2 SYNOPSIS

NAME OF COMPANY **Genzyme Europe B.V.** **Gooimeer 10** **1411 DD Naarden** **The Netherlands** **Assistance Publique-Hôpitaux de Paris** **Délégation à la Recherche Clinique** **1, Avenue Claude Vellefaux** **75475 Paris Cedex 10 - France** NAME OF FINISHED PRODUCT **Not applicable** NAME OF ACTIVE INGREDIENT **Autologous Cultured Skeletal Myoblast Cells**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

Evaluation of Skeletal Myoblast Transplant for Treating Ischemic Heart Failure Phase 2 Study Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) Study

INVESTIGATORS / STUDY CENTER(S):

A total of 40 clinical study sites in Europe participated in this study of which 27 sites screened at least 1 patient and 22 sites treated at least 1 patient.

PUBLICATION (REFERENCE):

Abstract: Menasché on behalf of the MAGIC investigators - "Implanting muscle cells to treat heart failure seems safe, promising" - *American Heart Association's Scientific Sessions,* Chicago, IL, USA, November 2006

Publication: Menasche P, Alfieri O, Janssens S, McKenna W, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation, 2008;117(9):1189-200.

STUDIED PERIOD:

First Patient Enrolled (date when the first patient was treated): 06 December 2002

Last Patient Last Study Contact: 19 April 2007[1]

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

To assess the safety and efficacy of two doses of skeletal myoblasts, as compared to placebo control, in the treatment of ischemic heart failure.

METHODOLOGY:

This was a prospective, randomised, double blind (masked observer), placebo controlled, parallel arm study that was to be conducted in up to 50 centres. The study employed a double blind, masked observer

[1] 19 April 2007 is the date of last patient contact according to protocol amendment 5 reducing follow-up from 2 to 1 year. This amendment was not approved in Italy where the patients had to complete a 2 years follow up. Five of these patients completed the study after the last visit of the last patient in the other countries. The 2 year data of these 5 patients where not entered in the database, but were reviewed at a later stage to check that the statistical conclusion of the clinical study report (CSR) was not affected.

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design in that the patient and the cardiology team which conducted all efficacy evaluations remained blinded to the treatment assignment during the patient's participation in the study, whereas the surgical team was not blinded to the treatment assignment. Three parallel treatment groups were evaluated (2 different doses of myoblasts and a placebo control). The 2 active doses of skeletal myoblasts were 800 (± 100) x 10^6 cells and 400 (± 100) x 10^6 cells. In this study, patients were to be enrolled with an ICD in place, or were to receive one either before CABG surgery or prior to discharge from the hospital after CABG surgery. The requirement for study patients to have an ICD was for safety precautions in case a patient developed an arrhythmia requiring defibrillation. In addition, the ICD readings were used to assess whether the therapy had any effect on the occurrence of cardiac arrhythmia. The study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and in accordance with all federal or regional regulations. In this study, an independent Data Monitoring Committee (DMC) provided an ongoing, expert, independent review of safety data to assure that the risks to study patients were minimised during the conduct of the study.

Echocardiography was used to assess the co-primary endpoints of recovery of contractility of akinetic left ventricular segments and of left ventricular ejection fraction. A central and standardised image acquisition technique was used for echocardiography. In addition, radionuclide angiocardiography (e.g., multiple uptake gated acquisition [MUGA] scan) was optional and performed in a sub-set of patients according to country-specific procedures to assess left ventricular function. Doppler tissue imaging, and positron emission tomography (PET) imaging were also planned and were carried out in a subset of patients however the subset was not of a sufficient size to warrant statistical analysis of the collected data. The evaluation of echocardiography results were conducted in a centralised manner. In addition, an independent Clinical Endpoint Committee (CEC) was to adjudicate all Major Adverse Cardiac Events (MACE) (i.e., all-cause mortality, cardiovascular related death, non-cardiovascular related death, congestive heart failure, resuscitated sudden death, myocardial infarction, stroke) and clinically significant arrhythmias while also blinded with respect to the treatment group.

The duration of each patient's participation in the study was originally planned for 2 years. Each patient underwent an approximate 4-week screening phase. When eligible, patients were randomised and underwent a skeletal muscle biopsy. This was followed, approximately 21 days after muscle biopsy, by elective coronary bypass surgery and study treatment administration and a planned 2 years follow-up phase which was later amended to 1 year follow-up with protocol amendment 5. This amendment was accepted and implemented everywhere except in Italy, at which time 43 patients had a 2 year follow-up and 37 patients had a 1 year follow up. Five patients from Italy with a 2-year follow-up completed the study between 01 March 07 and 25 October 2007 and these 2-year data were not entered in the database.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Allowing for withdrawals, sample size calculations had shown that approximately 300 patients were to be enrolled in the study with 100 patients per treatment arm to be randomised to achieve 90% power. Sample size estimation was based on consideration of the recovery of contractility (co-primary efficacy endpoint), left ventricular ejection fraction (LVEF) 6-month change from baseline (co-primary efficacy endpoint),

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and time to first MACE (secondary efficacy endpoint).

In February 2006, the DMC reviewed an unblinded interim analysis of safety and efficacy data from the trial and recommended to stop further patient enrolment. This recommendation was based on an assessment of all available efficacy and safety data from the study and reflected the conclusion that there was not a reasonable likelihood of the trial achieving its primary endpoints, and that in that context the study hypothesis had been adequately tested and it was not appropriate to enrol additional patients in the trial. The sponsors accepted this recommendation.

A total of 189 patients were screened for this study. Of the screened patients, 120 patients were randomised and as 7 patients discontinued the study prior to muscle biopsy, 113 patients underwent muscle biopsy. Index CABG was performed on 98 patients of which 97 received study treatment, and 80 patients completed at least one year of follow-up[2].

The Safety Set, as defined by protocol, comprised the 113 patients who underwent skeletal muscle biopsy. The modified Intent-To-Treat (mITT) Population consisted of 97 patients who received study treatment (i.e., receiving myoblast cells or placebo). The Per Protocol Set was not defined as the study was stopped prematurely for reasons indicated above.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

This study was conducted in patients with Congestive Heart Failure New York Heart Association (NYHA) Class I, II or III, and therefore at high risk for morbidity and mortality following coronary artery bypass graft (CABG) surgery inherent to their cardiac disease. To identify co-morbidities that increase short-term risk for mortality, study investigators were required to complete a baseline risk assessment with questions derived from the European System for Cardiac Operative Risk Evaluation (EuroSCORE). In cases where the risk assessment indicated that a patient was at high risk for perioperative death, the Genzyme Medical Monitor was to contact the Investigator to review the suitability of the patient for enrolment in the study. If, in the opinion of the Medical Monitor, there was a significant risk profile that jeopardised short-term survival, the Investigator was advised not to enrol the patient. For those patients who were enrolled, the Investigator completed a second risk assessment questionnaire after surgery to determine the full EuroSCORE. The risk assessment results were reviewed by the DMC on at least a quarterly basis in order to develop a risk profile of patients in the study.

Inclusion: Patients who met the following criteria were eligible to participate in this study:

1. Patient had to be ≥ 18 and ≤ 80 years of age.
2. Patient had a recommendation for a coronary bypass, preferably with cardiopulmonary bypass support. All patients meeting this criterion could be included, including those with target injection

[2] One patient was re-screened and underwent a second biopsy after dropping out a first time from the study. This patient is only counted one time in the dataset. This explains the difference of 1 patient screened, randomised and in number of biopsies from protocol Amendment 5.

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areas that may or may not be amenable to revascularisation.

3. Patient had an alteration in left ventricular function, defined as an ejection fraction (EF) of ≤ 35% and ≥ 15% (determined by echocardiography and confirmed by the core laboratory).
4. The left ventricular myocardial infarction (Q wave or positive enzyme) targeted for study injections had occurred ≥ 4 weeks prior to screening.
5. Patient had significant myocardial dysfunction from a previous myocardial infarction demonstrated by the existence of akinesia affecting more than 2 accessible, contiguous left ventricular segments (out of 16) on a basal state echocardiogram, with no viability after stimulation with low dose dobutamine.
6. Patient had qualified for insertion of an implantable cardioverter defibrillator (ICD) device. Patient had an ICD upon enrolment, received an ICD before CABG surgery and study treatment or received an ICD prior to discharge from the hospital following CABG surgery.
7. Patient was a NYHA functional class I-III, who was receiving optimal contemporary medical management (e.g., angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, etc).
8. Fertile female patients had a negative urine pregnancy test at screening and on the day of treatment prior to autologous skeletal myoblast administration.
9. Fertile female patients had agreed to follow an approved method of contraception to avoid pregnancy for 60 days after receiving autologous skeletal myoblast administration (or longer if required by concomitant medication [e.g., amiodarone]).
10. Patient was committed to following the protocol requirements for 2 years as evidenced by written informed consent.

NOTE: The NYHA functional classification is most often used to characterise a patient's limitation from ventricular failure. Patients treated with β-blockers, ACE inhibitors, and diuretics may have improved functional capacity, and may have presented at screening without oedema and dyspnoea at rest. Because patients in this study were required to have optimal medical treatment for at least 3 months before screening, they could present as NYHA functional classification I at rest, but had very limited myocardial reserve and an inadequate cardiac response to minimal exertion. Diagnostic tests performed during the screening period, including cardiac catheterisation and echocardiogram, provided an objective assessment of the extent of ischaemia and the amount of myocardial reserve. Investigator review of both NYHA functional class *and* the severity of disease were factored into the decision to enrol a patient.

Exclusion: Patients were excluded from this study if they did not meet the specific inclusion criteria, or if they met any of the following exclusion criteria:

1. Patient had a need for a rapid surgical coronary revascularisation (≤ 21 days).
2. Patient had a need for any other related cardio-surgical measure during coronary surgery (e.g., mitral valve repair or valve replacement).

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3. Patient with a left ventricular aneurysm who was a candidate for left ventricular aneurysmectomy or left ventricular reduction surgery.
4. Patients who received left or biventricular pacing therapy for heart failure (unless the patient has stabilised after 6 or more months of this therapy).
5. Patient with cardiomyopathy presumed to be of non-ischemic origin (e.g., hypertrophic cardiomyopathy).
6. Patient for whom adequate echocardiography, or other required study procedures, could not be performed for technical reasons.
7. Patient for whom low dose of dobutamine, required for the identification of non-viable, scarred myocardium, was contra-indicated (e.g., recent sustained ventricular tachycardia and ventricular fibrillation).
8. Patient with advanced heart failure (e.g., NYHA IV heart failure symptoms, or in need of a heart transplant) who did not respond to optimal medical therapy and did not improve to at least Class III symptoms 30 days prior to skeletal muscle biopsy.
9. Patient was infected with the hepatitis C virus; the hepatitis B virus (HBs + antigen); patient who was HIV-1 or HIV-2 positive; human T-lymphotropic virus (HTLV-1) positive; Ag P24 positive (this exclusion criteria refers only to regions where this testing was required (France and Germany).
10. Patient with haemophilia; long-term immunosuppressive treatment, including with corticosteroids; stage III-IV arteriopathy of the lower limbs; significant muscular amyotrophia; peripheral muscular illness; serious intellectual deterioration or neuro-psychiatric disorders that would make follow-up difficult.
11. Patient with allergies to gentamicin or other aminoglycosides, allergies to study required medications or imaging agents.
12. Female patient who was pregnant, nursing, or fertile and using either no or an inadequate form of contraception.
13. Illness other than ischemic heart failure that makes the short-range prognosis for survival questionable
14. Simultaneous participation in another study with an investigational study agent.

NOTE: If, during CABG but prior to treatment, the patient emergently developed cardiogenic shock (systolic blood pressure less than 90 mm Hg with adequate preload) and reduced cardiac output indicative of left ventricular dysfunction, that requires intra aortic balloon pump (IABP), high dose vasopressors and/or inotropes, or other mechanical assistance to support the circulation, the investigator was NOT to proceed with study injections.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

After screening, eligible patients were randomised and underwent a biopsy at which time a minimum size

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sample of 10 grams of muscle was removed from the vastus lateralis muscle and sent to a central laboratory for culturing. For patients randomised to receive active treatment, skeletal myoblasts were cultured. For patients randomised to placebo, the biopsy was stored but not cultured.

If the patient was randomised to receive active treatment, the patient received a dose of cells not to exceed the maximum dosage specified for that treatment group. However, if there were fewer cells produced than the minimum dosage specified for that treatment group, the investigator was to proceed with the administration of these cells.

The total dose of skeletal myoblasts was administered as one treatment of approximately 30 to 35 direct intramyocardial injections, each of a fixed volume of 200 µL, into multiple sites in the myocardium for a total injection volume of 6 mL.

All skeletal myoblast injections were administered to a single discrete area of scar tissue and peri-infarct zone of the akinetic region of myocardium.

The following 2 doses plus placebo control were studied:

Treatment group 1: Dose of 800 (± 100) x 10^6 myoblast cells;

Treatment group 2: Dose of 400 (± 100) x 10^6 myoblast cells;

Treatment group 3: Placebo (suspension medium).

A batch number was assigned per patient treatment.

DURATION OF TREATMENT:

The injections were administered during the surgical procedure. Injection placement was expected to take 15 to 20 minutes, but the actual median injection time was 12 to 15 minutes. Patients were followed for a minimum of 1 year thereafter.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Suspension medium without skeletal myoblasts were used as placebo control treatment.

A batch number was assigned per patient treatment.

CRITERIA FOR EVALUATION:

The sponsors have decided not to pursue the studied indication at the present time, and will therefore present the data as an abbreviated clinical study report in which the safety and safety-related secondary efficacy results, but not the efficacy results (co-primary endpoints) are discussed. Efficacy data are provided in listings only.

Safety Variables: The safety of transplanting skeletal myoblasts into an akinetic area was evaluated in terms of adverse events (AEs), serious adverse events (SAEs) (including MACE, the individual

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components of MACE, and ventricular arrhythmias), concomitant medications, physical examination findings, vital sign parameters, monitoring of cardiac rhythm including electrocardiogram (ECG) and ICD interrogation, intra-operative and postoperative monitoring, and clinical laboratory evaluations conducted routinely throughout the study.

Efficacy Variables: The efficacy of transplanting skeletal myoblasts into an akinetic area was evaluated by co-primary endpoints:

- the recovery of contractility within previously akinetic myocardial segments at Month 6
- the absolute change from baseline to Month 6 in LVEF

The recovery of contractility and LVEF was assessed using echocardiography. The recovery of contractility was defined as improvement in at least one segment (by ≥1 grade, using a standard 5-grade regional wall motion grading system within a 16-segment model) and no deterioration in any segment (from akinetic to dyskinetic) in the transplanted area at Month 6.

According to protocol, secondary and tertiary efficacy assessments had to include time to first MACE, aggregate occurrence of MACE, all-cause mortality, other left ventricular size (end-diastolic and end-systolic volume,) and function (mitral regurgitation) parameters, NYHA classification, quality of life change, metabolic viability in the transplant area, and blood flow in the transplant area.

STATISTICAL METHODS:

Patient Populations:

All patients who were randomised and underwent skeletal muscle biopsy comprised the Safety Population. All patients who underwent the CABG surgery and skeletal myoblast transplantation (SMT) comprised the mITT Population.

Demographics:

Baseline demographic and background variables were summarised by treatment group. For categorical variables, frequencies and percentages are presented. For continuous variables, descriptive statistics including sample size, mean, median, standard deviation, minimum, and maximum are presented.

Safety:

AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs were tabulated by treatment group. AEs were categorised by System Organ Class (SOC), severity, and relationship to study treatment. Additionally listings of SAEs, as well as discontinuations due to SAEs, were generated by treatment group.

All MACE, individual MACE components, and ventricular arrhythmias were tabulated and are presented.

If a patient had more than one occurrence of the same AE, he/she was counted only once with that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme

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relationship of the AE to the study procedures, was indicated in cases of multiple occurrences of the same AE. All AE's are presented in a listing.

Safety laboratory tests, vital signs, and physical examination findings were tabulated.

Concomitant medications and treatments were categorised using the MedDRA standardised coding dictionary and summarised.

Efficacy:

Since recruitment was stopped prematurely, only efficacy data of 97 of the planned 300 patients were collected. Therefore, the study was not statistically powered and the primary efficacy analysis was not performed.

Only the safety-related secondary efficacy assessment were analysed including time to first MACE and NYHA classification.

***Time to first MACE*:** Parameterisation was based on a review of the medical literature published between 1996 and 2001, which presented a 1-year survival rate of 86% to 94% in patients with left ventricular dysfunction (EF ≤ 35%) who had undergone coronary bypass revascularisation. One of these studies appeared to enrol a patient population similar to that being selected in this Phase 2 study (i.e., 94% with a previous myocardial infarction, average EF of 28% and 32% with symptomatic heart failure). At one year, in that study, the freedom from recurrent heart failure was found to be 78 +/- 11%. Additional assumptions for the time to first MACE power calculations were the following:

- Hypothesis test was a comparison between treated patients (pooled across high and low dose) and placebo patients and that the distribution of time to first MACE in the 2 treatment groups was equal
- The Log-Rank test was used
- Significance level of 5% (no Bonferroni adjustment for multiple comparisons with secondary efficacy endpoints)
- Time to first MACE follows an exponential distribution
- All MACE were observed

The planned study had approximately 84% power to detect a 15% difference in the percentage of patients experiencing MACE in the pooled treatment group and the placebo group during the 12 month postoperative period when the percentage of patients with MACE in the placebo group was 30% based on a Log-Rank test of time to first MACE and a 5% significance level.

Interim Safety Analyses: Interim safety analyses were planned at regular intervals (approximately 50, 100, 200 patients treated and followed for at least 30 days) to summarise and evaluate blinded aggregate safety data, including the frequency of SAEs, deaths, MACE, and arrhythmias. Results of the interim safety analyses were to be presented to the DMC.

Actual: In April 2005, a 30 days follow-up safety interim analysis on 46 patients was performed for the

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DMC. In October 2006, a 6 month follow-up interim analysis on 97 patients was performed. From these data a publication was prepared (Menasché, 2008, *Circulation*).

Futility Analysis: In January 2006, a futility analysis was performed by Genzyme's Biomedical Operations group when approximately 75 patients had completed 6 months of follow-up. The analysis computed conditional power, which was the conditional probability of rejecting the null hypothesis at the final analysis of the data based on the observed data available at the time of the futility analysis. As there was no intention of stopping the study for efficacy but only for lack of efficacy based on the conditional power calculation, no adjustment to the type I error was necessary. The project team was not to be involved in the Futility Analysis and was only to be informed of the decision to continue or stop the trial based on the conditional power.

SUMMARY – CONCLUSIONS

Of the 189 patients that consented to participate in the study, 120 were eligible and randomised to study treatment. A total of 23 patients discontinued the study after randomisation but prior to injections with cells or placebo: 7 patients discontinued the study prior to the muscle biopsy due to AEs (n=4, of which 3 deaths), wish to withdraw (n=1), lost to follow-up (n=1), or early discontinuation of the study (n=1); 16 patients discontinued the study before injection with the cells or placebo due to AEs (n=8, of which 4 deaths), no release of study treatment (n=7), or early discontinuation of the study (n=1). A total of 97 patients were treated with Myoblast cells or placebo: 33 patients were treated with 400 (±100) x 10^6 cells (Myoblast-Low group) of which 25 patients completed the study; 30 patients were treated with 800 (±100) x 10^6 cells (Myoblast-High group) of which 25 patients completed the study; and 34 patients were placebo treated of which 30 patients completed the study. Treated patients had an ICD in place at time of treatment or received it after CABG. The patients were mainly Caucasian males ranging in age from 40 to 79 years. Only 4 females participated in the study. About 75% of the patients had multivessel coronary heart disease, and about 12% of the patients had currently unstable angina. A percutaneous transluminal coronary angioplasty with stent (PTCA/STENT) was performed in the past in about 24% of the patients, while only a few patients (5%) had undergone a previous CABG. About 20% of the patients had concurrent valvular heart disease and about 45% of the patients had hypertension; these last 2 ailments were not as equally divided over the treatment groups as the other ones. The Myoblast-High group had fewer patients with valvular heart disease or hypertension than in the other 2 groups. Many of the patients were further affected by diabetes, obesity, hypercholesterolaemia, or peripheral vascular disease, and almost all patients were current or former smokers. All patients further presented with other medical/surgical histories which currently was mainly in the metabolic, endocrine, and nutritional body systems. All patients used a large variety of concomitant medications.

SAFETY RESULTS:

Twenty-one (21) of the 113 patients (18.6%) in the Safety population died on study after muscle biopsy due to cardiac related events (Myoblast-High 17.1%; Myoblast-Low 26.3%; placebo 12.5%). Four

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patients died after biopsy but before treatment, 5 patients died within 30 days of CABG, 3 patients within 90 days of CABG, 4 patients within 6 months of CABG, 1 patient within 1 year of CABG, and 4 patients within 2 years of CABG. Major Adverse Cardiac Events were reported in 53 patients (46.9%) (16 patients in Myoblast-High; 22 patients in Myoblast-Low; 15 patients in placebo). Ventricular arrhythmias were reported as treatment emergent adverse events in the following number of patients: ventricular fibrillation in 11 patients (9.7%) (4 patients in Myoblast-High; 2 patients in Myoblast-Low; 5 patients in Placebo), ventricular arrhythmia in 2 patients (1.8%) (1 patient in Myoblast-High; 1 patient in Placebo), ventricular tachycardia in 36 patients (31.9%) (14 patients in Myoblast-High; 11 patients in Myoblast-Low; 11 patients in Placebo), ventricular extrasystoles in 6 patients (5.3%) (2 patients in Myoblast-High; 1 patient in Myoblast-Low; 3 patients in Placebo). No statistically significant differences were observed between the treatment groups with respect to the number of deaths. The number of MACEs or ventricular arrhythmias was not clearly different between the treatment groups. In the mITT population, there was no statistically significant difference between the treatment groups in the time to the first treatment-emergent MACE, although the mean time in the Placebo group was numerically longer (494 days) than in the Myoblast-High and –Low groups (333 and 356 days, respectively).

A total of 875 treatment-emergent AEs were reported during the study in 104 of the 113 patients in the Safety population without difference between the treatment groups. Events occurred most commonly in the SOCs of Cardiac Disorders (75.2% of the patients), Injury, Poisoning, and Procedural Complications (36.3%), Infections and Infestations (35.4%), and Respiratory, Thoracic, and Mediastinal Disorders (28.3%). Overall, the most frequently occurring AEs (in > 10% of the patients) by preferred term were ventricular tachycardia (31.9% of the patients), cardiac failure (31.0%), atrial fibrillation (22.1%), procedural pain (15.0%), constipation (12.4%), anaemia (11.5%), post procedural haematoma (11.5%), peripheral oedema (10.6%), and cardiac failure congestive (10.6%). Thirteen patients (11.5%) had a haematoma following the skeletal muscle biopsy; in 6 cases this was reported as an SAE. Treatment-emergent SAEs were experienced by 82 patients (72.6%), severe AEs by 54 patients (47.8%), and related AEs by 53 patients (46.9%). The highest percentage of patients with related AEs were present in the Myoblast-High group (54.3%), while it was 36.8% in the Myoblast-Low group and 50.0% in the Placebo group. These related events were mainly in the SOC of Cardiac Disorders with ventricular tachycardia as the most present AE.

The 5 Italian patients reported at year 2, comprise one high dose patient, with one non related SAE and no abnormal ICD findings, one low dose patient with no abnormal ICD findings, and 3 placebo patients of which two had reported arrhythmic events and one had a missing ICD evaluation. These safety related findings observed in a subgroup of 5 patients two years following treatment are in line with the observations made for all patients at one year following treatment and therefore would not change the conclusion of the Clinical Study Report.

EFFICACY:

Cessation of patient recruitment resulted in the loss of statistical power to assess efficacy of the study

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objectives. **CONCLUSION:** [redacted]		