Author's response to reviews

Title: A Multicenter, Prospective, Randomized, Controlled Trial Evaluating the Safety and Efficacy of Intracoronary Cell Infusion Mobilized with Granulocyte colony-stimulating factor and Darbepoetin after Acute Myocardial Infarction: Study Design and Rationale of the 'MAGIC Cell-5-Combination Cytokine Trial'

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Version: 4 Date: 8 December 2010

Author's response to reviews:

To Editor of ‘Trials’

Subject: Submission of revised manuscript entitled “A Multicenter, Prospective, Randomized, Controlled Trial Evaluating the Safety and Efficacy of Intracoronary Cell Infusion Mobilized with Granulocyte colony-stimulating factor and Darbepoetin after Acute Myocardial Infarction: Study Design and Rationale of the MAGIC Cell–5–Combination Cytokine Trial”.

Dear Editor,

We would like thank you and the reviewer for taking the time and effort to review our manuscript. After going over the reviewer’s comments, we have made some corrections and clarifications in the manuscript in hopes of improving our paper. We hope that the revised manuscript better meets the requirement of the journal. We believe that these revisions greatly strengthen our manuscript and hope to hear good news in the near future. We thank you again for your constructive and detailed reviews.

Best regards,

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Responses to the reviewer’s comments:

a) Whether this is an early phase (I or II) trial or a late phase (III) is not stated. Because the primary outcome is not a clinical finding, but rather the result of an imaging test, I tend to think of it as an early phase study. The journal guidelines would generally not include such protocols. Here, however, I would favor publishing it, given that large, clinical outcome trials with these sorts of interventions are not yet common. It would be useful, though, if the investigators would indicate where they intend to go after this. Far too many agents that showed promise by improving ejection fraction turned out to be harmful when clinical outcomes (eg, death) were the endpoints in the phase III trials.

# As a reviewer mentioned, this is a phase 2 trial. We described it at page 6, line 2. If this novel stem cell therapy show better results than other control therapy, we will consider a larger randomized controlled trial (phase 3) to evaluate the effects of novel therapy on clinical outcomes.

b) The authors say that they will use a “modified intention-to-treat analysis,” yet they indicate they will include all “who signed the written informed consent and were randomized to receive any part of active treatment.” Who among those randomized will not be included? And how will drop-outs be handled?

# We will evaluate 2 different key endpoints: efficacy and safety. For evaluation of efficacy endpoints, patients who completed stem cell infusion will be included. If these patients dropped out before follow-up efficacy evaluation, we will make every effort to collect information about their clinical status during planned follow-up period. For evaluation of safety endpoints, patients who received any part of active treatment will be included. If patients who did not receive stem cell infusion drop out, we will follow them at least till 1 month after index hospitalization. We revised manuscript and added these at page 9, 10.

c) A one-sided alpha of 0.05 is not particularly rigorous. How was it justified?

# This is a phase 2 trial. And it is difficult to recruit patients in the trial which evaluate novel therapy. Considering practical aspects for recruiting patients and funding, we had to accept this statistical power for sample size calculation.

d) There are a few grammatical/spelling errors (eg, page 5, line 6 from bottom—“is” should be “are”; page 6, “Amegen” should be “Amgen”; page 14, line 11—“to” after “Regarding” should be deleted). The authors should carefully re-read the manuscript for others.

# We corrected them.