 |
| Sex, M/F | 13/2 | 22/2 | 19/2 | 0.720 | 0.889 |
| Family history, CAD | 9 (64)* | 12 (52)* | 15 (71) | 0.657 | 0.19 |
| Smoking | | | | | |
| Former | 9 (60) | 18 (75) | 11 (52) | 0.650 | 0.114 |
| Current | 5 (33) | 5 (21) | 5 (24) | 0.529 | 0.811 |
| Arterial hypertension | 7 (47) | 13 (54) | 9 (43) | 0.820 | 0.450 |
| Diabetes mellitus | 4 (27) | 8 (33) | 4 (19) | 0.588 | 0.280 |
| on diet | 1 (7) | 3 (13) | 1 (5) | 0.806 | 0.363 |
| NIDDM | 1 (7) | 2 (8) | 2 (10) | 0.760 | 0.889 |
| IDDM | 2 (13) | 3 (13) | 1 (5) | 0.359 | 0.363 |
| Hypercholesterolemia | 15 (100) | 24 (100) | 16 (76) | 0.042 | 0.011 |
| on diet | 1 (7) | 1 (4) | 0 (0) | 0.230 | 0.344 |
| on statins | 14 (93) | 23 (96) | 16 (76) | 0.174 | 0.053 |
| Cardiac history | | | | | |
| ICD implant | 3 (20) | 8 (38) | 10 (48) | 0.089 | 0.329 |
| CRT implant | 1 (7) | 2 (8) | 1 (5) | 0.801 | 0.632 |
| PCI | 14 (93) | 21 (38) | 17 (81) | 0.290 | 0.545 |
| CABG | 3 (20) | 8 (33) | 4 (19) | 0.943 | 0.280 |
| MI | 15 (100) | 23 (96) | 21 (100) | N/A | 0.344 |
| Other cardiac surgery | 1 (7) | 2 (8) | 2 (10) | 0.760 | 0.889 |
| Sustained VT or VF | 5 (33) | 9 (33) | 4 (19) | 0.329 | 0.173 |
| Atrial Fibrillation | 2 (13) | 3 (13) | 4 (19) | 0.650 | 0.545 |
| Medication profile | | | | | |
| ACE inhibitor | 13 (87) | 19 (79) | 18 (86) | 0.935 | 0.567 |
| ATR1-blocker | 2 (13) | 4 (17) | 3 (14) | 0.935 | 0.826 |
| Beta-blocker | 11 (73) | 19 (79) | 20 (95) | 0.061 | 0.114 |
| Diuretic agent | 13 (87) | 19 (79) | 18 (86) | 0.935 | 0.567 |
| Antiplatelet agent | 15 (100) | 23 (96) | 20 (86) | 0.391 | 0. 923 |
| Statins | 14 (93) | 23 (96) | 17 (8l) | 0.290 | 0.113 |
| Hypoglycemic agent | 2 (13) | 4 (17) | 2 (10) | 0.720 | 0.482 |
| Antiarrhythmic agent | 2 (13) | 4 (17) | 9 (43) | 0.058 | 0.531 |
| Calcium antagonist | 1 (7) | 1 (4) | 3 (14) | 0.473 | 0.234 |
| Nitrate or molsidomine | 5 (33) | 7 (29) | 2 (10) | 0.075 | 0.100 |

*Family history of CAD of one control was not available.

**It would be extremely helpful if the authors could resolve these and other uncertainties to aid interpretation (see Online Appendix for a detailed list of discrepancies and citations).**

Additional information is provided as a reply to the Online Appendix (3).

In conclusion, the C-CURE study is the first clinical study to evaluate lineage-specified stem cells as a potential therapeutic option in chronic disease (1). Specifically, the C-CURE trial achieved clinical translation of the cardiopoiesis platform (5–9), adding a lineage-specifying step to existing cell therapy paradigms in order to prime patient-derived naive stem cells for enhanced therapeutic impact in the failing heart. This initial experience is now being tested in the larger CHART-1 study (4). These studies exemplify a broad range of ongoing efforts in translating advances in regenerative science into novel therapies.

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## APPENDIX

**For additional issues and responses, please see the online version of this article.**