TITLE PAGE

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Dutogliptin in Combination with Filgrastim in Early Recovery Post-Myocardial Infarction.

Effective Date: 05-JUL-2021

Study Initiation Date: 10-Oct-2018

Study Completion Date: 25-FEB-2021

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Indication Studied: ST-Elevation Myocardial Infarction

Compound: Dutogliptin

Study Number: REC-DUT-002

EudraCT Number: 2018-000916-75

ClinTrials.gov Identifier: NCT03486080

Study Phase: Phase 2

This study was performed in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP). Essential documents were archived according to ICH-GCP.

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I confirm that:

This report contains an accurate description of the conduct of this study.

This study was performed in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if required) and which was given approval/favorable opinion by the local Institutional Review Board/Independent Ethics Committee (IRB/IEC):

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council for Harmonisation (ICH) harmonised tripartite guideline regarding Good Clinical Practice (GCP; E6 R2, November 2016)
- Any amendments to these regulations
- Local laws and regulations

Essential documents were archived according to ICH-GCP.

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Medical University of Graz,

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1. SYNOPSIS

Name of Sponsor/Company: RECARDIO, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: N/A		
Name of Active Ingredient: Dutogliptin		

Title of Study:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Dutogliptin in Combination with Filgrastim in Early Recovery Post-Myocardial Infarction (MI).

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Publication (reference):

Study not yet published.

Studied Period (years):	Phase of Development:

Name of Sponsor/Company: RECARDIO, Inc. Name of Finished Product: N/A Name of Active Ingredient: Dutogliptin	Individual Study Table Referring to Part of the Dossier Volume: Page:	(*For National Authority Use Only*)
Date of first enrolment: 06-DEC-2018 Date of last completed: 25-FEB-2021	Phase 2	

Objectives:

The primary study objective was to:

- Evaluate the safety and tolerability of dutogliptin in co-administration with filgrastim in subjects with STEMI compared with placebo

The secondary objectives of the study were to:

- Explore the efficacy of dutogliptin in co-administration with filgrastim in subjects with STEMI compared with placebo, based on cMRI assessments, clinical endpoints and biomarkers

Methodology:

Study REC-DUT-002 is a multicenter, randomized, double-blind, placebo-controlled study to explore the safety, tolerability, and efficacy of dutogliptin administered in co-administration with filgrastim in subjects with STEMI following PCI and stent implantation. Eligible subjects received local standard of care procedures including PCI and stent implantation (bare metal or drug-eluting). The allowable time between onset of STEMI symptoms and stent implantation (time of first balloon inflation) is up to 24 hours. Eligibility was evaluated in a stepwise manner. Medical history, physical examination, and safety laboratory screening tests were completed prior to conducting the cardiac echocardiogram (cECHO). Subjects received study treatment within 36 hours after stent implantation. Upon discharge from the hospital, adequate supplies of investigational medicinal products (IMPs) to complete all dosing was issued to the homecare nursing service, which administered all remaining doses to the subject at home.

Safety assessments were performed on Day 0, Day 1 (baseline), Day 2, Day 3, Day 5, Day 15, and Day 90. Safety assessments included physical examinations, vital signs, laboratory tests, ECG, and an assessment of adverse events (AEs).

Efficacy assessments were performed within 72 hours after PCI (baseline) and on Day 90. Efficacy assessments included cardiac function (cardiac magnetic resonance imaging cMRI) and clinical endpoints, and biomarkers. An optional cMRI was offered on Day 180.

Number of Subjects (Planned and Analyzed):

It was planned to randomize 140 subjects to have 110 evaluable subjects. The study was however closed-out early due to the C-19 pandemic, which made it impossible to continue recruitment: 48 subjects were finally randomized (ITT Population) of which 47 received treatment.

Main Criteria for Inclusion:

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1. Male or female, age 18 to 85, body weight <96 kg
2. Diagnosis of STEMI (defined as new ST-segment elevation at the J point of at least two continuous leads of >2 mm [0.2 mV] in men or >1.5 mm [0.1 mV] in women in leads V2 and V3 or >1 mm in any other contiguous precordial leads or the limb leads [for both men and women]) with PCI (bare metal or drug-eluting stent) and thrombolysis in myocardial infarction flow grade 2 or 3 occurring up to 24 hours after symptom onset (to time of first balloon inflation)
3. Left ventricular ejection fraction (LVEF) ≤45% obtained by cECHO performed within 36 hours post-stent placement
4. Standard medical therapy for post-MI treatment, according to local procedures and the Principal Investigator's discretion

Test Product, Dose and Mode of Administration, Batch Number:

Dutogliptin 60 mg was administered twice daily by subcutaneous (SC) injection for 14 days (batch number 9080444A, 9080444B, 9080444F). Filgrastim 10 µg/kg (batch number 9080444E) was co-administered for the first 5 days.

Duration of Treatment:

The duration of treatment was 14 days, the total duration of study participation for each subject was 3 months, with an additional, optional cMRI assessment at 6 months.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching SC dutogliptin placebo (60 mg; batch number 9080444A, 9080444B, 9080444F) injection for 14 days. Matching filgrastim placebo (10 µg/kg; batch number 9080444E) was administered for the first 5 days.

Criteria for Evaluation:

Safety:

- Safety assessments included reported treatment-emergent AEs (TEAE), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations

Efficacy:

- Change in cardiac function (cMRI) from baseline to Day 90: Left Ventricular Ejection Fraction, (LVEF), Left Ventricular End Systolic Volume (LVESV; absolute and indexed). Left Ventricular End Diastolic Volume (LVEDV; absolute and indexed), infarct size, left ventricular mass (absolute and indexed), and regional wall motion

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- Individual clinical endpoints, including recurrent non-fatal MI, non-fatal stroke, death due to any cause, cardiovascular death (death due to acute MI, chronic heart failure [CHF], stroke, or sudden cardiac death, stent thrombosis or CHF hospitalization
- Composite clinical endpoints (MACE), including non-fatal MI, non-fatal stroke, cardiovascular death, stent thrombosis, and CHF hospitalization
- Time to cardiovascular event, as defined by the time from randomization to the first occurrence of recurrent non-fatal MI, non-fatal stroke, death due to any cause, stent thrombosis, and CHF hospitalization
- Biomarkers (N-terminal pro b-type natriuretic peptide [NT-proBNP] and high sensitivity troponin) measurements were optional

Pharmacokinetics/ Pharmacodynamics (in a subset):

- Not performed due to the early closeout of the study caused by the COVID-19 pandemic

Statistical Methods:

This is an exploratory study. No formal sample size calculation was performed. The intention-to-treat (ITT)-population included all randomized subjects (N=48), the PP-population comprised 34 subjects, and the Safety Population 47 subjects. The safety evaluations are based on descriptive statistics of the Safety Population. The efficacy evaluations are based on the PP-population.

Changes from baseline to Day 90 in cardiac function parameters, infarct size, left ventricular mass and regional wall motion were evaluated using an analysis of covariance model with randomization stratification factors as covariates. The Wilcoxon test for unpaired observations was used to compare groups. Frequencies of individual and combined clinical endpoints on Day 15 and Day 90 are summarized in frequency tables. Logistic regression models were applied using the randomization stratification factors as covariates. In addition, differences between the two treatment groups were tested for statistical significance using Fisher's exact test. Time to cardiovascular event was descriptively analyzed using the Kaplan-Meier method. Median time to cardiovascular event per treatment group and the hazard ratio between the two treatment groups was calculated along with 95% confidence intervals. A Cox regression model was applied for the time to cardiovascular event with randomization stratification factors as covariates. A log-rank test was conducted to test significance between treatment groups.

Summary of Results:

Safety:

Frequencies of TEAEs were similar both treatment groups (active group: 17 [68.0%] subjects,

placebo group: 17 [77.3%] subjects), five subjects had severe TEAEs (active group: 2 [8.0%] subjects, placebo group: 3 [13.6%] subjects), eight subjects had related TEAEs (active group: 5 [20.0%] subjects, placebo group: 3 [13.6%] subjects), and nine subjects had serious AEs (SAEs; active group: 5 [20.0%] subjects, placebo group: 4 [18.2%] subjects). No subjects experienced related severe TEAEs or related serious TEAEs. In addition, no TEAEs led to withdrawal of any treatment; dutogliptin, filgrastim or placebo. There were no statistically significant TEAE differences between treatment groups. No TEAEs were considered "related" to dutogliptin. Frequencies of possibly related and related TEAEs were similar between the active and placebo groups. No TEAEs judged to be related to IMP were of severe intensity. No SAEs that were considered related to dutogliptin or filgrastim. The only SAEs experienced by more than one subject were pneumonia (4 [8.5%] subjects/ 2 in each group) and acute myocardial infarction (2 [4.3%] subjects in the active group). No subject was withdrawn from drug treatment or from the study following administration of dutogliptin + filgrastim and no subject died following administration of dutogliptin + filgrastim treatment.

There were no clinically relevant differences between treatment groups regarding physical examinations, electrocardiograms (ECGs), or vital signs.

All laboratory safety tests were within acceptable limits and there were no statistical differences between treatment groups. There were no evident patterns in absolute values or changes from baseline on any of the assessment days regarding clinical chemistry, hematology and quantitative urinalysis in either treatment group. Elevated liver enzyme values at the start of the treatment returned rapidly to normal following the PCI and they were judged unrelated to dutogliptin or filgrastim.

Efficacy:

Left ventricular parameters: In the PP Population, increases in mean change from Day 3 (baseline) against Day 90 values were seen for end diastolic volume (EDV; placebo group: 13.7, active group: 17.4), EDVI (derived; placebo group: 8.4, active group: 8.6), and EF (placebo group: 5.7, active group: 5.2). Decreases in mean change from baseline values were seen for mass (placebo group: -16.1, active group: -14.4) and mass index (derived; placebo group: -8.3, active group: -7.4). No statistically significant difference was found between treatment groups in change from baseline for left ventricular parameters EDVI (derived), ESVI (derived), and EF over time. P-values were not calculated for other left ventricular parameters. Mean change from baseline values indicated positive trends for ESV (active group: 1.3; placebo group: 0.1) and EDV (active group: 17.4; placebo group: 13.7).

In the ITT Population, increases in mean change from Day 3 (baseline) against Day 90 values

were seen for EDV (placebo group: 13.7, active group: 15.7), EDVI (derived; placebo group: 8.4, active group: 7.7), and EF (placebo group: 5.7, active group: 5.9). Decreases in mean change from baseline values were seen for mass (placebo group: -16.1, active group: -15.1) and mass index (derived; placebo group: -8.3, active group: -7.9). No statistically significant difference was found between treatment groups in change from baseline for left ventricular parameters EDVI (derived), ESVI (derived), and EF over time. P-values were not calculated for other left ventricular parameters.

Right ventricular parameters: In the PP Population, similar increases were seen in both groups in mean changes from baseline against Day 90 for EDV (placebo group: 16.2, dutogliptin + filgrastim: 22.1) and ESV (placebo group: 7.0, active group: 6.5). Differences between treatment groups were not tested statistically. Especially in the right ventricular parameters multiple positive non-significant trends were seen for mean changes from baseline for the active group compared to placebo for EDVI (derived; active group: 11.0; placebo group: 9.3), ESVI (derived; active group: 3.2; placebo group: 0.1), and EF (active group: 2.8, placebo group: -0.3). These trends of better right ventricular function in the dutogliptin + filgrastim group revealed a strong trend to more potential effect size in larger MIs, which is of prognostic value for dilated cardiomyopathy.

In the ITT Population similar increases were seen in both groups in the mean changes from baseline against Day 90 for EDV (placebo group: 16.2, active group: 22.7), EDVI (derived; placebo group: 9.3, active group: 11.4), ESV (placebo group: 7.0, active group: 6.7), and ESVI (derived; placebo group: 0.1, active group: 3.4). There were no statistically significant differences between treatment groups.

Tissue characterization parameters: In the PP Population, decrease in mean change from Day 3 against Day 90 was observed for the following tissue characterization parameters: FWHM LGE mass (INF; placebo group: -12.7, active group: -20.1), relative FWHM LGE mass (INF/VV; placebo group: -6.6, active group: -13.3), 2SD LGE mass (placebo group: -15.3, active group: -19.3), relative 2SD LGE mass (placebo group: -8.2, active group: -11.6), 5SD LGE mass (placebo group: -15.5, active group: -18.8), and relative 5SD LGE mass (placebo group: -9.2, active group: -11.5). Mean change from Day 3 against Day 90 values for border zone mass (2SD-5SD) were very small for both groups. There were no statistically significant differences between treatment groups in change from baseline for FWHM LGE mass and relative FWHM LGE mass. P-values were not calculated for any other tissue characterization parameters.

In the ITT Population decrease in mean change from Day 3 against Day 90 was observed for the following tissue characterization parameters: FWHM LGE mass (INF; placebo group: -12.7, active group: -19.9), relative FWHM LGE mass (INF/VV; placebo group: -6.6, active group: -12.7), 2SD

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LGE mass (placebo group: -15.3, active group: -19.0), relative 2SD LGE mass (placebo group: -8.2, active group: -11.1), 5SD LGE mass (placebo group: -15.5, active group: -18.7), and relative 5SD LGE mass (placebo group: -9.2, active group: -11.1). Mean change from Day 3 against Day 90 values for border zone mass (2SD-5SD) were very small for both groups. There were no statistically significant differences between treatment groups in change from baseline for FWHM LGE mass (INF; p=0.2320), and relative FWHM LGE mass (INF/VV; p=0.2411). P-values were not calculated for any other tissue characterization parameters.

Clinical endpoints: None of the subjects experienced any of the following clinical endpoints: non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death). Recurrent non-fatal myocardial infarction occurred in one case and hospitalization due to chronic heart failure also in one case (both in the active group).

Biomarkers: Sample sizes for biomarker assessments at various time points were low. In the PP Population, decreases in mean change from baseline values were seen for NT-proBNP in both treatment groups over the course of the study. The mean decrease in NT-proBNP from Day 1 to Day 90 was -1287.8 for the active group and -3048.3 for placebo. Mean values for high sensitivity troponin biomarker showed decreases over the course of the study. Change from Day 1 to Day 90 was not calculable for the active group as no subjects provided data.

In the ITT Population, decreases in mean change from baseline values were seen for NT-proBNP (placebo group: -3048.3, active group: -1740.0) and high sensitivity troponin (placebo group: -9837.8, active group: -3399.0). Measurements were performed infrequently; results were variable and no statistically significant difference between the treatment groups was seen.

Conclusions:

Due to the COVID-19 pandemic, the study had to be closed-out early and therefore the sample size was smaller than planned and clinically meaningful differences between treatment groups may not have reached statistical significance. One should however keep in mind that this is an exploratory and not a confirmatory trial.

The two treatment groups were comparable regarding baseline characteristics and concomitant treatments.

Safety:

- Treatment-emergent AEs were seen in similar frequencies in the active and placebo group (overall, related, or serious AEs)

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- Treatment with dutogliptin in co-administration with filgrastim was well tolerated and no safety issues were detected. There were no clinically or statistically significant differences in safety between active and placebo groups
- There were no deaths or withdrawals in the active group. There was one death in the placebo group

Efficacy:

- Cardiac function and tissue characterization parameters assessed by cMRI show similar positive trends in both treatment groups; no statistically significant differences between groups were detected, possibly due to the smaller sample size
- Especially in the right ventricular parameters multiple positive non-significant trends are seen for the active group compared to placebo revealing a strong trend to more potential effect size in larger MIs, which is of prognostic value for DCM [Doesch, 2014]
- Only two cardiovascular events were observed and therefore no further analysis could be performed
- Biomarkers assessments were optional and infrequently performed, showing improvements with large variability in both treatment groups; no significant differences between groups could be demonstrated

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3. ABBREVIATIONS

2D	Two-dimensional
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CD	Cluster of differentiation
cECHO	Cardiac echocardiogram
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration
cMRI	Cardiac magnetic resonance imaging
cMRI LV	Cardiac magnetic resonance imaging left ventricular
cMRI RV	Cardiac magnetic resonance imaging right ventricular
COVID-19	Coronavirus disease 19
CXCR	Chemokine receptor
DPP4	Dipeptidylpeptidase-IV
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	End diastolic volume
EDV(i)	End diastolic volume (index)
EF	Ejection fraction
ESV	End systolic volume
ESV(i)	End systolic volume (index)
FWHM	Full width at half maximum
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
ICF	Informed consent form
ICH	International council for harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
INF	Absolute myocardial infarction size
INF/VV	Infarct size as a proportion of ventricular volume
INR	International normalized ratio
IRB	Institutional review board
ITT	Intention-to-treat
IRT	Interactive web response system
KDR	Kinase-insert domain-containing receptor
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
LVEDV(i)	Left ventricular end diastolic volume (index)
LVESV(i)	Left ventricular end systolic volume (index)
MACE	Major adverse cardiac event
MedDRA	Medical dictionary for regulatory activities

MI	Myocardial infarction
MSI	Myocardial salvage index
NT-proBNP	N-terminal pro b-type natriuretic peptide
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous (ly)
SD	Standard deviation
SDF	Stromal derived factor
SOC	System organ class
STEMI	ST-elevation myocardial infarction
TBL	Total bilirubin
TE	Transmural extent
TEAE	Treatment-emergent adverse event
TIMI	Thrombolysis in myocardial infarction
ULN	Upper limit of normal
VV	Ventricular volume
WBC	White blood cells

4. ETHICS

4.1. Institutional Review Board/ Independent Ethics Communications

Prior to study initiation, the Investigator had written and dated approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study protocol, written informed consent form (ICF), consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information that was provided to the subjects. A current copy of the Investigator's Brochure was provided to the IRB/IEC as part of the written application. During the study, the Investigator/institution provided the IRB/IEC with any amended versions of approved documents for review. Such amendments were not implemented without approval except when they were classed as an urgent safety measure.

4.2. Ethical Conduct of the Study

This study was performed in compliance with:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- Any amendments to these regulations
- Local laws and regulations

4.3. Subject Information and Consent

In obtaining and documenting informed consent, the Investigator complied with the applicable regulatory requirements and adhered to International Council for Harmonization (ICH)/Good Clinical Practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki.

The written ICF and any other written information were provided to subjects and were to be revised whenever important new information became available that may have been relevant to their consent. Any revised written ICF and written information received the IRB/IEC's approval/favorable opinion in advance of use. The subject was informed in a timely manner if new information became available that may be relevant to their willingness to continue participation in the study. The communication of this information was documented.

The Investigator fully informed the subject of all pertinent aspects of the study, including the written information and the approval/favorable opinion by the IRB/IEC. Before informed consent was obtained, the Investigator provided the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study had to be answered to the satisfaction of the subject.

Prior to a subject's participation in the study, the ICF was signed and personally dated by the subject and by the person who conducted the informed consent discussion.

Prior to participation in the study, the subject received a copy of the ICF and any other written information provided to the subjects. During a subject's participation in the study, the subject received a copy of the signed and dated consent form updates and a copy of any amendments to the written information.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

5.1. Investigators

The following Investigators were involved in this study:

Investigators	Affiliation
Dirk von Lewinski (Principal)	Medical University of Graz, Clinical department of Cardiology, Graz, Austria
Richard Schatz	Scripps Clinical Medical Group, San Diego, CA, USA
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Jan Debrauwere	Department of Internal Medicine and Cardiology, Aalst, Belgium
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Andrzej Kleinrok	Department of Cardiology 22-400 Zamosc, ul. Aleje Jana Pawia 1110

5.2. Study Administration

The following contractors and committee members were involved in this study:

Role	Individual and Affiliation
Steering committee	Richard Schatz, Chairman, Scripps Clinical Medical Group, San Diego, CA, USA Bernd Jilma, Associate Professor of Clinical Pharmacology and Internal Medicine, Vice Chair department of Clinical Pharmacology, Medical University of Vienna, Austria Jacek Kubica, Professor of Medicine,

Role	Individual and Affiliation
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Independent Data Monitoring Committee	Andrew JS Coats Prof. Dr., DSMB chairman Cardiology, Heart Failure, Clinical Trials Monash – Warwick Alliance Wellington Road, Clayton Victoria 3800, Australia
Contract research organisations/Monitoring	Qbex Office Vienna Mariannengasse 28/2 1090 Vienna Research Professionals Ltd. Soroksári út 44. II. em. Budapest 1095 Hungary Sacura GmbH Technologiehof Mendelstr. 11 48149 Münster, Germany Altiora, d.o.o. Seferova 8, 10000 Zagreb, Croatia
Statistician	Assign Data Management and Biostatistics GmbH, Stadlweg 23 6020 Innsbruck Austria

Role	Individual and Affiliation
Core laboratory for cMRI	Cardiac Imaging Research (CIR) SAHMRI, North Terrace, Adelaide SA 5000 Australia PO Box 11060, Adelaide SA 5001
Local laboratory	At each study site
Contract research organization for eTMF	Montrium Hosted Solutions Inc. 507 Place d'Armes Suite 1050, Montreal QC H2Y 2W8, Canada
Clinical trial supply management	ABF Pharmaceutical Services GmbH Brunner Strasse 63/18-19, 1230 Wien, Austria Catalent Pharma Solutions 3031 Red Lion Road, Philadelphia, PA 19114, USA
Other service providers (nursing, shipping, refrigerators)	CTS – Clinical Trial Service Gronausestraat 98 7581 CJ Losser The Netherlands RESEARCH PROFESSIONALS LTD. Soroksári út 44. II. em. Budapest 1095 Hungary GNN GmbH & Co KG Gewerbeparkstrasse 3 AT-8143 Dobl. Austria Clinichain bv Draaibrugweg 19 1332 AB Almere The Netherlands
Medical writing	Niche Science & Technology Richmond-upon-Thames Surrey, UK

6. INTRODUCTION

6.1. Background Information

An acute ST-elevation myocardial infarction (STEMI) is an event in which myocardial injury and necrosis results from an abrupt disruption of blood flow to the heart muscle caused by the occlusion of one or more of the coronary arteries. STEMI is typically the consequence of a complete and persistent occlusion with a fibrin-rich thrombus that results in larger infarctions and scars relative to non-ST-elevation myocardial infarction (nSTEMI). The major risk factors for ST-elevation myocardial infarction are dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of coronary artery disease.

According to AHA 2019 statistics, the US annual incidence of MI is 805,000 where 605,000 (75%) are new cases and 200,000 are recurring [Virani, 2020]. It is estimated that 32%–37% of MI's are STEMI [Vallabhajosyula, 2020]. Patients with STEMI are at high risk of poor outcomes. While the use of percutaneous coronary interventions with stents has driven a reduction in overall inpatient mortality following MI from 20% in the late 1980s to approximately 5%–10%, close to 50% need re-hospitalization within the same year [Mechanic, 2021]. A recent retrospective analysis of 62,048 eligible patients with STEMI, in which 32.9% were women and 14.9% did not have traditional cardiovascular risk factors, showed in-hospital mortality of 9.6% for patients without cardiovascular risk factors compared to 6.5% for others while combined major adverse cardiovascular events were 30.2% and 28.9%, respectively. Mortality in women was double that of men with and without risk factors [Figtree, 2021].

Longer term complications from STEMI are also significant. Adverse left ventricular remodeling occurs in a wide proportion of patients with STEMI. In a Dutch study of STEMI with PCI and long term follow-up, half of all patients experienced a deterioration of the left ventricle between 4 and 24 months [Hassell, 2017]. Left ventricle aneurysm formation is another complication that affects 2.1% of patients with STEMI, acutely,[2] but aneurysm presence after weeks, months, or a year is much higher and under-reported. Both remodeling and aneurysms are associated with higher all-cause death, hospitalization for heart failure (HF), and the composite occurrence of all cause death or HF hospitalization within 1 year [Stone, 2016].

Acute ST-elevation myocardial infarction is also associated with a heavy cost burden. In a prospective study of 11,969 US patients at 233 US hospitals (the TRANSLATE-ACS registry) it was shown that index hospital costs averaged $19 327 for STEMI with 45% attributed to catheterization laboratory and 20% attributable to post-procedure hospital stay. The mean index length of stay was 3.1 days and mean intensive care unit length of stay was 1.4 days. Post-discharge 1-year costs averaged $8037 and 48% of patients were re-hospitalized (half within 2 months and 57% with a cardiovascular diagnosis) [Cowper, 2019]. The total annual cost of acute myocardial infarction (AMI) in 2016 dollars was estimated to be $84.9 billion, including $29.8 billion in excess direct medical

expenditures, $14.6 billion in lost productivity from morbidity and $40.5 billion in lost productivity from premature mortality between 2003 and 2014 [Bishu, 2020].

Although the pathophysiology of STEMI has been clearly defined in animal models, it remains challenging to treat in a clinical setting due to the various interdependent mechanisms involved. Ischemia, cardiomyocyte structural changes, edema and cell death develop at the onset. Acute contractile dysfunction, oxidative stress, and calcium overload follow. Once blood flow is restored, reperfusion itself causes a second wave of injury, by production of reactive oxygen species, embolization of thrombotic debris, plugging by inflammatory cells, and release of vasoactive mediators from damaged endothelium. Myocardial injury leads to activation of the classic inflammatory cascade and an eventual transition to repair with activation of fibroblasts and progressive scar deposition. Over time there is compensatory activation of the renin-angiotensin and sympathetic nervous systems and pathological remodeling with changes to the ventricular geometry, wall thinning, ischemic mitral regurgitation, and further cardiomyocyte loss. Developing an effective therapy in view of these challenges has been elusive. Harnessing the body's own repair mechanisms with a biologic and regenerative approach is appropriate.

Cardiac regenerative medicine is emerging as a viable alternative designed to treat cardiovascular failure and its consequences in an early stage. In particular, the potential of progenitor stem cells to alter the maladaptive healing process through their paracrine effects leading to neo-angiogenesis and prevention of apoptosis is being elucidated. A recent murine systems proteomic study assessed the proteomic myocardial alterations within minutes to 1-month post-infarction and showed that stem cell treatment reduced and reversed a large proportion of proteome changes, rectifying 85% of the functional categories most affected by infarction [Arrell, 2020].

Outcomes from early promising stem cell trials which typically consisted of cell mobilization, harvest, ex-vivo concentration, and reinfusion have not been confirmed in larger multicenter randomized controlled studies. The major hurdles in successful clinical translation are poor cell survival, retention, and sustained activity in the infarcted heart – a critical requirement for effective treatment. To enable stem cells to exert their therapeutic benefit in a clinical setting more effectively, an alternative strategy was developed that does not require harvest and reinfusion but relies on the intrinsic homing and migration of mobilized cells to the area of injury. This strategy consists of sustained mobilization of stem cells into circulating blood with granulocyte colony-stimulating factor (G-CSF) and inhibition of dipeptidyl peptidase 4 (DPP-4), which degrade the stem cell binding chemokine to sustain stem cell recruitment and mobilization to the injured myocardium.

The development program of DPP-4 inhibition employing approved gliptins in co-administration with G-CSF treatment in regenerative treatment after myocardial infarction was first investigator-driven.

The use of G-CSF in clinical settings to induce hematopoietic stem and progenitor cell (HSPC) mobilization had been well-established. In AMI patients, clinical studies used G-CSF to mobilize peripheral blood progenitor cells/bone marrow cells and then collect these cells for direct infusion into the infarct artery. No major safety issues were identified in this application. In STEMI, the potential of G-CSF (filgastrim; 10 µg/kg body weight per day, subcutaneously) to improve myocardial function and survival in patients was also investigated in academia, revealing a positive influence on myocardial perfusion if G-CSF is given early, but no overall improvement of myocardial functioning and survival when used as a single substance (G-CSF-STEMI Trial, incl. post-hoc analysis [Engelmann, 2010].

In a meta-analysis of eight eligible studies (n=385 patients), G-CSF monotherapy (median of 10 µg/kg body weight daily) was assessed in patients with AMI [Abdel, 2008]. Compared with controls, G-CSF therapy increased left ventricular (LV) ejection fraction (EF) by 1.09%, increased LV scar size by 0.22%, decreased LV end diastolic volume (EDV) by 4.26 mL, and decreased LV end-systolic volume (ESV) by 2.50 mL. None of these effects was statistically significant in the meta-analysis. The risk of death, recurrent myocardial infarction, and in-stent restenosis was similar in G-CSF-treated patients and controls. It was concluded that G-CSF therapy in unselected patients with AMI is safe but does not provide an overall benefit.

Following the preclinical proof-of-concept of DPP-4 inhibitor myocardial infarction studies in a CD1 mice model, RECARDIO initiated clinical studies with the DPP-4 inhibitor dutogliptin in co-administration with G-CSF to investigate its use as a regenerative (short-term) treatment of acute myocardial infarction.

Dipeptidyl peptidase 4, also known as the T-cell antigen CD26, is a ubiquitous multi-functional protein which, besides its catalytic activity, also functions as a binding protein and a ligand for a variety of extracellular molecules. It is an integral membrane protein on cells but also circulates as a soluble protein in plasma. A large number of bioactive molecules can be cleaved by DPP-4. One of these is glucagon-like peptide-1 (GLP-1), which plays an important role in the maintenance of normal glucose homeostasis. Inhibition of GLP-1 was targeted pharmacologically through the development of DPP-4 inhibitors, and these are now a successful class of anti-hyperglycemic agents used to treat type 2 diabetes (T2DM) [Deacon, 2019].

DPP-4 inhibition can also be employed as a therapeutic strategy targeting other chemokines in other indications. After STEMI, using a DPP-4 inhibitor will prevent the degradation of stromal cell-derived factor 1 alpha (SDF-1a). Stromal cell-derived factor 1 alpha and its corresponding receptor CXCR4 have been identified as key regulators in stem cell homing to ischemic and injured myocardium. Stromal cell-derived factor 1 alpha is upregulated by hypoxia and facilitates chemotaxis, stem-cell recruitment and cardiomyocyte survival via its G-protein coupled receptor, CXCR47. SDF-1a and CXCR4 are up-regulated in the heart in both experimental and clinical studies of MI. In addition to mobilization and migration of stem cells, SDF-1a is also thought to confer direct protection against ischemia-reperfusion (IR) injury via the same signaling

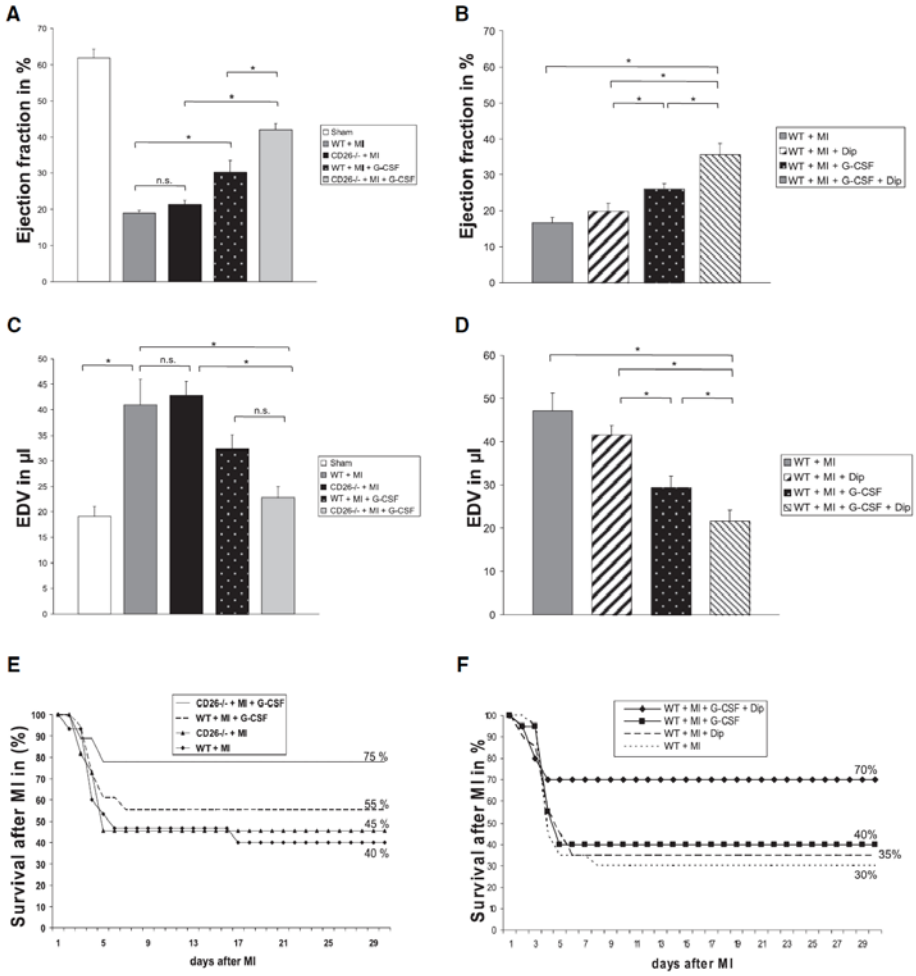
pathways implicated in ischemic conditioning. Stromal cell-derived factor 1 alpha, therefore, exhibits pleiotropic effects on ischemic myocardium: gradient-guided homing of stem cells towards sites of myocardial injury and direct protection via intracellular pro-survival signal transduction pathways [Penn, 2009].

While local increase of SDF-1 by DPP-4 inhibition represents a promising approach to treat ischemic disorders, pre-clinical research established that SDF-1 alone did not provide a significant benefit in terms of neovascularization, apoptosis, and survival [Zaruba, 2009]. This was confirmed in a randomized controlled clinical setting where a naked DNA plasmid encoding SDF-1 was delivered post-MI. After 1 year, there was no difference in the primary endpoint and secondary endpoints were not statistically significant [Ziff, 2018]. However, if stem cells were first mobilized into circulating blood by G-CSF administration DPP-4 inhibition led to significant benefits in the preclinical setting as discussed further below.

Granulocyte colony-stimulating factor has been used extensively in the clinic and is indicated to mobilize stem cells from bone marrow in peripheral blood stem cell protocols to support treatment in various indications. Granulocyte colony-stimulating factor administration significantly increases blood cluster of differentiation (CD)45 leukocytes, including subtypes of CD34 positive cells: CD45+/CD34+, 13-fold, CD45+/CD34+/CD31+, 9-fold; CD45+/CD34+/Sca-1+, 6-fold; CD45+/CD34+/c-kit+, 31-fold. These CD34+ and CD31+ stem cells induce neovascularization and G-CSF results in differentiation into endothelial cells and cardiomyocytes (Sca-1 and c-kit positive cells). However, as stated previously, G-CSF alone has been shown overall to be clinically ineffective [Engelmann, 2010; Abdel, 2008].

Having established that DPP-4 inhibition alone and G-CSF stem cell mobilization alone did not provide a significant enough benefit, the concept of synchronizing both was investigated. Academic research and the Sponsor demonstrated in a standard LAD mouse model used for AMI that the treatment with various DPP-4 inhibitors along with G-CSF leads to a significant reduction of mortality and improvement of hemodynamic parameters [Zaruba, 2009]. Outcomes of the murine LAD model by Zaruba [Zaruba, 2009] are shown in figure below.

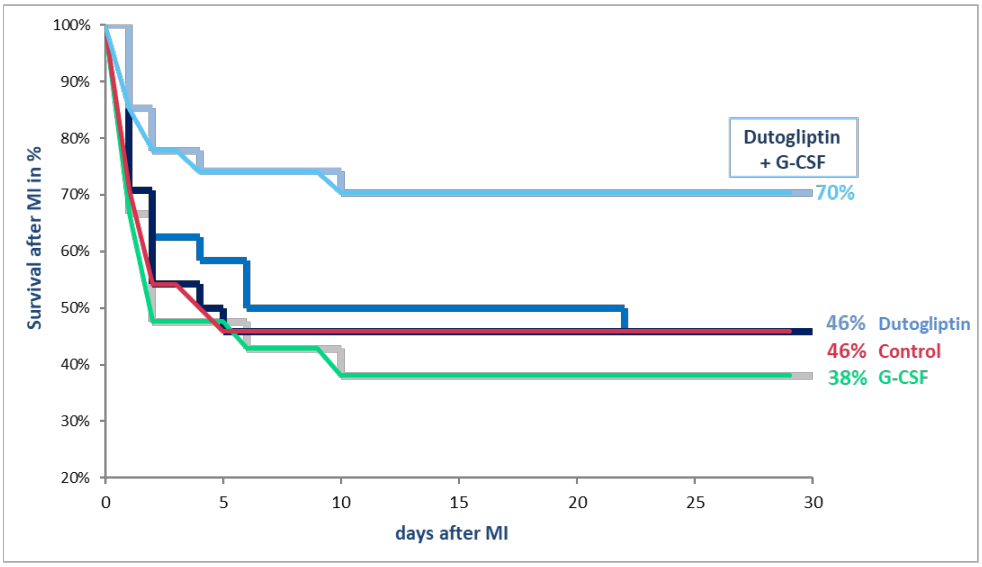
Figure 1 **Granulocyte Colony-Stimulating Factor-Treated CD26 KO and Granulocyte Colony-Stimulating Factor -DipA Mice Reveal Improved Survival and Myocardial Function after MI**



EDV=end diastolic volume; G-CSF=granulocyte colony-stimulating factor; MI=myocardial infarction WT=wild type
A, B; Corresponding bar graphs representing the ejection fraction (EF) of CD26 KO or WT mice receiving saline, G-CSF, Diprotin A, or both at day 30 after LAD ligation.
C, D; Diagrams show enddiastolic volume of CD26 KO or WT mice at day 30 after MI. Data represent mean ± SEM (n=8); *p <0.05; n.s., not significant.
E, F; Kaplan-Meier curves showing survival rates of CD26 KO or WT mice treated either with saline, G-CSF, Diprotin A, or both after MI. All mice (n=20 in each group) revealed histologically confirmed MIs.
Source: Zaruba, 2009

The strategy to synchronize G-CSF and DPP-4 inhibition after AMI as well as the outcomes above were largely confirmed in another study where dutogliptin, a new potent DPP-4 inhibitor, was administered along with a short course of G-CSF in a murine model. Survival and myocardial properties both improved [Schenk, 2016] as shown in Figure 2.

Figure 2 Significant Survival Benefit for Dutogliptin plus G-CSF as shown in a Murine LAD-ligation Model



G-CSF=granulocyte colony-stimulating factor; MI=myocardial infarction
Source: Nix and Schenk, 2016

Thus, RECARDIO developed a therapeutic approach consisting of the adjunct treatment of acute MI with dutogliptin along with a loading dose of recombinant human G-CSF. The goal is to sustain and to boost the body's initial stem cell recruitment mechanisms and allow for cardiomyocytes to be replenished and to enhance revascularization and apoptotic effects in the affected infarct area, resulting in an improved restored cardiac function and reduction of mortality.

This novel treatment approach is based on the co-administration of two pharmacological actions:

- Mobilization and recruitment of stem cells by G-CSF after the initial injury, and
- Dutogliptin related inhibition of the DPP-4 related degradation of the chemokine SDF-1α resulting in prolonged SDF-1α activity with sustained directing and homing of the mobilized stem cells to the site of cardiac injury

Besides the sustained recruitment of stem cells by preventing DPP-4 from cleaving SDF-1a, DPP4 inhibition has been associated with additional cardio-protective effects through several mechanisms (Table 1).

Table 1 Dipeptidylpeptidase-IV Inhibition Associated with Cardioprotective Effects through Several Mechanisms and Pathways

Reduced Degradation of	Leading to
Incretins (GLP-1 and GIP)	GLP-1R dependent cardioprotection / vasodilation (cAMP/PKA pathway)
	GLP-1R independent cardioprotection / vasodilation (NO+/cGMP pathway)
	Glucagon / insulin regulation leading to reduced hyperglycemia
Substance P	Endothelial NO+ release; tPA stimulation
Peptide YY	NO production
G-CSF	Antiapoptotic activation of JAK/STAT3 pathway
EPO	Angiogenesis

cAMP=cyclic adenosine monophosphate ; EPO=erythropoietin ; G-CSF=granulocyte colony-stimulating factor; GIP=gastric inhibitory polypeptide; GLP-1=glucagon-like peptide-1; JAK=Janus kinase; NO=nitric oxide; STAT3=signal transducer and activator of transcription 3; tPA=tissue plasminogen activator
Source: Rankovic, 2021

Finally, a growing body of evidence has implicated insulin resistance, hyperinsulinemia and the resulting blood sugar dysregulation as the underlying drivers of metabolic syndromes such as central obesity, dyslipidemia, hyperglycemia, hypertension, impaired fibrinolysis, and atherosclerosis [Virani, 2020; Rewers, 2004; Wilson, 2005; Benjamin, 2017]. Blood sugar dysregulation post a traumatic event (e.g., traumatic accident or myocardial infarction [MI]) or serious illness (e.g., infection, sepsis, liver disease) has also been well documented, and is present regardless of underlying metabolic health [Li, 2021]. It is therefore unsurprising that drugs recently used exclusively to manage blood sugar levels in type 2 diabetics are now being studied for their ability to mitigate cardiovascular damage post-MI [Tripolt, 2020; Spertus, 2021]. For example, several phase 3 studies on Empagliflozin (NCT04509674) and Invokana (NCT04252287) are now underway to determine the benefit of these type 2 diabetes drugs in the setting of cardiovascular diseases (MI and [HF]).

Considering the multiple cardioprotective effects of DPP-4 inhibition by dutogliptin, the proposed co-administration of G-CSF and the DPP4 inhibitor dutogliptin represents a valid and promising approach to treat post-STEMI patients. Clinical development is aligned to the intended claim. Particular attention is being drawn to the doses of the gliptin component in the regenerative myocardial infarction treatment setting, which are expected to be basically as in the type 2 diabetes mellitus treatment setting, relying on substantial DPP-4 inhibition over the dosing interval.

Dosing of the G-CSF component in the myocardial infarction treatment setting is deemed to correspond with the approved posology for stem cell mobilization (10 µg/kg body weight per day) and has already been implemented in preceding clinical studies (see above). The approved doses for stem cell mobilization are reasonably expected to correspond with the dose range appropriate for mobilizing stem cells in the myocardial

infarction setting. As part of the pathophysiological processes associated with AMI, stem cell mobilization is already triggered as part of physiological processes to counteract and repair damaged tissue. To further enhance stem cell mobilization in this acute setting, evaluated, recommended and approved G-CSF doses for stem cell mobilization have been chosen.

6.2. Rationale of the Study

Pre-clinical studies have demonstrated that G-CSF-based stem cell mobilization in co-administration with genetic or pharmaceutical CD26/DPP4 inhibition after acute MI results in improved cardiac homing of stem cells, enhanced heart function, and increased survival. In mice, combining genetic and pharmacologic inhibition of DPP4 with G-CSF mediated stem cell mobilization after MI led to (1) decreased myocardial DPP4 activity, (2) increased myocardial homing of circulating CXCR4+ stem cells, (3) reduced cardiac remodeling, and (4) improved heart function and survival [Zaruba, 2009; Theiss, 2013; Nix and Schenk 2016].

In a Phase 1 study in healthy volunteers, dutogliptin was administered as single and multiple daily subcutaneous (SC) doses ranging from 30 to 120 mg. Inhibition of plasma DPP4 increased in duration with increasing dose. However, complete (≥80%) inhibition could not be achieved for 24 hours with daily doses up to 120 mg. Sustained inhibition was observed to last for 8–12 hours following a single 60 mg dose, therefore twice daily 60 mg dosing has been selected as the active dose for this study. Single doses up to 120 mg were well tolerated in the Phase 1 study.

The current Phase 2 study will investigate the safety and efficacy of dutogliptin administered in co-administration with filgrastim, a G-CSF medication, compared with placebo in subjects with ST-elevation myocardial infarction (STEMI) who were successfully re-vascularized following percutaneous coronary intervention (PCI) and stent implantation.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. Objectives

7.1.1. Primary Objective

- Evaluate the safety and tolerability of dutogliptin in co-administration with filgrastim in subjects

7.1.2. Secondary Objectives

- Assess preliminary efficacy of dutogliptin in co-administration with filgrastim in subjects with STEMI compared with placebo
- Determine the pharmacokinetics (PK) of dutogliptin in a subset of the study population
- Establish the pharmacodynamics (PD) of dutogliptin (plasma DPP4 activity) in a subset of the study population
- Evaluate the change from baseline in plasma biomarkers N-terminal pro-b-type natriuretic peptide (NT-proBNP) and high sensitivity troponin

7.2. Endpoints

7.2.1. Primary Endpoint

- Safety assessments included reporting of adverse events (AEs) and serious adverse events (SAEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations

7.2.2. Secondary Endpoints

Change from baseline to Day 90 (and Day 180, optional assessment) in the following cardiac functional parameters was assessed by central, blinded review of cardiac magnetic resonance imaging (cMRI):

- Left ventricular ejection fraction (LVEF)
- Left ventricular end systolic volume (LVESV; absolute and indexed)
- Left ventricular end diastolic volume (LVEDV; absolute and indexed)
- Infarct size
- Left ventricular mass (absolute and indexed)
- Regional wall motion

Further endpoints assessed on Day 90 included:

- Individual clinical endpoints, including recurrent non-fatal MI, non-fatal stroke, death due to any cause, cardiovascular death (death due to acute MI, chronic heart failure [CHF], stroke, or sudden cardiac death, stent thrombosis or CHF hospitalization
- Composite clinical endpoints (MACE), including non-fatal MI, non-fatal stroke, cardiovascular death, stent thrombosis, and CHF hospitalization
- Time to cardiovascular event, as defined by the time from randomization to the first occurrence of recurrent non-fatal MI, non-fatal stroke, death due to any cause, stent thrombosis, and CHF hospitalization

7.2.3. Other Endpoints/Parameters

The following PK endpoints were planned to be evaluated:

- Plasma dutogliptin concentration profiles
- Trough dutogliptin concentrations
- Maximum plasma concentration (C_{max})
- Time corresponding to C_{max}
- Area under the drug concentration-time curve
- Additional parameters may also be determined (volume of distribution, clearance and terminal phase half-life)

Further PD endpoints included:

- Plasma DPP4 activity as maximum effect on plasma DPP4 activity
- Trough plasma DPP4 activity
- Change in plasma biomarkers NT-proBNP and high sensitivity troponin

Pharmacokinetic/PD assessments were not performed due to the early closeout of the study caused by the Coronavirus disease 19 (COVID-19) pandemic (Section 8.5.2.5).

8. INVESTIGATIONAL PLAN

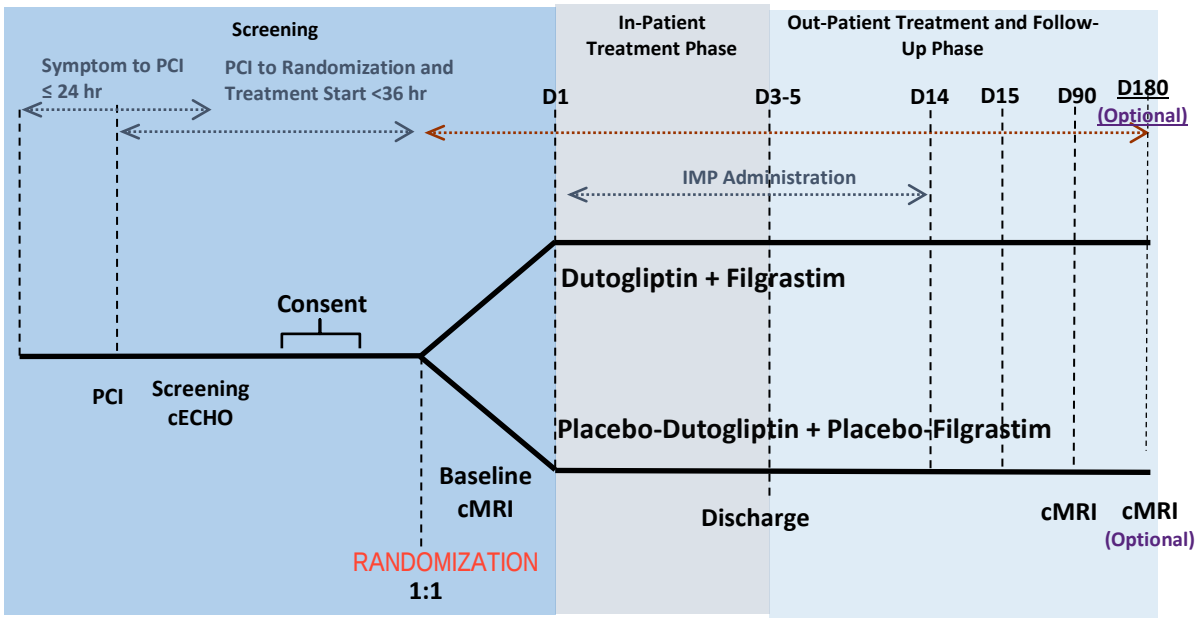
8.1. Overall Study Design and Plan

Study REC-DUT-002 was a multicenter, randomized, double-blind, placebo-controlled study that explored the safety, tolerability, and efficacy of dutogliptin administered in co-administration with filgrastim to subjects with STEMI following PCI and stent implantation. Exploration of subject eligibility started after hospital admission. One hundred and forty eligible subjects were planned to receive local standard of care procedures including PCI and stent implantation (bare metal or drug-eluting). The allowable time between onset of STEMI symptoms and stent implantation (time of first balloon inflation) was up to 24 hours. Eligibility was evaluated in a step-wise manner. It was recommended that medical history, physical examination, and safety laboratory screening tests were completed prior to conducting the cardiac echocardiogram (cECHO).

The total duration of study participation for each subject was 3 months, with an additional, optional cMRI assessment at 6 months. Randomized subjects received twice daily SC injections of 60 mg dutogliptin (batch number 9080444A, 9080444B, 9080444F) for 14 days in co-administration with 10 μg/kg filgrastim (batch number 9080444E) for 5 days or matching dutogliptin placebo for 14 days in co-administration with matching filgrastim placebo for 5 days (if the first dose was administered on Day 1 evening, treatment continued until Day 15 morning), as specified in Figure 3. Subjects were randomized and received study treatment within 36 hours after stent implantation. Study treatment was administered SC to subjects by the site hospital staff at the Day 1 visit and while the subject remained hospitalized. Upon discharge, adequate supplies of investigational medicinal products (IMPs) to complete all dosing was issued to the homecare nursing service, which administered all remaining doses to the subject at home. The primary analysis was based on database snapshot performance of subjects up to Day 90. An optional cMRI follow-up on Day 180 was analyzed separately. A final database closure was performed when the subjects agreed to the Day 180 assessment completed the tests. A secondary analysis of the resulting additional data was then performed.

To ensure subject safety, an independent Data Safety Monitoring Board (DSMB) reviewed study data following completion of Day 90 by the initial 30 subjects and evaluated if it was appropriate to continue the study according to the protocol. The DSMB met and reviewed the study data at least biannually and, if appropriate, made safety recommendations to the Sponsor.

Figure 3 Design of REC-DUT-002 Study



cECHO=cardiac echocardiogram; cMRI=cardiac magnetic resonance imaging; D=Day

An additional, optional cMRI assessment was performed on Day 180.

8.2. Discussion of the Study Design Including the Choice of Control Groups

This is a proof-of-concept study, where dutogliptin was co-administered with filgrastim and compared with placebo in subjects with STEMI who were successfully re-vascularized following PCI and stent implantation. Filgrastim is a recombinant form of G-CSF, and the purpose of utilization of G-CSF after MI is to increase and mobilize the release of bone marrow stem cells into the circulation. It was reported that the administration of G-CSF significantly increases the expression of CD45 leukocytes in blood [Deindl, 2006]. However, the use of G-CSF alone has been shown overall to be clinically ineffective, possibly due to the lack of proper homing and migration of the mobilized cells to the area of injury [Doesch, 2014 Engelmann, 2006; Brunner, 2008a; Brunner, 2008b; Abdel-Latif, 2008].

Preclinical studies have demonstrated that G-CSF-based stem cell mobilization in co-administration with genetic or pharmaceutical CD26/DPP4 inhibition after acute MI resulted in improved cardiac homing of stem cells, enhanced heart function, and increased survival. In murine models, combining genetic and pharmacologic inhibition of DPP4 with G-CSF-mediated stem cell mobilization after MI led to (1) decreased

myocardial DPP4 activity, (2) increased myocardial homing of circulating CXCR4+ stem cells, (3) reduced cardiac remodeling, and (4) improved heart function and survival [Zaruba, 2009; Theiss, 2013; Nix and Schenk 2016]. Therefore, the inclusion of filgrastim in this study was expected to enhance the effect of dutogliptin. Please refer to Section 8.4.4 for details about the choice of dose selection.

8.3. Study Population

8.3.1. Inclusion Criteria

To be eligible for this study, subjects had to meet all of the following inclusion criteria:

1. Male or female, age 18 to 85 (reached 18 and before reached 86 at the time of ICF signing)
2. Body weight <96 kg (212 lb)
3. Able to provide written informed consent, including signing and dating the ICF
4. Diagnosis of STEMI (defined as new ST-segment elevation at the J point of at least two continuous leads of >2 mm [0.2 mV] in men or >1.5 mm [0.1 mV] in women in leads V2 and V3 or >1 mm in any other contiguous precordial leads or the limb leads [for both men and women]) with PCI (bare metal or drug-eluting stent) and thrombolysis in myocardial infarction flow grade 2 or 3 occurring up to 24 hours after symptom onset (to time of first balloon inflation)
5. Left ventricular ejection fraction) ≤45% obtained by cECHO performed within 36 hours post-stent placement
6. Received standard medical therapy for post-MI treatment, according to local procedures and the Principal Investigator's discretion
7. Female subjects of childbearing potential had a negative serum pregnancy test at Screening and an additional negative urine pregnancy test prior to the first dose of IMP unless regulated differently by national legislation
8. Sexually active female subjects of childbearing potential (i.e., women who were not postmenopausal or who had not had a bilateral oophorectomy, hysterectomy, or tubal ligation) and all male subjects (who had not been surgically sterilized by vasectomy) agreed to use highly effective contraception during treatment and for 4 weeks after the last dose

8.3.2. Exclusion Criteria

Subjects who met any of the following exclusion criteria were excluded from the study:

1. Previous MI prior to Screening
2. Complex peri/post-MI clinical course, including arrhythmias, cardiogenic shock, pulmonary edema required mechanical ventilation, or required vasopressor medications

3. Significant pre-existing cardiomyopathy with known LVEF ≤45% or moderate to severe mitral or aortic valvular disease
4. Amyloidosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or constrictive pericarditis
5. Existing heart transplant
6. Ventricular tachycardia or fibrillation not associated with an acute ischemic episode
7. Uncontrolled hypertension (systolic >180 mmHg or diastolic >120 mmHg)
8. Treated with any DPP4 inhibitors (e.g., alogliptin, linagliptin, vildagliptin, saxagliptin, sitagliptin) or G-CSF medication (e.g., filgrastim, lenograstim, pegfilgrastim, lipegfilgrastim) within 4 months prior to randomization
9. Contraindication to treatment with filgrastim, including known allergy to filgrastim or other G-CSF medication
10. Anemia defined as hemoglobin <9 g/dL prior to randomization
11. Thrombocytosis (platelets >500 k/µL)
12. Known positive serology for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV), any other indication of liver disease or injury
13. Alanine aminotransferase (ALT) concentrations >3 times the upper limit of normal (ULN) and total bilirubin (TBL) >2 x ULN, or international normalized ratio (INR) >1.5 prior to randomization, according to local laboratory assessments, and/or any indication of liver disease or injury. If ALT was between >3 and 8 x ULN, and all other admission criteria were met, the test was repeated within the time window before randomization
14. History of cirrhosis and Child-Pugh score B or C
15. Current fever greater than 101.4°F (38.6°C) or recent systemic infection within 2 weeks prior to randomization
16. Contraindication to cMRI procedure, including prior implantable cardioverter defibrillator placement, known reaction to gadolinium, claustrophobia, non-MRI compatible, cochlear implant, morbid obesity, or presence of ferromagnetic material including shunts, shrapnel, penile prostheses, or blood vessel coil
17. Pregnant, planned to become pregnant, or nursing female subjects. Autoimmune disease required immunosuppressive therapy or chronic steroid treatment >5 mg/day prednisolone or equivalent
18. Significant renal impairment defined as estimated glomerular filtration rate <45 mL/min/1.73 m2, using the chronic kidney disease epidemiology collaboration equation
19. Active neoplasm required surgery, chemotherapy, or radiation within the past 12 months (subjects with a history of malignancy who had undergone curative

resection or otherwise did not required treatment for at least 12 months prior to Screening with any detectable recurrence were allowed)

20. Malignant hematological disease, i.e., chronic myeloid leukemia or myelodysplastic syndrome
21. History of cerebrovascular accident or transient ischemic attack in the past 6 months
22. History of pneumonia in the last 4 weeks
23. History of any significant medical or psychiatric disorder that in the opinion of the Investigator would made the subject unsuitable for participation in the study
24. Treatment with an investigational drug within 30 days or five half-lives (whichever was longer) or treatment with an investigational biologic drug within 6 weeks prior to randomization
25. Participation in another concurrent clinical trial involved a therapeutic intervention (participation in observational studies and/or registry studies was permitted)
26. Unable or unwilling to complied with the requirements of the study
27. Subject and/or an immediate family member was an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization
28. Considered by the Investigator to be unsuitable to participate in the study for any other reason
29. Persons who were in an institution as a result of an administrative or judicial order, or soldiers
30. History of alcohol or drug abuse

8.3.3. Removal and Replacement of Subjects from Treatment or from the Study

8.3.3.1. Withdrawal of Consent

A subject was able to withdraw consent to continue study treatment in this study at any time without penalty or loss of benefits to which the subject was otherwise entitled. When a subject wished to withdraw consent, it was important to distinguish between withdrawing his/her consent for a particular study procedure or visits versus withdrawing his/her consent from the study entirely (i.e., premature discontinuation). If a subject withdrew consent for study treatment only, the subject was scheduled for an Early Termination visit, to occur at approximately Day 15. When a subject withdrew consent from the study (or study procedure), the reason(s) for withdrawal were recorded by the Investigator or designee in the source documents.

8.3.3.2. Premature Discontinuation

Every reasonable effort was made to encourage retention of subjects in the study, maximized compliance with study procedures (including IMP administration), and facilitated attendance at all scheduled study visits/assessments.

A subject could be withdrawn from the study for any of the following reasons:

- Withdrawal of consent for IMP administration
- Withdrawal of consent from the study and all follow-up procedures
- Noncompliance (defined as refusal or inability to adhere to the study procedures)
- Pregnancy while receiving IMP
- Used of any other investigational treatment
- Withdrawal due to the relevant AE at the request of the Sponsor, regulatory agencies, or IRB/IEC
- Lost to follow-up
- Study termination by Sponsor
- Elevations in liver enzymes (see inclusion criteria, Section 8.3.1)

8.3.3.3. Replacement of Subjects

Subjects who prematurely discontinued participation in the study were not replaced.

8.4. Treatments

8.4.1. Study Treatment Administered

The IMPs dutogliptin, filgrastim, and matching placebo were supplied as intravenous vials for SC injection as follows:

- Dutogliptin: 200 mg single-use vial (100 mg/mL)
- Dutogliptin Placebo: single use vial
- Filgrastim (Neupogen): 480 µg single-use vial (300 µg/mL)
- Filgrastim Placebo: single use vial

Further details about which IMPs and doses subjects received are presented in Section 8.1. Subjects received IMPs within 36 hours after stent implantation. The IMPs were administered at approximately the same time each day (where possible) with a minimum of 10 hours between the two daily dutogliptin doses and 16 hours between filgrastim doses. Subjects were not allowed to self-administer the IMPs.

8.4.2. Identity of Investigational Product(s)

Investigational medicinal product vials (dutogliptin, batch number 9080444A, 9080444B, 9080444F; filgrastim, batch number 9080444E) were shipped directly to the investigational site, after all required regulatory and legal documents were received by the Sponsor. Details of the IMP are described in the Investigators Brochure. Investigational medicinal product was shipped in containers to maintain temperatures of 2–8°C. Transportation of IMP by the homecare nursing service is detailed in the Pharmacy Manual and Nursing Off-Site Manual.

The dispenser verified the condition of the study supplies and performed IMP accountability upon receipt. Acknowledgement of receipt was then documented in the interactive web response system (IRT). The site stored the IMPs vials at 2°C to 8°C protected from sources of heat, light, and damage. The IMP vials were stored in a secure refrigerator with access restricted only to authorized personnel. After the subject was discharged for the outpatient portion of the trial, vials were stored in a locked refrigerator monitored electronically and reviewed by the homecare nursing service on a regular basis (at every home visit) and recorded onto a temperature log sheet. If a refrigerator's temperature strayed outside the 2–8°C range, the Sponsor or their designee was contacted immediately. Contact details were provided in the Pharmacy Manual. The study monitor performed regular reviews of storage conditions at site, the homecare nursing service at the subject home.

The homecare nursing service received an IMP kit for each subject that included the appropriate number of vials containing IMP (according to randomization). Used and unused IMP vials were retained by the homecare nursing service and returned to the site for accountability. It was the responsibility of the site and homecare nurse to ensure that a current record of inventory/IMP accountability was maintained. Inventory records were readily available for check and verification by the study monitor and were open to inspection by the US Food and Drug Administration or other US and EU regulatory authorities at any time. For further details, please consult the Pharmacy Manual.

The study site staff recorded the return of all used and unused IMP vials and kept the electronic case report form (eCRF) appropriately updated. The Clinical Research Associate conducted the final reconciliation prior to close of the study site.

8.4.3. Treatment Assignment

Subjects who met all admission criteria were randomized (stratified by study site) and received dutogliptin in co-administration with filgrastim or matching placebo. Subjects were assigned to study arms in a blinded fashion using the IRT.

8.4.4. Dose Selection

In the Phase 1 dose finding study, dutogliptin was administered as single and multiple daily SC doses ranging from 30 to 120 mg. Inhibition of plasma DPP4 increased in

duration with increasing dose. However, complete (≥80%) inhibition could not be achieved for 24 hours with daily doses up to 120 mg. Sustained inhibition was observed to last for 8–12 hours following a single 60 mg dose, therefore twice daily 60 mg dosing was selected as the active dose for this study.

8.4.5. Individual Subject Dose Selection and Timing

Doses were administered at approximately the same time each day (where possible) with a minimum of 10 hours between the two daily dutogliptin doses and 16 hours between filgrastim doses (where applicable). Subjects were not allowed to self-administer the IMPs.

When the subject missed a dose of IMP, the next planned dose was administered as scheduled and the Investigator was contacted as soon as possible. When the subject missed consecutively two or more doses, the Investigator was notified immediately by the hospital or homecare nursing service staff and the medical monitor was consulted.

8.4.6. Blinding

This was a double-blind study. Subjects and study staff remained blinded to treatment assignments for the duration of their involvement in this study. The homecare nursing service was also blinded to study allocation.

An independent DSMB reviewed study data on an ongoing basis during the study. Some DSMB reviews were performed on unblinded data. Staff (Sponsor and site) involved in the preparation of study data for DSMB reviews were not involved in the regular conduct of the study. The Sponsor (except the drug supply manager) remained blinded to treatment assignments and study data at all times.

8.4.6.1. Emergency Unblinding

The IMP treatment assignment was unblinded only in emergency situations when knowledge of the treatment assignment was considered absolutely necessary for medical management of the subject or for clinical decision-making (i.e., when knowledge of the treatment assignment impacted a treatment decision). The Investigator had unrestricted and immediate access to unblind the treatment code through the eCRF system. The instructions for unblinding are described in the eCRF Investigator Manual.

In the event unblinding was necessary, the Investigator was strongly encouraged to contact the appropriate medical monitor to discuss the situation and the subject's medical status prior to unblinding. When a subject's treatment assignment was unblinded, a comprehensive source note was completed by the Investigator specifying date, time and reason(s) for unblinding.

In the event the Investigator chose to discuss the unblinding with the medical monitor, the source note included a record of the discussion. It was mandatory that all personnel who were involved in the unblinding and who had access to the unblinded treatment

assignment information maintained the confidentiality of the information by not divulging the treatment assignment. Following emergency unblinding, the subject's further participation in the study was discussed with the medical monitor.

8.4.7. Prior and Concomitant Medication

All prescriptions and over-the-counter medications (including vitamins and natural products) were taken during the 30 days prior to randomization through to Day 90/Early Termination visit was documented.

Concomitant medications included any prescription or over-the-counter medication (e.g. vitamins and natural products) that were ongoing on Day 1 or that were initiated following the first dose of IMP on Day 1.

At study entry, subjects received all concomitant medications for other concurrent conditions (e.g., hypertension, diabetes, dyslipidemia, gout) within 14 days prior to hospitalization. Medications, included over the counter therapeutics, natural products, and vitamins, were not changed during Screening or treatment with IMP, unless medically necessary. All concomitant medications necessary for the health and well-being of a subject were permitted.

Medications were recorded on the subject's source documents and entered on the appropriate eCRF. Any changes to concomitant medications during the study were recorded in the eCRF.

8.4.8. Treatment Compliance

It was the responsibility of the pharmacist and/or site and homecare nurse to ensure that a current record of inventory/IMP accountability was maintained. Inventory records were readily available for check and verification by the study monitor and were open to inspection by the US Food and Drug Administration or other US and EU regulatory authorities at any time. More details are presented in the Pharmacy Manual.

Medications were recorded on the subject's source documents and entered on the appropriate eCRF. Any changes to concomitant medications during the study were recorded in the eCRF. The study site staff recorded the return of all used and unused IMP vials and kept the eCRF appropriately updated. The Clinical Research Associate conducted the final reconciliation prior to closure of the study site.

8.5. Study Procedures and Flow Chart

8.5.1. Flow Chart

Assessments were performed during the study at the visits on Day 0, Day 1 (baseline), Day 2, Day 3, Day 5, Day 15, Day 90, and Day 180 (the latter was optional and included only cMRI), as specified in Table 2.

Table 2 Time and Events Table

Study Procedure	Scr.	Day 1	Day 2	Day 3	Day 5	Day 15 (+ 1 day)	Day 90 (± 7 days) or at ET[a]	Day 180 (Optional)
Review eligibility[b]	X							
Medical history[c] and demographics	X							
Height[d] and weight	X					X	X	
Prior and concomitant medications[e]	X	X	X	X	X	X	X	
Informed consent[b]	X							
Randomization[f]	X							
Safety								
Full physical examination	X					X	X	
Abbreviated physical examination[g]		X	X	X	X			
Vital signs[h]	X	X	X	X	X	X	X	
12-lead electrocardiogram[i]	X	X				X	X	
Hematology/Chemistry – local laboratory[j]	X	X	X	X	X	X	X	
Urinalysis	X					X	X	
Pregnancy test[k]	X	X					X	
Adverse events[l]	X	X	X	X	X	X	X	
Efficacy								
2D echocardiogram[m]	X							
cMRI[n]		X[n]					X[a,n]	X
Clinical endpoints							X	
Pharmacokinetic Sampling								
Dutogliptin plasma PK[o]		X	X	X	X	X[o]		
Assessments								
DPP4 inhibition[o]		X	X	X	X	X[o]		
Biomarker[p]		X			X	X	X	
IMP								
Dutogliptin or placebo administration D1–D14		→	→	→	→	→	→	
Filgrastim or placebo administration D1–D5		→	→	→	→	→	→	

ET=early termination; 2D=2 dimensional; cMRI=cardiac magnetic resonance imaging; D=day; DPP4=dipeptidyl peptidase 4; Hb=hemoglobin; Hct=hematocrit; IMP=investigational medicinal product; KDR=kinase-insert domain-containing receptor; PK=pharmacokinetic Scr=screening

a. If a randomized subject prematurely discontinued from the study at any time prior to completion of the Day 90 visit, the subject should have returned to clinic for an Early Termination visit. All of the assessments of the Day 90 visit were performed at an Early Termination visit, with the exception of the cardiac magnetic resonance imaging scan (see footnote 'n' below)

b. Procedures performed as standard of care during the Screening Period may have been used to determine eligibility. Informed consent had to be obtained prior to performing any study-specific procedures that were not standard of care

c. Screening included cardiac disease history with diagnosis of ST-elevation myocardial infarction with percutaneous coronary intervention (bare metal or drug-eluting stents) and thrombolysis in myocardial infarction flow grade of 2 or 3 within the 36 hours prior to Randomization

d. Height was measured only at Screening

e. All prescriptions and over-the-counter medications (including dosages) taken during the 30 days prior to Randomization and throughout the study were documented

f. Eligible subjects were randomized and had to receive study treatment within 36 hours of stent implantation (Note: It may have taken time to organize the IMP after Randomization)

g. The abbreviated physical examination was performed preferably before the IMP administration mornings (required) and evenings (optional) until the subject was discharged

h. The vital signs assessment included measurement of heart rate, body temperature, and blood pressure after the subject had rested for at least 5 minutes in the sitting position. The vital signs assessment had to be performed at screening and from Day 1 (preferably before the morning administration of the IMP) during hospitalization (except Day 4) until the subject was discharged
i. A single 12-lead electrocardiogram recording had to be obtained before and after percutaneous coronary intervention. Single electrocardiograms were obtained at all defined study visits
j. Local laboratory samples had to be collected at screening and from Day 1(preferably before morning administration of the IMP) as indicated in the table above until the patient was discharged
k. For all female subjects of childbearing potential, a negative serum pregnancy test had to be documented at Screening. A urine pregnancy test was performed prior to first dose and at the Day 90/Early Termination visit or any date required by national regulation
l. All AEs and SAEs had to be monitored until resolution or stabilization. Serious adverse events that occurred within 30 days after the last dose of IMP had to be reported using the procedures outlined in the protocol
m. A 2-dimensional (2D) echocardiogram with Doppler was performed during Screening within 36 hours' post-stent placement for evaluation of left ventricular ejection fraction, which had to be ≤45%. If the subject met the echocardiogram criteria and all other inclusion and exclusion criteria the subject was enrolled, randomized and receives therapy. If LVEF was >45%, the subject was considered as a screening failure and could not be randomized
n. Scanning had to occur according to the standard cardiac magnetic resonance imaging protocol provided to sites by the MRI core laboratory. Both 1.5 and 3 Tesla scanners may have been used during the study. The serial cardiac magnetic resonance imaging scan obtained for each subject had to be performed using the same scanner. The cardiac magnetic resonance imaging assessment had to be completed within 72 hours' post-stent placement period if the subject met all other inclusion and exclusion criteria and had been enrolled and randomized. If a randomized subject prematurely discontinued study participation prior to the Day 90 visit, a second cardiac magnetic resonance imaging scan did not have to be performed
o. Blood samples for PK/PD analysis were obtained from subjects at selected centers on Day 1 and Day 5 at the following time points in relationship to IMP dosing:
    i. Pre-dose
    ii. 1 hour post-dose
    iii. 2 hours post-dose
    iv. 6 hours post-dose
    v. 8 hours post-dose
    vi. 12 hours post-dose (or pre-next dose)

    Trough samples were drawn pre-dose on Day 2 and Day 3; Day 15 samples were collected approx. 12 hours after the last dose (full details of the sampling window are described in the pharmacokinetic/pharmacodynamic Manual)
p. Blood samples for biomarker testing were obtained from subjects prior to administration of IMP on Day 1, Day 5 (or on day of discharge), Day 15 ~12 hr post last dose, and on Day 90

8.5.2. Study Procedures

Clinically significant and relevant medical history (including surgical history) was documented at the Screening visit to assess subject eligibility. The following demographic data were collected: date of birth, gender, and race. The Screening assessment also included cardiovascular disease history with documentation of the diagnosis of STEMI. In addition, height (cm) was collected at the Screening visit only. Weight (kg) was measured at Screening, Day 15, and Day 90/Early Termination visit.

8.5.2.1. Subject and Baseline Disease Characteristics

Clinically significant and relevant medical history (including surgical history) was documented at the Screening visit to assessed subject eligibility. The following demographic data were collected: date of birth, gender, and race. The Screening assessment also included cardiovascular disease history with documentation of the diagnosis of STEMI.

Subject's height (cm) was collected at the Screening visit only, and their weight (kg) was measured at Screening, Day 15, and Day 90/Early Termination visit.

8.5.2.2. Safety Procedures

Safety assessments were performed on Day 0 (after the ICF] was signed), Day 1 (baseline), Day 2, Day 3, Day 5, Day 15, and Day 90. If the subject was discharged before Day 5, assessments were performed on the day of discharge and then again on Day 15. Safety assessments included reporting of AEs and SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations at each time point.

Treatment-Emergent Adverse Events

An AE was any untoward medical occurrence during the clinical study, which did not necessarily have a causal relationship with study treatment. A treatment-emergent adverse event (TEAE) was an AE that either emerged after first treatment or worsened (in severity) relative to the pre-treatment state after first administration. A TEAE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following was not considered a TEAE:

- Pre-existing conditions that, in the opinion of the Investigator, did not worsen or progress after IMP administration

Non-treatment-emergent AEs were documented in the AE section of the eCRF.

Serious Adverse Events

An SAE was considered any AE that:

- Resulted in death
- Was life-threatening (note that this referred to an event in which the subject was at risk of death at the time of the event; it did not referred to an event that hypothetically might had caused death if it was more severe)
- Required hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Resulted in a congenital anomaly/birth defect

An SAE could also be any other important medical event that was not immediately life-threatened or resulted in death or hospitalization but jeopardized the subject or required intervention to prevent one of the other outcomes listed in the definition above. Examples of such events included intensive treatment in an emergency room or at home for bronchospasm, hyperkalemia, or convulsions that did not resulted in a formal hospitalization.

The following were not considered to be SAEs and were not reported (but were documented in the corresponding Medical History/Concomitant Treatment section of the eCRF):

- Routinely scheduled procedures or treatment
- Elective procedures that were scheduled prior to study participation (i.e. signing of the ICF)

For the population in this study, the following SAEs were not considered unexpected by the Sponsor, but were evaluated and reviewed by the DSMB:

- Myocardial Infarction
- Stent thrombosis
- Malignant cardiac arrhythmia
- Hospitalization for acute heart failure
- Cerebrovascular accident
- Sudden cardiac death

Severity of Adverse Events

The severity of an AE represented the intensity of the event as reported by the subject or assessed by the Investigator. It did not reflect the clinical seriousness of the event. The intensity was evaluated independently from the relation to the study treatment according to the following guidelines:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. No limitation of usual activities
- Moderate: Minimal, local or non-invasive intervention indicated. Some limitations of usual activities
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated. Inability to carry out usual activities

Causality of Adverse Events

The causal relationship of the AE to IMP was assessed by the Investigator. The assessment of causal relationship to IMP was evidence-based, and not based on the premise that all AEs were causally related to IMP until proven otherwise. Default categorization of ‘related’ without supportive evidence for a causal relationship to IMP was generally uninformative and did not contribute to understanding of the safety profile of the IMP with respect to the intended population.

Examples of evidence that suggested a causal relationship between the IMP and the AE included the occurrence of an AE that was known to be strongly associated with drug exposure or an AE that was otherwise uncommon in the study population. Lack of efficacy of IMP, in isolation, lead to unmasking of underlying symptoms and signs of disease, were not considered evidence of relatedness.

The causal relationship of each AE was assessed using the following definitions:

- Related: There was evidence to suggest a causal relationship, and the influence of other factors was unlikely
- Possibly Related: There was reasonable evidence to suggest a causal relationship between the IMP and AE
- Unlikely Related: No temporal association or the cause of the event had been identified, or the drug or biologic could not be implicated
- Not Related: No reasonable causal relationship between the IMP and the AE exists. There was evidence of an alternative explanation that was more likely the cause of the AE

Laboratory Tests

Safety laboratory tests for this study (chemistry, hematology, and urinalysis) were performed at the local laboratory. Values from local laboratories were used to determine eligibility for study enrollment and as the basis for clinical decisions. Please refer to the Time and Events Table (Table 2) for details regarding sample collection for local laboratory testing.

Hematology and Chemistry

Hematology and Chemistry tests were performed as specified in the Time and Events Table (Table 2). Hematology tests were performed to measure hematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell count (RBC), and INR. Chemistry tests were performed to measure ALT, aspartate aminotransferase (AST), bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, and uric acid.

Liver Enzyme Elevations

Liver parameters (ALT, AST, and bilirubin) were monitored each day (except Day 4) while the subject was hospitalized (but no longer than Day 5) and on Day 15, and Day 90 through local chemistry laboratory tests.

The IMP was permanently discontinued in any subjects who – if following repeat testing within 48 hours the abnormalities were confirmed/experienced an increase in:

- Alanine aminotransferase or AST >8xULN, or

- Alanine aminotransferase or AST >3xULN and TBL >2xULN, or INR >1.5
- Alanine aminotransferase or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Infection/Sepsis

If a subject developed a fever greater than 101.5°F (38.6°C) or other signs of infection, a clinician who was not responsible for study conduct reviewed any laboratory data with the white blood cells (WBCs) and differential, and prescribed the appropriate treatment without revealing the WBC results to the study team. This procedure was required in order to maintain the study blind.

Urinalysis

A urinalysis was performed to measure pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin or RBC, and cells (WBC).

Pregnancy Testing and Contraception

A serum pregnancy test for human chorionic gonadotropin was performed on female subjects of childbearing potential at Screening. A urine dipstick pregnancy test (human chorionic gonadotropin) was performed on female subjects of childbearing potential prior to the first dose and at the Day 90 (Month 3)/Early Termination visit prior to cMRI unless regulated differently by national legislation. Negative pregnancy test results were documented before dosing was started.

Sexually active female subjects of childbearing potential (i.e., women who were not postmenopausal [postmenopausal is defined >12 months amenorrhea] or who had not have a bilateral oophorectomy, hysterectomy, or tubal ligation) and all male subjects (who had not been surgically sterilized by vasectomy) agreed to use highly effective contraception during the study. Highly effective contraception was defined as:

- Combined hormonal contraception or progesterone-only hormonal contraception associated with inhibition of ovulation (e.g., oral contraceptive, transdermal contraceptive, contraceptive implant, or injectable hormonal contraceptive) for at least 3 months prior to IMP administration, throughout the treatment, and for 4 weeks after the last dose of IMP
- Intrauterine contraception/device starting at the Screening visit, throughout the treatment, and for 4 weeks after the last dose of IMP
- Total abstinence from sexual intercourse (only acceptable if it was the preferred and usual lifestyle of the subject) for at least one complete menstrual cycle prior to the Screening visit, throughout treatment, and for 4 weeks after the last dose of IMP

- Maintenance of a monogamous relationship with a male partner who had been surgically sterilized by vasectomy
- Bilateral tubal occlusion

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides, and lactational amenorrhea were not acceptable methods of contraception. In addition, male subjects with a partner of child-bearing potential had to use condoms during treatment and for 4 weeks after the last dose of IMP.

Electrocardiogram

A single 12-lead ECG recording was obtained at Screening, on Day 1, Day 15, and Day 90. All ECGs were performed with the subject in a supine position having rested in this position for at least 5 minutes. Twelve-lead ECGs were assessed as normal or abnormal by the Investigator; any abnormal findings were described in the eCRF and the Investigator assessed the clinical significance. The ECG recording was signed and dated by the Investigator and stored in the medical records.

Vital Signs

Vital signs were assessed at Screening, during hospitalization (except Day 4) until the subject was discharged, on Day 15, and on Day 90 and/ or at the Early Termination visit. Vital signs (heart rate, body temperature, and blood pressure) were measured after the subject had been resting for at least 5 minutes in the sitting position. If blood samples were scheduled at the same time, vital signs were measured before the blood draw. Blood pressure was measured manually or by an automated device, preferably using the non-dominant arm. The same measurement technique was used throughout the study for all the subjects.

Physical Examination

A full physical examination was performed on all subjects at Screening, on Day 15, Day 90/or Early Termination, preferably before drug administration, and included the following assessments:

- General inspection
- Examination of the injection site and draining nodes (just on Day 15)
- Head/ears/eyes/nose/throat examination
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Assessment for neurological deficits
- Musculoskeletal assessment

Any abnormalities found were recorded in the eCRF. Clinically significant physical examination abnormalities were included and summarized as Medical History or AEs, as appropriate. At all other study visits (per Time and Events Table), an abbreviated, symptom-directed physical examination was performed (morning and optional in the evening), preferably before drug administration.

An abbreviated physical examination included the following assessments:

- General inspection
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)

8.5.2.3. Safety Reporting

The investigator made every effort to properly evaluate all information relevant to the reported AEs in such a way that a diagnosis can be confidently made and reported. For example, it is preferable to report 'pneumonia' as the AE rather than its symptoms (e.g., rales or fever) as separate AEs.

When recording and/or reporting AEs or SAEs, the following elements were included:

- The fulfilled criteria for seriousness as presented in Section 8.5.2.2.
- The severity of the event as defined in Section 8.5.2.2.
- The relationship of the event to study treatment as defined in Section 8.5.2.2.

Actions taken in relation to the AE were recorded as: drug withdrawn, drug interrupted, no action taken, not applicable, unknown, and/or other action (e.g., drug therapy started; diagnostic test performed, medical procedure started; withdrawn from study). Any medication given to treat the AE was recorded separately in the concomitant medication list of the eCRF.

The outcome of the AE was recorded as date ended, ongoing, or resulting in death with date of death.

Any of the following abnormal liver function test results were reported within 1 day to the RECARDIO safety department for expedited reporting to the regulatory authorities:

- Alanine aminotransferase or AST >8 x ULN, or
- Alanine aminotransferase or AST >3 x ULN and TBL >2 x ULN, or INR >1.5
- Alanine aminotransferase or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Treatment Emergent Adverse Events

Pre-existing conditions that were detected prior to signing the ICF and not worsened in severity afterwards were recorded as part of the medical history. Pre-existing conditions that were detected prior to signing the ICF and did worsen in severity after the first IMP administration were recorded as TEAEs.

For all subjects, the AE reporting period started with the signing of the ICF on Day 0 and ended with the final study visit, after which no new non-SAEs were reported. The subjects were monitored throughout the study for any AEs, including clinically significant findings at vital signs measurements, spontaneous reports by study subjects, and observations by the study personnel. When possible, ongoing AEs assessed as related to the IMP were followed until resolved or stabilized.

All AEs were recorded in the eCRF. The Investigator assessed and recorded any AE in detail including the date and time of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date or ongoing), relationship of the AE to IMP, and actions taken. All AEs were reported separately (i.e., one record per event). Reporting of AEs was event-based (i.e., an ongoing event was not closed until resolved or at the end of study). For the AE description, a diagnosis was preferred over symptoms. If no diagnosis was made, each symptom was reported as a separate AE. Abbreviations were avoided, and descriptive words were used for ongoing conditions were applicable (e.g., worsening of eczema).

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 20.1 or higher) after the eCRFs had been monitored and signed by the investigator.

Serious Adverse Events

Any SAE experienced by the subject from signing the ICF through the last study visit or through 30 days after the last dose of IMP (whichever was longer), regardless of severity or causality, was recorded on the eCRF and SAE forms. Refer to Section 8.5.2.2 for disease-related SAEs that were considered unexpected during the conduct of this study.

The study site formally notified the Sponsor of the SAE within 24 hours from the time the study site became aware of the SAE. A formal notification was submitted to the Sponsor regardless of the following:

- Severity
- Causality
- Whether or not the subject received study treatment or underwent study related procedures

The IRB/IEC was notified as required by local regulations. The Investigator was responsible for submitting the required safety information to the appropriate IRB/IEC,

including any safety reports received from the Sponsor, as well as, any SAE occurring at his/her site.

The Sponsor, or designee, prepared any required safety reports for regulatory authorities and all active Investigators. These reports were provided as addenda to the Investigator's Brochure, and the Investigator placed these with the Investigator's Brochure in the local site files.

Abnormal Laboratory Values

All local laboratory data generated during the study were included in standard Statistical Analysis System datasets. Throughout this study, samples were analyzed by local laboratories. Investigators reported AEs based upon local laboratory values, where clinically relevant. In this event, the actual value and the normal range for the local laboratory was recorded on the local laboratory eCRF.

Medical Monitoring

All AEs were medically monitored by the Investigator until resolution or stabilization.

Any SAE that was continuing at the time of subject discontinuation or study completion was monitored by the Investigator until resolution or stabilization. For subjects who prematurely discontinued study treatment or study participation, SAEs that occurred within 30 days after the last dose of IMP were reported using the same procedures outlined in Section 8.5.2.3. These SAEs were recorded in the eCRF.

Special Circumstances

Pregnancy

Subjects and their partners avoided pregnancy throughout the course of the study. Pregnancy in a study subject or partner was reported to the Sponsor within 24 hours of the study site became aware of the pregnancy. Subjects with a positive pregnancy test before IMP dosing were not dosed. Information regarding a pregnancy occurrence in a study subject or partner and the outcome of the pregnancy was collected.

Pregnancy in a study subject or partner was not, in itself, considered an AE. However, in order to begin follow-up and to assure that the Sponsor obtained data on the medical outcome of the pregnancy, any pregnancy during the study was reported to the Sponsor utilizing the procedures for reporting of SAEs (Section 8.5.2.3.).

The medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly was considered an SAE and was reported to the Sponsor within 24 hours of the site became aware of the event. The procedure of elective abortion was not reported as an AE.

No subjects became pregnant during the study.

Other

Other safety events that occurred in association with IMPs required reporting. These events included, but were not limited to, the following:

- Overdose of the medicinal product, where 'overdose' was defined as a subject receiving more than 1.5 times the intended dose for any given SC injection
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving IMP (with or without subject exposure to the Sponsor's medicinal product, e.g., name confusion)

The site notified the Sponsor immediately if any of the above events occurred during the study. If these events were associated with an AE/SAE, they were reported on the corresponding AE/SAE forms.

8.5.2.4. Efficacy Procedures

The efficacy of dutogliptin + filgrastim in subjects with STEMI compared with placebo was assessed. Efficacy assessments were performed within 72 hours after PCI (baseline) and on Day 90.

Efficacy assessments included an evaluation of cardiac functional parameters obtained by cECHO (2-dimensional (2D) echocardiogram) and determined by cMRI and individual and combined clinical endpoints. On Day 180 an optional cMRI was performed.

Cardiac Function Parameters

2-Dimensional Echocardiogram

A 2D cECHO with Doppler was performed during Screening within 36 hours' post-stent placement for evaluation of LVEF, which had to be ≤45%. If LVEF was >45%, the subjects were recorded as a Screening failure and not subjected to randomization or treatment. The Sponsor could request a copy of the 2D echocardiogram to independently review the data post-randomization.

Cardiac Magnetic Resonance Imaging

Cardiac MRI scans were performed according to the standard cMRI protocol provided to sites by the MRI core laboratory. Both 1.5 and 3 Tesla scanners were used during the study. The serial cMRIs obtained for each subject were performed using the same scanner.

The cMRI scan was performed within 72 hours after PCI and after the subject was enrolled and randomized. If a randomized subject prematurely discontinued study

participation prior to the Day 90 visit, a second cMRI scan was performed during the Early Termination visit.

At baseline, on Day 90, and on Day 180 (the latter was optional), the following cardiac functional parameters were assessed using blinded review of cMRI scans:

- Left ventricular ejection fraction
- Left ventricular and systolic volume
- Left ventricular and diastolic volume
- Infarct size
- Left ventricular mass
- Regional wall motion

Additional details regarding cMRI assessments are described in the manual provided by the MRI core laboratory.

Clinical Endpoints

The following clinical endpoints were evaluated on Day 90:

- Individual clinical endpoints, including recurrent non-fatal MI, non-fatal stroke, death due to any cause, cardiovascular death (death due to acute MI, CHF, stroke, or sudden cardiac death), stent thrombosis or CHF hospitalization
- Composite clinical endpoints (MACE) including non-fatal MI, non-fatal stroke, cardiovascular death, stent thrombosis, and CHF hospitalization
- Time to cardiovascular event, was defined by the time from Randomization to the first occurrence of recurrent non-fatal MI, non-fatal stroke, death due to any cause, stent thrombosis, and CHF hospitalization

The clinical endpoint assessment was planned in the protocol to be performed at the Day 90/Early Termination visit. Subjects who did not have this visit did not have these endpoints assessed and so were not included in this analysis.

8.5.2.5. Pharmacokinetic and Pharmacodynamic Procedures

Pharmacokinetic/PD assessment planned in up to 12 subjects at selected sites was not performed due to the early closeout of the study caused by the COVID-19 pandemic.

8.5.3. Appropriateness of Measurements

The safety, PK and PD assessments in the present study are standard, widely used, recognized as reliable and accurate and performed by experienced and skilled personnel using standardized and up-to-date resources.

8.6. Data Quality Assurance

Quality assurance and quality control systems were implemented and maintained with written standard operating procedures to ensure that the study was conducted and data were generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control was applied to each stage of data handling to ensure that all data were reliable and had been processed correctly.

An agreement was secured from all involved parties to ensure direct access to all study related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor, and of inspection by regulatory authorities.

8.6.1. Monitoring

On-site monitoring visits were conducted before, at regular intervals during, and after the study, as appropriate, by Sponsor-approved monitors. At a minimum, the accuracy and completeness of the eCRF entries, source documents, and other study-related records were checked against one another during these visits. After each monitoring visit, a report of any significant findings/facts, deviations, and deficiencies were communicated to the Investigator. The actions taken to address the findings and secure compliance were documented.

8.6.2. Audit

An audit may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

8.7. Statistical Methods

Full details of the statistical analysis are presented in the Statistical Analysis Plan (Appendix 16.1.9).

8.7.1. Statistical and Analytical Plans

8.7.1.1. Analysis Populations

The intention-to-treat (ITT) Population included all randomized subjects. Subjects were analyzed according to planned treatment (randomized group), rather than actual treatment.

The Per Protocol (PP) Population included all randomized subjects who had completed treatment with IMP, had a cMRI at baseline and Day 90 without protocol deviations relevant for efficacy analysis. Decisions on all protocol violations were made on a case-by-case decision in a blinded data review meeting before database closure.

The Safety Population included all randomized subjects who had received at least one dose of IMP, with subjects to be analyzed based on the actual treatment received for safety analysis. The Safety Population was used for all safety analyses.

8.7.1.2. Safety Analysis

Adverse Events

A full list of all the AEs was presented in frequency tables; corresponding details on the subject level were provided in data listings. Categories included the AE overview, AEs by system organ class (SOC) and preferred term (PT) for specific types of AEs (e.g. related AEs, SAEs), AEs by maximum severity and for specific types of AEs, AEs by strongest relationship/ causality and for specific types of AEs, and non-serious treatment emergent AEs occurring in more than 5% of subjects.

Derivations and definitions included the following:

- Percentages for AE frequencies were based on the total number of subjects in the Safety Population
- Adverse events were counted as related if assessed as possibly related or related by the Investigator. For tables by maximum severity and strongest causality, subjects were only counted once in highest grading category and events were counted in each reported grading category
- Adverse events were counted as TEAE if eCRF question “Was this adverse event a TEAE” was ticked with “yes” by the Investigator
- For the analysis of non-SAEs, only AEs (eCRF: Adverse Event page) for which the question “Serious” was ticked with “no” in the eCRF were included
- Adverse events were only included in this analysis if their occurrence by PT in at least one treatment group in the Safety Population was 5% or higher

The Inferential Analysis was performed as follows:

Ninety five percent (95%) confidence intervals according to Altman were provided for the AE summary table. The presence of any AEs and SAEs and other AE rates in the AE summary table were compared between the two groups by means of a Fisher’s exact test as part of the frequency tables. No formal sample size calculation was performed to power this explorative study for assessment for all safety and tolerability endpoints and p-values were interpreted accordingly.

Laboratory Parameters

Laboratory data from scheduled visits were tabulated. Listings included results from unscheduled visits and scheduled visits. Descriptive analyses were done for the clinical chemistry, hematology, and urinalysis laboratory assessments, which were recorded in the eCRF. A full list of the laboratory assessments is presented in the Statistical Analysis Plan.

The following parameters were summarized by time point (for each available time point):

- Actual values
- Change from baseline
- Frequency of values out of normal ranges (for chemistry, hematology and urinalysis) and abnormal results (quantitative and qualitative parameters)
- Urinalysis results (summary statistics for quantitative parameters, frequency statistics for qualitative parameters)
- Listings for abnormal liver enzyme values is defined in the protocol

Derivations and definitions were as follows:

- Absolute change from baseline was calculated as difference from value of the current visit and baseline (pre-dose) value (Day 1). If no pre-dose values were presented, values from the measurement most closely preceding the pre-dose (e.g. Screening) were concerned as baseline
- Listings for abnormal liver enzyme values:
    - First listing of abnormal liver enzymes included all AST and ALT values greater than 8 times ULN (upper limit of normal range, according to local laboratory).
    - Second listing of abnormal liver enzymes were considered the following cases:
        - Aspartate aminotransferase greater than 3 times ULN, and bilirubin greater than 2 times ULN or INR greater than 1.5 times
        - Alanine aminotransferase greater than 3 times ULN and bilirubin greater than 2 times ULN or INR greater than 1.5 times
    - Third listing showed a combination of ALT and AST values greater than 3 times ULN together with the following AEs: fatigue, nausea, vomiting, abdominal pain upper, tenderness, pyrexia, rash, eosinophilia (use MedDRA preferred term). Therefore, such abnormal AST and ALT values were shown together with any of such AEs terms that were recorded as starting prior to or at the respective laboratory blood sampling and not ended before the blood sampling (i.e. being present at blood sampling).

Other Safety Parameters

The following parameters were summarized by time point (for each available time point): vital signs, full physical examination and 12-lead ECG findings.

- Vital signs: systolic blood pressure, diastolic blood pressure, heart rate, and body temperature
- Full physical examination: general inspection, examination of the injection site and draining nodes, head/ears/eyes/nose/throat examination, cardiac examination, auscultation of lungs, abdominal examination (liver, spleen and lower abdomen), assessment for neurological deficits, musculoskeletal assessment
- Twelve-lead ECG findings: actual values (blood pressure, heart rate, and body temperature), change from baseline (blood pressure, heart rate, and body temperature), frequency of abnormal physical examination findings and abnormal clinically relevant examination findings, and frequency of body temperature values greater than 38.6°C

The following information was only listed: abbreviated physical examination and pregnancy test.

8.7.1.3. Efficacy Analysis

The following information was analyzed descriptively per time point for all time points available (absolute values, as well as, absolute change from baseline) and corresponding details on the subject level was provided in data listings. Cardiac magnetic resonance imaging scans of not acceptable quality were only included in listings.

- Cardiac magnetic resonance imaging Core Lab
    - Cardiac magnetic resonance imaging - left ventricular (cMRI LV)
        - End diastolic volume (EDV)
        - End diastolic volume index (EDVi derived)
        - End systolic volume (ESV)
        - End systolic volume index (ESVi derived)
        - Mass (VV; ventricular volume)
        - Mass index (derived)
        - Ejection fraction (EF)
    - Cardiac magnetic resonance imaging - right ventricular (cMRI RV)
        - End diastolic volume
        - End diastolic volume index (derived)
        - End systolic volume

- End systolic volume index (derived)
- Ejection fraction

- Tissue characterization
  - Late gadolinium enhancement (LGE) ventricular scar/fibrosis
  - Number of myocardial segments affected
    - Full width at half maximum (FWHM) late gadolinium enhancement mass (INF; absolute MI size)
    - Relative full width at half maximum late gadolinium enhancement mass (INF/VV, infarct size as a proportion of ventricular volume)
    - 2 Standard deviation (SD) late gadolinium enhancement mass
    - Relative 2 Standard deviation late gadolinium enhancement mass
    - 5 Standard deviation late gadolinium enhancement mass
    - Relative 5 Standard deviation late gadolinium enhancement mass
    - Borderzone mass (2 SD – 5 SD mass)
- Contrast-enhanced steady-state free precession
- Regional wall motion (was listed only)
- Transmural extent (TE) (was listed only)

- Clinical endpoints (two analyses were performed: clinical endpoints up to Day 15 and all reported clinical endpoints)
  - Recurrent non-fatal myocardial infarction
  - Non-fatal stroke
  - Stent thrombosis
  - Hospitalization due to chronic heart failure
  - Cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death)
  - Death due to any (other) cause
- Combined clinical endpoints
- Time to cardiovascular event
- Biomarkers (NTproBNP, High sensitivity troponin)

Definitions

- Cardiac MRI scans were considered as of acceptable quality if the eCRF question “Overall quality of scan acceptable” was ticked with “yes” by the Investigator

- A subject was considered to have fulfilled the combined clinical endpoint if any of the following was reported:
  - Recurrent non-fatal myocardial infarction
  - Non-fatal stroke
  - Stent thrombosis
  - Hospitalization due to chronic heart failure
  - Cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death)
- Clinical endpoints up to Day 15 were only considered clinical endpoints that started within 14 days after first IMP. In case of incomplete dates on the clinical endpoints page and it cannot be decided if the endpoints started within 14 days after first IMP (e.g. by using the reported month and year only), the endpoint was considered up to Day 15
- Time to cardiovascular event, as defined by the time (in days) from Randomization to the first occurrence of one of the clinical endpoints (other than death to any other cause). Subjects without any clinical endpoints reported were censored at last attended visit (last possible visit for this calculation is Day 90 visit since endpoints were not assessed at Day 180)

Inferential Analysis

Changes from baseline in LVEF, left ventricular end systolic volume index (LVESVi), left ventricular end diastolic volume index (LVEDVi), infarct size as a proportion of ventricular volume (INF/VV, ="relative FWHM LGE mass"), myocardial salvage index MSI and absolute MI size (INF, ="FWHM LGE mass") were evaluated for statistical significance using an analysis of covariance model with treatment group as independent variable and the following covariates:

- Relative FWHM LGE mass at Day 3 (INF/VV)
- Myocardial salvage index (derived) at Day 3

Additionally, a Wilcoxon test for unpaired observations were included in summary tables for change from baseline in LVEF, LVESVi, LVEDVi, relative FWHM LGE mass (INF/VV), MSI and absolute MI size (INF= FWHM LGE mass) by time point. Additionally, the number of subjects with a relative FWHM LGE mass (INF/VV) of >19% of the LV measured at Day 90 was tabulated by treatment group. Odds ratios were calculated for the active group against the placebo group, along with its 95% confidence interval.

Presence of individual and combined clinical endpoints on Day 15 and Day 90 were compared between the two groups by means of a logistic regression model with treatment group as independent variable. In addition, Fisher’s exact test to compare the two treatment groups will be included in the frequency tables.

Standard 95% confidence intervals were generally provided for LVEF, LVESVi, LVEDVi, relative FWHM LGE mass (= INF/VV), MSI and absolute MI size (INF= FWHM LGE mass). The 95%-confidence intervals according to Altman were calculated for the presence of individual and combined clinical endpoints.

The time to cardiovascular event was analyzed by means of Kaplan-Meier method (including median time to cardiovascular event per treatment group). A Cox regression model was applied for the time to cardiovascular event using the same covariates as for analysis of covariance models described above. Additionally, a log-rank test was conducted to test significance between treatment groups.

8.7.2. Determination of Sample Size

No formal sample size calculation was performed to power this explorative study for assessment for all safety and tolerability endpoints. Nonetheless, to illustrate, 70 subjects per treatment group were allowed the detection of a difference in AE rates of 15.2% for dutogliptin in co-administration with filgrastim versus 1% for placebo with Fisher's exact test with a power of 80% and a two-sided significance level of 5%.

All efficacy evaluations were secondary objectives and were only to support the design and planning of further studies. Enrolment of 70 subjects per group were for example allowed for the detection of a difference of 3.8 in mean change in LVEF from baseline to 90 days between the two treatment groups with a power of 80% using a t-test with a significance level of 5% (two-sided) and assuming a standard deviation of 7.0 in both groups, as well as, a drop-out rate of 20% (30 subjects) after 90 days.

8.8. Statistical/Analytical Issues

8.8.1. Adjustments for Covariates

No adjustments for covariates were performed in this study.

8.8.2. Handling of Dropouts and Missing Data

Missing values were not imputed. In case of missing seriousness, severity and causality for AEs, a worst case approach was applied.

8.8.3. Interim Analyses and Data Monitoring

No interim analyses were performed in this study.

8.8.4. Multi-center Studies

Since recruitment numbers were expected to be very low at some study sites, it was decided not to use the study site as covariate in the statistical models as planned in the study protocol. Subjects were tabulated by country and by study site. Further details are provided in the overall study design and plan Section 8.1.

8.8.5. Multiple Comparisons

No multiple comparisons were performed in this study.

8.8.6. Use of an "Efficacy Subset" of Subjects

No efficacy subset was used in this study.

8.8.7. Active-Control Studies Intended to Show Equivalence

No equivalence was shown in this study.

8.8.8. Examination of Subgroups

Not applicable.

8.8.9. Tabulation of Individual Response Data

Individual response data are presented in Subject Data Listings section.

8.9. Changes in the Study Plan

8.9.1. Changes in the Conduct of the Study or Planned Analysis

8.9.1.1. Reasons for Early Termination

When the COVID-19 pandemic started in 2020 and based on EMA recommendation to halt clinical studies, enrolment at all sites was stopped for 4 months. When reopened, enrolment was extremely slow. Fewer qualifying patients were admitted to hospital, and of those qualifying, even fewer were willing to give informed consent due to concerns of staying in hospital longer than absolutely necessary and were not willing to have home administration visits by qualified nurses during the ongoing pandemic as before. In addition, sites were unable to dedicate staff for data collection and patient follow-up as required in the protocol.

Since recruitment numbers were expected to be very low at some study sites, it was decided not to use the study site as covariate in the statistical models as planned in the study protocol.

The Sponsor decided to stop recruitment and thus, terminated the study early. For this reason, the following changes were applied:

There was only one statistical analysis after database closure, based on all available data (no separate addendum analysis for Day 180 cMRI data).

Other than a recruitment pause during the COVID-19 pandemic, no impact of the pandemic was observed or was expected at the time of generation of the Statistical

Analysis Plan. No specific analysis was planned to investigate the influence of the pandemic. However, such analyses to investigate, e.g., the treatment effect stratified by infected/non-infected subjects or analyses with imputation of endpoints (due to large portions of missing data), were done post hoc.

8.9.1.2. Cancellation of Pharmacokinetics / Pharmacodynamics

Not performed due to logistical reasons and the early closeout of the study caused by the COVID-19 pandemic.

8.9.1.3. Liver Enzymes Reporting to United States Food and Drug Administration

In an attempt to better distinguish drug induced liver injury from AMI, and in line with the FDA guidance paper on drug induced liver injury, we proposed the following thresholds (results to be confirmed within 48 hours) for the expedited reporting: ALT or AST >8xULN, or ALT or AST >3xULN and (TBL >2xULN, or INR >1.5), or ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). These thresholds would also require discontinuation of treatment. The proposal was approved by communication from the FDA on Sep 30, 2019 and implemented in the Clinical Study Protocol Version 1.3, which has been approved and endorsed by all investigational sites, ethics committees, and local competent authorities.

The results show that there were often rapid and dramatic liver enzyme changes before and after PCI, returning to normal ranges quickly thereafter. These are evidently related to the AMI, and not to the IMPs, which were administered following the occurrence of these events and only for a short time period.

8.9.1.4. Data Safety Monitoring Board Interim Analysis

A first interim safety data analysis (without unblinding the data) was performed on 24 patients and reviewed by the DSMB. The purpose of the data analysis was to detect any safety risks and to validate the new reporting specification agreed with the FDA (to detect drug induced liver injury). The Sponsor and the DSMB concluded that based on these results there are no safety concerns. The data and experience also indicated that new FDA approved definition of reportable cases appeared the best available solution to detect liver injuries caused by the IMP and to avoid inefficient over-reporting. A second interim safety analysis was performed on 30 patients. The DSMB members were able to review unblinded safety data and did not raise any safety concerns.

9. STUDY SUBJECTS

9.1. Disposition of Subjects

A total of 48 subjects (98.0%) were randomized and 47 (95.9%) of these received treatment. A summary of the subject overview information is presented in Table 3.

Table 3 Summary of Subject Overview (All Subjects)

Subject Overview	Active Group (N=26) n (%)	Placebo Group (N=22) n (%)	ITT Population (N=48) n (%)	All subjects (N=49) n (%)
Eligible	26 (100)	22 (100)	48 (100)	48 (98.0)
Randomized	26 (100)	22 (100)	48 (100)	48 (98.0)
Treated	25 (96.2)	22 (100)	47 (97.9)	47 (95.9)
ITT Population	26 (100)	22 (100)	48 (100)	48 (98.0)
Safety Population	25 (96.2)	22 (100)	47 (97.9)	47 (95.9)
PP Population	19 (73.1)	15 (68.2)	34 (70.8)	34 (69.4)

ITT=intention-to-treat, PP=per-protocol, N=number of subjects with events, percentages based on N
Source: Table 14.1.0.1

Subject 0805-001 was included in the All Subjects population but not the ITT population as they were unwilling or unable to comply with the requirements of the study, and therefore withdrew consent to participate and were not randomized (Listing 16.2.1.2 and Listing 16.2.1.3).

All 48 subjects attended Screening and visits up to and including Day 3, 45 subjects (93.8%) attended Day 5 and Day 15 visits, and 40 subjects (83.3%) attended the Day 90 visit (Table 14.1.1.6). In addition, two subjects (4.2%) attended an early termination visit. A summary of subjects by site and country is presented in Table 14.1.0.2; Screening failures and reasons are summarized in Table 14.1.0.3, inclusion/exclusion criteria not met are presented in Table 14.1.0.4, and study administration by time point is presented in Table 14.1.1.5.

Eight subjects underwent early study termination: four in each of the active and placebo groups. The most frequent reason for early termination was “at the request of the sponsor/authority”: one subject in each group. Three subjects were terminated early for “other” reasons, but when listed specifically, each of these occurred in only one subject (MRI failure; not enough IMP at the site for randomization; Sponsor decision to stop IMP).

A summary of subject overview and early termination details information is presented in Table 3 and Table 4, respectively.

Table 4 Summary of Early Termination Details (ITT Population)

Early termination and reasons	Active Group (N=26) n (%)	Placebo Group (N=22) n (%)	ITT Population (N=48) n (%)
Early termination and primary reasons	4 (15.4)	4 (18.2)	8 (16.7)
Withdrawal due to AE	0 (0.0)	1 (25.0)	1 (12.5)
At the request of the sponsor/authority	1 (25.0)	1 (25.0)	2 (25.0)
Study terminated by sponsor	0 (0.0)	1 (25.0)	1 (12.5)
Death	0 (0.0)	1 (25.0)	1 (12.5)
Other	3 (75.0)	0 (0.0)	3 (37.5)
Early terminations with other reason	3 (11.5)	0 (0.0)	3 (6.3)
MRI failure. Not possible to perform MRI within 72 hours after PCI. Sponsor request	1 (33.3)	0 (NC)	1 (33.3)
There was no enough IMP at the site for randomization	1 (33.3)	0 (NC)	1 (33.3)
Sponsor's decision to stop with IMP	1 (33.3)	0 (NC)	1 (33.3)

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, AE=adverse event, MRI=magnetic resonance imaging, PCI=percutaneous coronary intervention, IMP=Investigational medicinal product, NC=not calculable
Source: Table 14.1.1.6

Visit attendance status and early termination details are presented in Table 14.1.2.6 for the Safety Population and in Table 14.1.3.6 for the PP Population.

9.2. Protocol Deviations

A total of 35 subjects (72.9%) had a protocol deviation, although the proportion who had a relevant protocol deviation was lower: 13 subjects (27.1%), compared with those who had a not relevant protocol deviation (29 subjects; 60.4%). The proportion of subjects with protocol deviations was slightly higher in the placebo group than in the active group, more markedly for deviations judged to be not relevant.

A summary of protocol deviations information is presented in Table 5.

Table 5 Summary of Protocol Deviations (ITT Population)

Protocol Deviations	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Any Relevant and not Relevant Protocol Deviations	16 (61.5) 138	19 (86.4) 95	35 (72.9) 233
Not relevant	12 (46.2) 53	17 (77.3) 46	29 (60.4) 99
Relevant	6 (23.1) 85	7 (31.8) 49	13 (27.1) 134

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, Obs=number of events
Source: Table 14.1.1.7

Protocol deviations information for the Safety Population is presented in Table 14.1.2.7 and for the PP Population in Table 14.1.3.7.

9.3. Data Sets Analyzed

The ITT Population comprised 48 subjects (98.0%), the Safety Population 47 subjects (95.9%), and the PP Population 34 subjects (69.4%).

A summary of the subject's overview information is presented in Table 3 in Section 9.1.

9.4. Demographic and Other Baseline Characteristics

9.4.1. Demographic Characteristics

The ITT Population was predominantly male and white, with a mean age of 56.1 years. No notable differences were observed between groups in demographic characteristics. A summary of demographic characteristics information is presented in Table 6.

Table 6 Summary of Demographic Characteristics (ITT Population)

Characteristic	Statistic	Active Group (N=26)	Placebo Group (N=22)	ITT Population (N=48)
Age at Screening [years]	Mean (SD)	55.1 (9.37)	57.2 (12.12)	56.1 (10.66)
Gender				
Male	n (%)	18 (69.2)	16 (72.7)	34 (70.8)
Female	n (%)	8 (30.8)	6 (27.3)	14 (29.2)
Race				
White	n (%)	25 (96.2)	22 (100)	47 (97.9)
Other	n (%)	1 (3.8)	0 (0.0)	1 (2.1)
Body weight at Screening [kg]	Mean (SD)	79.8 (12.24)	75.8 (12.94)	78.0 (12.59)
Body height at Screening [cm]	Mean (SD)	171.4 (10.98)	170.2 (7.41)	170.9 (9.44)

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, SD=standard deviation, kg=kilograms, cm=centimeters
Source: Table 14.2.1.1

Demographic characteristics information for the Safety Population is presented in Table 14.2.2.1 and for the PP Population in Table 14.2.3.1.

9.4.2. Medical History

Metabolism and nutrition disorders were the most frequent SOC with medical history: nine (34.6%) subjects in the active group and 13(59.1%) subjects in the placebo group. Overall, medical history events were generally similar between the two groups although metabolism and nutrition disorders were higher in the placebo group than in the active group, notably for hypercholesterolemia (six [27.3%] subjects versus three [11.5%] subjects) and diabetes mellitus (four [18.2%] subjects versus one [3.8%] subject).

A summary of medical history by SOC and PT information reported by more than one subject is presented in Table 7.

Table 7 Summary of Medical History Reported in More Than One Subject (ITT Population)

Event	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Any event	18 (69.2) 69	20 (90.9) 84	38 (79.2) 153
Metabolism and nutrition disorders	9 (34.6) 14	13 (59.1) 20	22 (45.8) 34
Hypercholesterolemia	3 (11.5) 3	6 (27.3) 6	9 (18.8) 9
Type 2 diabetes mellitus	3 (11.5) 3	3 (13.6) 3	6 (12.5) 6
Diabetes mellitus	1 (3.8) 1	4 (18.2) 4	5 (10.4) 5
Hyperlipidemia	3 (11.5) 3	2 (9.1) 2	5 (10.4) 5
Obesity	2 (7.7) 2	3 (13.6) 3	5 (10.4) 5
Hyperuricemia	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Vascular disorders	8 (30.8) 8	8 (36.4) 8	16 (33.3) 16
Hypertension	8 (30.8) 8	8 (36.4) 8	16 (33.3) 16
Surgical and medical procedures	4 (15.4) 7	7 (31.8) 11	11 (22.9) 18
Cholecystectomy	0 (0.0) 0	4 (18.2) 4	4 (8.3) 4
Cardiac disorders	3 (11.5) 4	4 (18.2) 5	7 (14.6) 9
Acute myocardial infarction	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Musculoskeletal and connective tissue disorders	5 (19.2) 5	2 (9.1) 3	7 (14.6) 8
Spinal osteoarthritis	2 (7.7) 2	1 (4.5) 1	3 (6.3) 3
Osteoarthritis	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Psychiatric disorders	5 (19.2) 6	2 (9.1) 4	7 (14.6) 10
Tobacco abuse	3 (11.5) 3	2 (9.1) 2	5 (10.4) 5
Depression	3 (11.5) 3	1 (4.5) 1	4 (8.3) 4
Respiratory, thoracic and mediastinal disorders	4 (15.4) 5	1 (4.5) 1	5 (10.4) 6
Chronic obstructive pulmonary disease	3 (11.5) 3	0 (0.0) 0	3 (6.3) 3
Blood and lymphatic system disorders	2 (7.7) 2	2 (9.1) 2	4 (8.3) 4
Leukocytosis	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Reproductive system and breast disorders	1 (3.8) 1	3 (13.6) 3	4 (8.3) 4
Benign prostatic hyperplasia	1 (3.8) 1	3 (13.6) 3	4 (8.3) 4
Endocrine disorders	1 (3.8) 1	2 (9.1) 2	3 (6.3) 3
Hypothyroidism	1 (3.8) 1	2 (9.1) 2	3 (6.3) 3
Investigations	0 (0.0) 0	3 (13.6) 3	3 (6.3) 3
C-reactive protein increased	0 (0.0) 0	3 (13.6) 3	3 (6.3) 3

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, Obs=number of events
Source: Table 14.2.1.2

Medical history information for the Safety Population is presented in Table 14.2.2.2 and for the PP Population in Table 14.2.3.2.

9.4.3. Two-Dimensional Echocardiogram

Mean (SD) LVEF at Screening was 38.5 (4.89)% for the active group, and 39.3 (5.52)% for placebo; for the ITT Population, mean (SD) LVEF at Screening was 38.9 (5.15)% (Table 14.2.1.3).

Two-dimensional echocardiogram information for the Safety Population is presented in Table 14.2.2.3 and for the PP Population in Table 14.2.3.3.

9.4.4. Disease History/ Surgery

All 48 subjects had undergone percutaneous coronary intervention (drug-eluting stent type). Most subjects had thrombolysis in myocardial infarction (TIMI) flow grade III (43 [89.6%] subjects). In terms of STEMI symptoms, all 48 subjects had new ST-segment elevation, and most had contiguous precordial/limb leads (39 [81.3%] subjects); 32 of the 34 males in the study had STEMI symptoms at J point and all 14 women had symptoms in leads V2 and V3.

A summary of disease history/ surgery information is presented in Table 8.

Table 8 Summary of Disease History/Surgery (ITT Population)

Disease History/ Surgery	Active Group (N=26) n (%)	Placebo Group (N=22) n (%)	ITT Population (N=48) n (%)
Percutaneous Coronary Intervention (by stent type)			
Drug eluting stent	26 (100)	22 (100)	48 (100)
TIMI flow grade			
2	3 (11.5)	2 (9.1)	5 (10.4)
3	23 (88.5)	20 (90.9)	43 (89.6)
STEMI symptoms			
New ST-segment elevation	26 (100)	22 (100)	48 (100)
At J point (Men)	17 (65.4)	15 (68.2)	32 (66.7)
In leads V2 and V3 (Women)	8 (30.8)	6 (27.3)	14 (29.2)
Contiguous precordial/limb leads	21 (80.8)	18 (81.8)	39 (81.3)

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, TIMI=thrombolysis in myocardial infarction, STEMI=ST-elevation myocardial infarction
Source: Table 14.2.1.4

Disease history/ surgery information for the Safety Population is presented in Table 14.2.2.4 and for the PP Population in Table 14.2.3.4.

9.4.5. Prior Procedures

One subject in each group had previously undergone an angiogram (Table 14.2.1.5). Prior procedures by SOC and PT are presented in Table 14.2.2.5 for the Safety Population and in Table 14.2.3.5 for the PP Population.

9.4.6. Concomitant Procedures

Twelve subjects (25%) underwent investigational concomitant procedures during the study period: six subjects (12.5%) had a chest X-ray, four subjects (8.3%) had an ECG, and three subjects (6.3%) had an angiogram. The proportion of subjects who underwent these procedures appeared slightly higher in the active group, but the small sample size involved makes it difficult to compare the two groups. During the study period, seven subjects (14.6%) underwent surgical and medical procedures, four (8.3%) of whom had a percutaneous coronary intervention and two (4.2%) underwent continuous positive airway pressure.

A summary of concomitant procedures by SOC and PT information reported by more than one subject is presented in Table 9.

Table 9 Summary of Concomitant Procedures in More Than One Subject (ITT Population)

Concomitant procedure	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Any concomitant procedures	9 (34.6) 23	5 (22.77) 33	14 (29.2) 56
Investigations	8 (30.8) 18	4 (18.2) 24	12 (25.0) 42
Chest X-ray	4 (15.4) 6	2 (9.1) 15	6 (12.5) 21
Electrocardiogram	3 (11.5) 5	1 (4.5) 2	4 (8.3) 7
Angiogram	3 (11.5) 3	0 (0.0) 0	3 (6.3) 3
Catheterization cardiac	0 (0.0) 0	2 (9.1) 2	2 (4.2) 2
Ultrasound doppler	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Ultrasound abdomen	1 (3.8) 1	1 (4.5) 1	2 (4.2) 2
Surgical and medical procedures	4 (15.4) 5	3 (13.6) 9	7 (14.6) 14
Percutaneous coronary intervention	2 (7.7) 2	2 (9.1) 2	4 (8.3) 4
Continuous positive airway pressure	1 (3.8) 2	1 (4.5) 1	2 (4.2) 3

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, Obs=number of events
Source: Table 14.2.1.6.

Concomitant procedures by SOC and PT information for the Safety Population are presented in Table 14.2.2.6 and for the PP Population in Table 14.2.3.6.

9.4.7. Prior Medications

Before study initiation, 34 subjects [70.8%] reported taking antithrombotic agents; an equal number of subjects (17) in each treatment group (active vs placebo). The next most frequent classes were cardiac therapy medications (22 [45.8%] subjects), analgesics (18 [37.5%] subjects), calcium channel blockers (15 [31.3%] subjects), blood substitutes and perfusion products (14 [29.2%] subjects), and contrast media (11 [22.9%] subjects. No other classes were taken by more than 20% of subjects overall.

The most frequent medications were antithrombotic agents (34 [70.8%] subjects) followed by opioid analgesics (18 [37.5%] subjects) and vasodilators used in cardiac diseases (16 [33.3%] subjects). There were no notable differences between groups in the frequency of prior medications.

A summary of prior medications by anatomical therapeutic chemical classification (ATC) level 2 and level 3 term information reported by more than 10% of subjects is presented in Table 10.

Table 10 Summary of Prior Medications in More Than 10% of Subjects (ITT Population)

Prior Medications	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Any prior medication	20 (76.9) 155	18 (81.8) 133	38 (79.2) 288
Antithrombotic agents	17 (65.4) 59	17 (77.3) 53	34 (70.8) 112
Antithrombotic agents	17 (65.4) 59	17 (77.3) 53	34 (70.8) 112
Cardiac therapy	11 (42.3) 15	11 (50.0) 18	22 (45.8) 33
Vasodilators used in cardiac diseases	8 (30.8) 8	8 (36.4) 10	16 (33.3) 18
Antiarrhythmics, class I and III	5 (19.2) 5	5 (22.7) 6	10 (20.8) 11
Analgesics	10 (38.5) 13	8 (36.4) 12	18 (37.5) 25
Opioids	10 (38.5) 13	8 (36.4) 10	18 (37.5) 23
Calcium channel blockers	8 (30.8) 8	7 (31.8) 7	15 (31.3) 15
Selective calcium channel blockers with direct cardiac effects	7 (26.9) 7	6 (27.3) 6	13 (27.1) 13
Blood substitutes and perfusion solutions	9 (34.6) 11	5 (22.7) 6	14 (29.2) 17
IV solutions	7 (26.9) 8	3 (13.6) 4	10 (20.8) 12
IV solution additives	3 (11.5) 3	2 (9.1) 2	5 (10.4) 5
Contrast media	6 (23.1) 6	5 (22.7) 5	11 (22.9) 11
X-ray contrast media (iodinated)	6 (23.1) 6	5 (22.7) 5	11 (22.9) 11
Agents acting on the renin-angiotensin system	5 (19.2) 6	3 (13.6) 4	8 (16.7) 10
ACE inhibitors (plain)	4 (15.4) 4	3 (13.6) 4	7 (14.6) 8
Beta-blocking agents	4 (15.4) 4	4 (18.2) 4	8 (16.7) 8
Drugs for acid related disorders			
Drugs for peptic ulcer and gastro-esophageal reflux disease	5 (19.2) 6	3 (13.6) 3	8 (16.7) 9
Antiemetics and antinauseants	2 (7.7) 2	3 (13.6) 3	5 (10.4) 5
Drugs for functional gastrointestinal disorders	4 (15.4) 4	1 (4.5) 1	5 (10.4) 5

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, Obs=number of events, IV=intraventricular, ACE=angiotensin-converting enzyme, Gord=gastro-esophageal reflux disease
Source: Table 14.2.1.7.

Prior medications by ATC level 2 and level 3 term information for the Safety Population is presented in Table 14.2.2.7 and for the PP Population in Table 14.2.3.7.

9.4.8. Concomitant Medications

During the study period, 46 subjects reported taking renin-angiotensin system-acting agents, antithrombotic agents, beta-blocking agents, and lipid-modifying agents, out of which 24 subjects were treated with dutogliptin + filgrastim and 22 were treated with placebo. The next most frequent classes were medications for acid related disorders (43 [89.6%] subjects), diuretics (31 [64.6%] subjects), blood substitutes and perfusion products (21 [43.8%] subjects), mineral supplements (18 [37.5%] subjects), cardiac therapy medications (16 [33.3%] subjects), analgesics (15 [31.3%] subjects), psycholeptics (13 [27.1%] subjects), systematic use antibacterials (11 [22.9%] subjects), and diabetes medication (11 [22.9%] subjects). No other classes were taken by more than 20% of subjects overall.

The most frequent medications were plain angiotensin-converting enzyme inhibitors (46 [95.8%] subjects), antithrombotic agents (46 [95.8%] subjects), beta-blocking agents (46 [95.8%] subjects) and lipid-modifying agents (46 [95.8%] subjects), followed by medications for peptic ulcer and Gord (43 [89.6%] subjects), potassium-sparing diuretic agents (27 [56.3%] subjects), blood substitutes and IV perfusion solutions (18 [37.5%] subjects) and potassium mineral supplement medications (16 [33.3%] subjects). Notable differences between groups in the frequency of concomitant medications were reported for subjects taking potassium-sparing agents (12 [46.2%] vs 15 [68.2%] subjects; active vs placebo group), blood glucose-lowering drugs (1 [3.8%] vs 7 [31.8%] subjects; active vs placebo group) and propulsives (1 [3.8%] vs 4 [18.2%] subjects; active vs placebo group).

A summary of concomitant medications by ATC level 2 and level 3 term information reported by more than 10% of subjects is presented in Table 11.

Table 11 Summary of Concomitant Medications in More Than 10% of Subjects (ITT Population)

Concomitant Medication	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Any concomitant medication	25 (96.2) 490	22 (100) 422	47 (97.9) 912
Agents acting on the renin-angiotensin system	24 (92.3) 46	22 (100) 36	46 (95.8) 82
ACE inhibitors (plain)	24 (92.3) 37	22 (100) 33	46 (95.8) 70
Antithrombotic agents	24 (92.3) 116	22 (100) 85	46 (95.8) 201
Antithrombotic agents	24 (92.3) 116	22 (100) 85	46 (95.8) 201
Beta-blocking agents	24 (92.3) 43	22 (100) 31	46 (95.8) 74
Beta-blocking agents	24 (92.3) 43	22 (100) 31	46 (95.8) 74
Lipid modifying agents	24 (92.3) 32	22 (100) 31	46 (95.8) 63
Lipid modifying agents (plain)	24 (92.3) 32	22 (100) 30	46 (95.8) 62
Drugs for acid related disorders	23 (88.5) 26	20 (90.9) 25	43 (89.6) 51
Drugs for peptic ulcer and gastro-esophageal reflux disease (Gord)	23 (88.5) 26	20 (90.9) 25	43 (89.6) 51
Diuretics	14 (53.8) 70	17 (77.3) 42	31 (64.6) 112
Potassium-sparing agents	12 (46.2) 22	15 (68.2) 19	27 (56.3) 41
High-ceiling diuretics	7 (26.9) 38	8 (36.4) 18	15 (31.3) 56
Blood substitutes and perfusion solutions	11 (42.3) 18	10 (45.5) 23	21 (43.8) 41
IV solutions	9 (34.6) 10	9 (40.9) 13	18 (37.5) 23
IV solution additives	5 (19.2) 8	2 (9.1) 3	7 (14.6) 11
Mineral supplements	10 (38.5) 34	8 (36.4) 12	18 (37.5) 46
Potassium	10 (38.5) 31	6 (27.3) 8	16 (33.3) 39
Other mineral supplements	3 (11.5) 3	3 (13.6) 3	6 (12.5) 6
Cardiac therapy	9 (34.6) 29	7 (31.8) 24	16 (33.3) 53
Vasodilators used in cardiac diseases	6 (23.1) 17	4 (18.2) 5	10 (20.8) 22
Cardiac stimulants (excluding cardiac glycosides)	3 (11.5) 5	4 (18.2) 9	7 (14.6) 14
Analgesics	7 (26.9) 15	8 (36.4) 15	15 (31.3) 30
Other analgesics and antipyretics	6 (23.1) 9	5 (22.7) 7	11 (22.9) 16
Opioids	3 (11.5) 6	5 (22.7) 8	8 (16.7) 14
Psycholeptics	7 (26.9) 10	6 (27.3) 10	13 (27.1) 20
Anxiolytics	4 (15.4) 7	4 (18.2) 4	8 (16.7) 11
Hypnotics and sedatives	2 (7.7) 2	3 (13.6) 5	5 (10.4) 7
Antibacterials for systemic use	5 (19.2) 8	6 (27.3) 14	11 (22.9) 22
Beta-lactam antibacterials (penicillins)	3 (11.5) 5	5 (22.7) 9	8 (16.7) 14
Drugs used in diabetes	4 (15.4) 13	7 (31.8) 13	11 (22.9) 26
Blood glucose lowering drugs (excluding insulins)	1 (3.8) 4	7 (31.8) 11	8 (16.7) 15
Insulins and analogues	4 (15.4) 9	2 (9.1) 2	6 (12.5) 11
Muscle relaxants	2 (7.7) 2	5 (22.7) 6	7 (14.6) 8
Muscle relaxants (centrally active agents)	2 (7.7) 2	4 (18.2) 4	6 (12.5) 6

Concomitant Medication	Active Group (N=26) n (%) Obs	Placebo Group (N=22) n (%) Obs	ITT Population (N=48) n (%) Obs
Drugs for functional gastrointestinal disorders	1 (3.8) 1	5 (22.7) 5	6 (12.5) 6
Propulsives	1 (3.8) 1	4 (18.2) 4	5 (10.4) 5
Calcium channel blockers			
Selective calcium channel blockers with direct cardiac effects	2 (7.7) 3	3 (13.6) 4	5 (10.4) 7

ITT=intention-to-treat, N=number of subjects with events, percentages based on N, Obs=number of events, ACE=angiotensin-converting enzyme, Gord=gastro-esophageal reflux disease, IV=intraventricular
Source: Table 14.2.1.8.

Concomitant medications by ATC level 2 and level 3 term information for the Safety Population is presented in Table 14.2.2.8 and for the PP Population in Table 14.2.3.8.

9.5. Treatment Compliance

All subjects received dutogliptin, filgrastim, or placebo as planned from Day 1 to Day 14 with the exception of the second dutogliptin/placebo dose on Day 3 (received by 44 of 47 subjects), Day 4 (received by 43 of 44 subjects), Day 11 (received by 41 of 42 subjects).

A summary of study treatment administration is presented in Table 14.1.1.5.

10. EFFICACY EVALUATION

10.1. Cardiac Magnetic Resonance Imaging Results over Time for Left Ventricular Parameters

A summary of cMRI results over time for left ventricular parameters (acceptable cMRI scans) is presented in Table 12 and change from Day 3 to Day 90 in cMRI results for left ventricular parameters is presented in Table 13.

In the PP Population, increases in mean change from Day 3 (baseline) against Day 90 values were seen for EDV (placebo group: 13.7, active group: 17.4), EDVI (derived; placebo group: 8.4, active group: 8.6), and EF (placebo group: 5.7, active group: 5.2). Decreases in mean change from baseline values were seen for mass (placebo group: -16.1, active group: -14.4) and mass index (derived; placebo group: -8.3, active group: -7.4). No statistically significant difference was found between treatment groups in change from baseline for left ventricular parameters EDVI (derived), ESVI (derived), and EF over time. P-values were not calculated for other left ventricular parameters.

In the ITT Population, increases in mean change from Day 3 values were seen for EDV, EDVI (derived), and EF parameters in both treatment groups; ESV and ESVI (derived) remained largely unchanged. Mean increases in EDV from Day 3 to Day 90 were 15.7 for the active group and 13.7 for the placebo group; respective values for EDVI (derived) were 7.7 and 8.4. The mean increase from Day 3 for EF was 5.9 for the active group and 5.7 for the placebo group. Decreases in mean change from baseline values were observed for mass and mass index (derived), in both treatment groups. The mean decrease change from baseline in mass was -15.1 for the active group and -16.1 for the placebo group; respective values for mass index (derived) were -7.9 and -8.3.

Wilcoxon test p-values were calculated for EDVI (derived), ESVI (derived), and EF. All p-values showed that there was no statistically significant difference between treatment groups in change from Day 3 for EDVI (derived), ESVI (derived), and EF. Wilcoxon test p-values were not calculated for any other variables.

Table 12 Summary of Mean Cardiac Magnetic Resonance Imaging Results for Left Ventricular Parameters (ITT and PP Populations)

Parameter (unit)	Day	ITT Population Mean (SD) n		PP Population Mean (SD) n	
		Active Group	Placebo Group	Active Group	Placebo Group
EDV (mL)	3	160.6 (40.10) 22	166.3 (41.13) 18	166.5 (39.91) 19	157.6 (29.84) 14
	90	182.3 (43.30) 21	170.0 (29.34) 16	183.8 (40.99) 19	170.2 (30.36) 15
EDVI (derived; mL/m^2)	3	83.5 (17.96) 22	89.2 (21.87) 18	85.9 (18.20) 19	85.5 (16.02) 14
	90	93.4 (18.94) 21	92.5 (19.77) 16	94.5 (18.14) 19	92.7 (20.44) 15
ESV (mL)	3	89.9 (34.37) 22	98.0 (39.07) 18	94.0 (34.97) 19	90.1 (23.20) 14
	90	94.5 (37.37) 21	87.6 (27.15) 16	96.6 (36.83) 19	86.9 (27.93) 15
ESVI (derived; mL/m^2)	3	46.5 (15.84) 22	52.7 (21.23) 18	48.3 (16.24) 19	49.0 (13.36) 14
	90	48.3 (17.97) 21	48.1 (18.02) 16	49.5 (17.76) 19	47.7 (18.60) 15
Mass (g)	3	121.4 (30.83) 22	129.9 (30.99) 18	124.7 (31.72) 19	126.5 (29.16) 14
	90	108.8 (28.96) 21	107.5 (25.78) 16	110.3 (27.97) 19	108.9 (26.08) 15
Mass Index (derived; %)	3	62.7 (11.83) 22	69.5 (16.46) 18	63.8 (12.26) 19	68.4 (15.43) 14
	90	55.5 (12.14) 21	58.2 (13.89) 16	56.4 (11.64) 19	58.9 (14.01) 15
EF (%)	3	44.4 (9.23) 22	42.5 (11.02) 18	43.7 (9.47) 19	43.3 (7.58) 14
	90	49.8 (10.48) 21	49.3 (9.62) 16	48.9 (10.40) 19	49.9 (9.68) 15

ITT=intent to treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, EDV=end diastolic volume, EDVI=end diastolic volume index, ESV=end systolic volume, ESVI=end systolic volume index, VV=ventricular volume, EF=ejection fraction
Source: Table 14.3.1.1, Table 14.3.3.1

Table 13 Summary of Mean Cardiac Magnetic Resonance Imaging Results for Left Ventricular Parameters: Change from Day 3 to Day 90 (ITT and PP Populations)

Parameter (unit)	ITT Population Mean (SD) n		PP Population Mean (SD) n	
	Active Group	Placebo Group	Active Group	Placebo Group
EDV (mL)	15.7 (28.09) 20	13.7 (27.50) 14	17.4 (27.79) 19	13.7 (27.50) 14
EDVI (derived; mL/m^2)	7.7 (14.09) 20	8.4 (15.31) 14	8.6 (13.89) 19	8.4 (15.31) 14
ESV (mL)	1.0 (25.95) 20	-1.2 (26.33) 14	2.6 (25.59) 14	-1.2 (26.33) 14
ESVI (derived; mL/m^2)	0.4 (12.87) 20	0.1 (14.74) 14	1.3 (12.57) 19	0.1 (14.74) 14
Mass (g)	-15.1 (11.42) 20	-16.1 (24.48) 14	-14.4 (11.26) 19	-16.1 (24.48) 14
Mass Index (derived; %)	-7.9 (5.89) 20	-8.3 (14.23) 14	-7.4 (5.73) 19	-8.3 (14.23) 14
EF (%)	5.9 (8.86) 20	5.7 (7.81) 14	5.2 (8.52) 19	5.7 (7.81) 14

ITT=intent to treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, EDV=end diastolic volume, EDVI=end diastolic volume index, ESV=end systolic volume, ESVI=end systolic volume index, VV=ventricular volume, EF=ejection fraction
Source: Table 14.3.1.1, Table 14.3.3.1

Analyses of covariance model data are presented in Table 14.3.1.11 (LVEF), Table 14.3.1.12 (LVESVi) and Table 14.3.1.13 (LVEDVi); no statistically significant effect on these parameters could be demonstrated.

10.2. Cardiac Magnetic Resonance Imaging Results over Time for Right Ventricular Parameters

A summary of cMRI results over time for right ventricular parameters (acceptable cMRI scans) is presented in Table 14 and change from Day 3 to Day 90 in cMRI results for right ventricular parameters in Table 15.

In the PP Population, similar increases were seen in both groups in mean changes from baseline against Day 90 for EDV (placebo group: 16.2, active group: 22.1), EDVI (derived; placebo group: 9.3, active group: 11.0), ESV (placebo group: 7.0, active group: 6.5), and ESVI (derived; placebo group: 0.1, active group: 3.2). Differences between treatment groups were not tested statistically.

In the ITT Population, in general, increases in mean change from Day 3 values were seen for EDV, EDVI (derived), ESV, and ESVI (derived), in both treatment groups. Mean increases in EDV from Day 3 to Day 90 were 22.7 for the active group, and 16.2 for the placebo group; respective values for EDVI (derived) were 11.4 and 9.3. The mean increase from Day 3 in ESV was 6.7 for the active group and 7.0 for the placebo group; for ESVI (derived), a mean increase of 3.4 was observed for the active group, while the placebo group remained unchanged (change from Day 3: 0.1). A mean increase from baseline of 2.7 was reported in EF for the active group and the placebo group remained unchanged (change from Day 3: -0.3). Wilcoxon test p values were not calculated for any right ventricular parameters.

Table 14 Summary of Mean Cardiac Magnetic Resonance Imaging Results for Right Ventricular Parameters (ITT and PP Populations)

Parameter	Day	ITT Population Mean (SD) n		PP Population Mean (SD) n	
		Active Group	Placebo Group	Active Group	Placebo Group
EDV (mL)	3	106.6 (31.11) 22	120.1 (40.95) 18	110.5 (31.52) 19	111.2 (33.03) 14
	90	133.6 (37.87) 21	125.0 (31.12) 16	132.6 (37.48) 19	127.6 (30.47) 15
EDVI (derived; mL/m^2)	3	55.2 (13.39) 22	63.9 (20.14)18	56.8 (13.51) 19	59.8 (15.61) 14
	90	68.1 (15.55) 21	67.4 (15.32) 16	67.8 (15.64) 19	68.8 (14.78) 14
ESV (mL)	3	43.5 (18.51) 22	52.5 (28.61) 18	46.1 (18.48) 19	43.3 (19.52) 14
	90	52.1 (21.20) 21	49.3 (23.02) 16	52.7 (21.66) 19	50.4 (23.32) 14
ESVI (derived; mL/m^2)	3	22.4 (7.91) 22	30.9 (18.10) 18	23.6 (7.79) 19	27.0 (16.45) 14
	90	26.4 (9.23) 21	26.4 (11.45) 16	26.8 (9.45) 19	27.0 (11.55) 14
EF (%)	3	59.7 (7.88) 22	57.9 (14.67) 18	58.4 (7.68) 19	62.1 (10.15) 14
	90	61.9 (6.79) 21	61.8 (8.42) 16	61.3 (6.81) 19	61.7 (8.70) 14

ITT=intent to treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, EDV=end diastolic volume, EDVI=end diastolic volume index, ESV=end systolic volume, ESVI=end systolic volume index, EF=ejection fraction
Source: Table 14.3.1.3, Table 14.3.3.3

Table 15 Summary of Mean Cardiac Magnetic Resonance Imaging Results for Right Ventricular Parameters: Change from Day 3 to Day 90 (ITT and PP Populations)

Parameter	ITT Population Mean (SD) n		PP Population Mean (SD) n	
	Active Group	Placebo Group	Active Group	Placebo Group
EDV (mL)	22.7 (32.45) 20	16.2 (23.19) 14	22.1 (33.23) 19	16.2 (23.19) 14
EDVI (derived; mL/m^2)	11.4 (16.70) 20	9.3 (11.57) 14	11.0 (17.06) 19	9.3 (11.57) 14
ESV (mL)	6.7 (13.06) 20	7.0 (23.52) 14	6.5 (13.39) 19	7.0 (23.52) 14
ESVI (derived; mL/m^2)	3.4 (6.73) 20	0.1 (7.20) 14	3.2 (6.89) 19	0.1 (7.20) 14
EF (%)	2.7 (6.37) 20	-0.3 (11.80) 14	2.8 (6.50) 19	-0.3 (11.80) 14

ITT=intent to treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, EDV=end diastolic volume, EDVI=end diastolic volume index, ESV=end systolic volume, ESVI=end systolic volume index, EF=ejection fraction
Source: Table 14.3.1.3, Table 14.3.3.3

10.3. Tissue Characterization Parameters over Time

A summary of tissue characterization parameters over time (acceptable cMRI scans) is presented in Table 16 and from Day 3 to Day 90 is presented in Table 17.

In the PP Population, decrease in mean change from Day 3 against Day 90 was observed for the following tissue characterization parameters: FWHM LGE mass (INF; placebo group: -12.7, active group: -20.1), relative FWHM LGE mass (INF/VV; placebo group: -6.6, active group: -13.3), 2SD LGE mass (placebo group: -15.3, active group: -19.3), relative 2SD LGE mass (placebo group: -8.2, active group: -11.6), 5SD LGE mass (placebo group: -15.5, active group: -18.8), and relative 5SD LGE mass (placebo group: -9.2, active group: -11.5). Mean change from Day 3 against Day 90 values for border zone mass (2SD-5SD) were very small for both groups. There were no statistically significant differences between treatment groups in change from baseline for FWHM LGE mass and relative FWHM LGE mass. P-values were not calculated for any other tissue characterization parameters.

In the ITT Population, decreases in mean change from Day 3 values were reported for all parameters, in both treatment groups, although the change in borderzone mass (2SD-5SD) was very small. The mean decrease in FWHM LGE mass (INF) was -19.9 for the active group and -12.7 for the placebo group; respective values for relative FWHM LGE mass (INF/VV) were -12.7 and -6.6. The mean decrease in 2SD LGE mass was -19.0 for the active group and -15.3 for the placebo group; respective values for relative 2SD LGE mass were -11.1 and -8.2. The mean decrease in 5SD LGE mass was -18.7 for the active

group and -15.5 for the placebo group; respective values for relative 5SD LGE mass were -11.1 and -9.2. Mean change from Day 3 values for borderzone mass (2SD-5SD) were very small for both groups.

Wilcoxon test p-values were calculated for FWHM LGE mass (INF; p=0.2320), and relative FWHM LGE mass (INF/VV; p=0.2411). Both p-values showed that there was no statistically significant difference between treatment groups in change from baseline for FWHM LGE mass (INF), and relative FWHM LGE mass (INF/VV). Wilcoxon test p-values were not calculated for any other tissue characterization parameters.

Table 16 Summary of Tissue Characterization Parameters over Time (ITT and PP Populations)

Parameter; unit	Day	ITT Population Mean (SD) n		PP Population Mean (SD) n	
		Active Group	Placebo Group	Active Group	Placebo Group
FWHM LGE Mass (INF); g	3	42.2 (25.64) 23	41.0 (27.70) 17	44.3 (26.33) 19	37.6 (25.41) 14
	90	23.1 (15.13) 21	24.1 (16.61) 16	24.2 (15.17) 19	24.1 (17.19) 15
Relative FWHM LGE Mass (INF/VV); %	3	33.2 (19.82) 22	30.1 (16.67) 17	34.8 (20.25) 19	28.4 (15.68) 14
	90	20.5 (12.40) 21	21.6 (13.79) 16	21.5 (12.46) 19	21.2 (14.17) 15
2SD LGE Mass; g	3	48.0 (27.51) 23	49.2 (30.62) 17	50.5 (28.14) 19	45.6 (27.46) 14
	90	29.8 (17.21) 21	29.2 (18.68) 16	31.2 (17.00) 19	29.2 (19.34) 15
Relative 2SD LGE Mass; %	3	37.9 (18.95) 22	36.1 (17.65) 17	39.5 (18.85) 19	34.5 (16.26) 14
	90	26.7 (14.38) 21	26.1 (15.24) 16	27.9 (14.26) 19	25.6 (15.63) 15
5SD LGE Mass; g	3	44.5 (26.57) 23	44.2 (29.29) 17	46.8 (27.32) 19	40.6 (26.72) 14
	90	26.6 (16.53) 21	24.4 (17.30) 16	28.0 (16.46) 19	24.1 (17.86) 15
Relative 5SD LGE Mass; %	3	34.9 (18.34) 22	32.4 (17.41) 17	36.5 (18.40) 19	30.8 (16.45) 14
	90	23.7 (13.58) 21	21.7 (13.94) 16	25.0 (13.54) 19	20.9 (14.06) 15
Borderzone Mass (2SD-5SD); g	3	3.5 (3.19) 23	5.0 (4.77) 17	3.8 (3.41) 19	5.0 (5.02) 14
	90	3.2 (2.70) 21	4.8 (4.92) 16	3.2 (2.69) 19	5.1 (4.94) 15

ITT=intention-to-treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, D3=Day 3, FWHM LGE=full width at half maximum, late gadolinium enhancement, INF=absolute myocardial infarction size, VV=ventricular volume, 2SD=2 Standard deviation, p-values obtained via Wilcoxon test
Source: Table 14.3.1.5, Table 14.3.3.5

Table 17 Summary of Tissue Characterization Parameters from Day 3 to Day 90 (ITT and PP Populations)

Parameter; unit	ITT Population Mean (SD) n		PP Population Mean (SD) n	
	Active Group	Placebo Group	Active Group	Placebo Group
FWHM LGE Mass (INF); g	-19.9 (16.93) 21	-12.7 (17.23) 14	-20.1 (17.04) 19	-12.7 (17.23) 14
Relative FWHM LGE Mass (INF/VV); %	-12.7 (14.58) 20	-6.6 (10.06) 14	-13.3 (10.06) 19	-6.6 (14.74) 14
2SD LGE Mass; g	-19.0 (16.53) 21	-15.3 (16.58) 14	-19.3 (16.93) 19	-15.3 (16.58) 14
Relative 2SD LGE Mass; %	-11.1 (11.53) 20	-8.2 (8.17) 14	-11.6 (11.67) 19	-8.2 (8.17) 14
5SD LGE Mass; g	-18.7 (15.93) 21	-15.5 (15.90) 14	-18.8 (16.16) 19	-15.5 (15.90) 14
Relative 5SD LGE Mass; %	-11.1 (11.00) 20	-9.2 (8.12) 14	-11.5 (11.12) 19	-9.2 (8.12) 14
Borderzone Mass (2SD-5SD); g	-0.3 (2.57) 21	0.2 (6.34) 14	-0.5 (2.55) 19	0.2 (6.34) 14

ITT=intention-to-treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, D3=Day 3, FWHM LGE=full width at half maximum, late gadolinium enhancement, INF=absolute myocardial infarction size, VV=ventricular volume, 2SD=2 Standard deviation, p-values obtained via Wilcoxon test
Source: Table 14.3.1.5, Table 14.3.3.5

Analysis of covariance model data are presented in Table 14.3.1.14 (FWHM LGE) and Table 14.3.1.16 (FWHM LGE mass =INF); no statistically significant effect on these parameters could be demonstrated. Analysis of covariance for MSI was not conducted due to missing Day 90 values (Table 14.3.1.15).

10.4. Contrast-Enhanced Steady-State Free Precession Parameters over Time

Mean values at Day 90 and, therefore, mean change from Day 3 values, were not calculable for the three contrast-enhanced steady-state free precession parameters (area at risk mass, area at risk [derived], and MSI [derived]).

A summary of contrast-enhanced steady-state free precession parameters over time (acceptable cMRI scans) is presented in Table 18.

Table 18 Summary of Contrast-Enhanced Steady-State Free Precession Parameters over Time (ITT and PP Population)

Parameter (unit)	Day	ITT Population Mean (SD) n		PP Population Mean (SD) n	
		Active Group	Placebo Group	Active Group	Placebo Group
Area at Risk Mass (g)	3	61.6 (32.00) 21	64.8 (29.93) 17	64.9 (32.58) 18	61.1 (27.48) 14
	90	NC (NC) NC	NC (NC) NC	NC (NC) NC	NC (NC) NC
Area at Risk (derived; %)	3	46.9 (19.38) 21	48.5 (15.95) 17	48.0 (19.90) 18	47.2 (14.32) 14
	90	NC (NC) NC	NC (NC) NC	NC (NC) NC	NC (NC) NC
MSI (derived; %)	3	35.4 (17.29) 21	37.6 (22.81) 17	34.1 (17.07) 18	39.0 (24.30) 14
	90	NC (NC) NC	NC (NC) NC	NC (NC) NC	NC (NC) NC

ITT=intention-to-treat, PP=per protocol, SD=standard deviation, n=number of subjects with available result, NC=not calculable, MSI=myocardial salvage index
Source: Table 14.3.1.7, Table 14.3.3.7

10.5. Left Ventricular Relative Full Width at Half Maximum Late Gadolinium Enhancement Mass

A summary of patients with left ventricular relative FWHM LGE mass (=INF/VV) >19% (acceptable cMRI scans) is presented for the PP and ITT Populations in Table 19.

In the PP Population, 11 (57.9%) subjects in the active group and eight subjects (53.3%) in the placebo group experienced relative FWHM LGE mass (=INF/VV) >19%; eight (42.1%) subjects in the active group and seven (46.7%) subjects in the placebo group did not. There was no notable difference between treatment groups in subjects who experienced relative left ventricular FWHM LGE mass (=INF/VV) >19%.

In the ITT Population, 20 (54.1%) subjects experienced relative FWHM LGE mass (=INF/VV) >19% and 17 (45.9%) subjects did not. There was no notable difference between treatment groups in subjects who experienced relative left ventricular FWHM LGE mass (=INF/VV) >19%.

Table 19 Summary of Patients with Left Ventricular Relative Full Width at Half Maximum Late Gadolinium Enhancement Mass (=INF/VV)>19% (ITT and PP Population)

Relative FWHM LGE Mass (=INF/VV)	ITT Population n (%)		PP Population Mean (SD) n	
	Active Group	Placebo Group	Active Group	Placebo Group
Yes	11 (52.4)	9 (56.3)	11 (57.9)	8 (53.3)
No	10 (47.6)	7 (43.8)	8 (42.1)	7 (46.7)

FWHM LGE=full width at half maximum, late gadolinium enhancement; INF/VV=infarct size as a proportion of ventricular volume; ITT=intention-to-treat, PP=per protocol population; SD=standard deviation; n=number of subjects with available result, percentages are based on total information is tabulated regarding Day 90.
Source: Table 14.3.1.9, Table 14.3.3.9

10.6. Clinical Endpoints

A summary of clinical endpoints at Day 90 (including clinical endpoints until Day 15) is presented for the PP and ITT Populations in Table 20.

In the PP Population, 19 subjects in the active group and 15 subjects in the placebo group did not experience any of the following events during the study period: non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death); one subject [5.3%] in the active group experience hospitalization due to chronic heart failure and 15 subjects in the placebo group that provided data did not experience any.

In the ITT Population, 23 subjects in the active group and 20 subjects in the placebo group did not experience any of the following clinical endpoints during the study period: non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death). Five subjects did not have the Day 90/Early Termination visit and so were not included in this analysis.

Two subjects who received dutogliptin + filgrastim experienced recurrent non-fatal myocardial infarction. One subject per treatment group was hospitalized due to chronic heart failure. Three subjects who received dutogliptin + filgrastim and one who received placebo reported combined clinical endpoints. When clinical endpoints up to Day 15 were considered, one subject each in the active group experienced recurrent non-fatal myocardial infarction and combined clinical endpoints. One subject in the placebo group died due to another cause.

No statistically significant differences occurred between the two treatment groups for any of the clinical endpoints for either the PP or the ITT Population.

Table 20 Summary of Clinical Endpoints (ITT and PP Population)

Clinical Endpoints		ITT Population n (%)		PP Population n (%)	
		Active Group	Placebo Group	Active Group	Placebo Group
Clinical Endpoints Overall					
Recurrent non-fatal myocardial infarction	No	21 (91.3)	20 (100)	18 (94.7)	15 (100)
	Yes	2 (8.7)	0 (0.0)	1 (5.3)	0 (0.0)
Non-fatal stroke	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stent thrombosis	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization due to chronic heart failure	No	22 (95.7)	19 (95.0)	18 (94.7)	15 (100)
	Yes	1 (4.3)	1 (5.0)	1 (5.3)	0 (0.0)
Cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death)	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death due to any (other) cause	No	23 (100)	19 (95.0)	19 (100)	15 (100)
	Yes	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
Combined clinical endpoints	No	20 (87.0)	19 (95.0)	17 (89.5)	15 (100)
	Yes	3 (13.0)	1 (5.0)	2 (10.5)	0 (0.0)
Clinical Endpoints until Day 15					
Recurrent non-fatal myocardial infarction	No	22 (95.7)	20 (100)	19 (100)	15 (100)
	Yes	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal stroke	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stent thrombosis	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization due to chronic heart failure	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death)	No	23 (100)	20 (100)	19 (100)	15 (100)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death due to any (other) cause	No	23 (100)	19 (95.0)	19 (100)	15 (100)
	Yes	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
Combined clinical endpoints	No	22 (95.7)	20 (100)	19 (100)	15 (100)
	Yes	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)

ITT=intention-to-treat, PP=per protocol, n=number of subjects with events, percentages based on Total, MI=myocardial infarction, CHF=chronic heart failure, p-values obtained via Fisher Exact test
Source: Table 14.3.1.17, Table 14.3.1.19, Table 14.3.3.17 and Table 14.3.3.19

10.7. Time to Cardiovascular Event Estimates

A summary of time estimates to the cardiovascular event is presented for the PP Population in Table 14.3.3.23 and for the ITT Population in Table 14.3.1.23. Quartiles of time to cardiovascular event were not calculable due to too few events.

10.8. Biomarkers

A summary of biomarkers is presented in Table 21.

Sample sizes for biomarker assessments at various time points were low. In the PP Population, decreases in mean change from baseline values were seen for NT-proBNP in both treatment groups over the course of the study. The mean decrease in NT-proBNP from Day 1 to Day 90 was -1287.8 for the active group and -3048.3 for placebo. Mean values for high sensitivity troponin biomarker showed decreases over the course of the study. Change from Day 1 to Day 90 was not calculable for the active group as no subjects provided data.

In the ITT Population, decreases in mean change from baseline values were seen for NT-proBNP in both treatment groups over the course of the study. The mean decrease in NT-proBNP from Day 1 to Day 90 was -1740.0 for the active group and -3048.3 for the placebo group. Mean values for high sensitivity troponin biomarker decreased over the course of the study. Change from Day 1 to Day 90 was -3399.0 for the active group and -9837.8 for the placebo group, although by Day 90 data were available only for one and four subjects, respectively.

Table 21 Summary of Biomarkers (ITT and PP Population)

Biomarkers	ITT Population Mean ([95% CI] Mean]) n		PP Population Mean ([95% CI] Mean]) n	
	Active Group	Placebo Group	Active Group	Placebo Group
NT-proBNP				
Day 1	2515.2 [260.0, 4770.3] 6	3268.1 [808.9, 5727.3] 10	2234.2 [-591.9, 5060.3] 5	3596.7 [925.0, 6268.3] 9
Day 5	1704.6 [368.4, 3040.8] 7	1869.4 [612.8, 3126.0] 8	1652.7 [-0.7, 3306.1] 6	1869.4 [612.8, 3126.0] 8
Day 15	2159.5 [190.9, 4128.1] 8	2700.1 [841.2, 4559.1] 9	2262.0 [-72.4, 4596.4] 7	3016.1 [1027.7, 5004.6] 8
Day 90	792.2 [223.7, 1360.7] 10	1060.0 [55.6, 2064.4] 8	839.0 [202.4, 1475.6] 9	1060.0 [55.6, 2064.4] 8
Change from Day 1 to Day 90	-1740.0 [-4159.5, 679.5] 5	-3048.3 [-5626.0, -470.6] 7	-1287.8 [-4348.2, 1772.7] 4	-3048.3 [-5626.0, -470.6] 7
High sensitivity troponin				
Day 1	3871.0 [1295.8, 6446.2] 6	6489.3 [136.2, 12842.3] 8	4524.8 [68.8, 8980.7] 4	6489.3 [136.2, 12842.3] 8
Day 5	3620.9 [1062.1, 6179.6] 7	2697.6 [858.5, 4536.6] 9	3854.2 [753.8, 6954.6] 6	2697.6 [858.5, 4536.6] 9
Day 15	202.0 [-245.8, 649.8] 4	77.5 [-38.6, 193.6] 6	253.0 [-544.9, 1050.9] 3	90.2 [-57.2, 237.6] 5
Day 90	12.3 [7.0, 17.6] 6	27.8 [4.2, 51.5] 6	11.4 [5.2, 17.6] 5	27.8 [4.2, 51.5] 6
Change from Day 1 to Day 90	-3399.0 [NC, NC] 1	-9837.8 [-25373, 5697.1] 4	NC [NC, NC] 0	-9837.8 [-25373, 5697.1] 4

ITT=intention-to-treat, PP=per protocol, CI=confidence interval, n=number of subjects with available result, Inexact values (e.g., >505) are not included, NT-proBNP=N-terminal pro b-type natriuretic peptide, NC=not calculable
Source: Table 14.3.1.26, Table 14.3.3.26

10.9. Efficacy Conclusions

- Cardiac function and tissue characterization parameters assessed by cMRI show similar positive trends in both treatment groups; no statistically significant differences between groups were detected, possibly due to the smaller sample size
- Especially in the right ventricular parameters multiple positive non-significant trends are seen for the active group compared to placebo revealing a strong trend to more potential effect size in larger MIs, which is of prognostic value for DCM [Doesch, 2014]
- Only two cardiovascular events were observed and therefore no further analysis could be performed
- Biomarkers assessments were optional and infrequently performed, showing improvements with large variability in both treatment groups; no significant differences between groups could be demonstrated

11. SAFETY EVALUATION

11.1. Extent of Exposure

Study treatment administration by time point in the Safety Population is presented in Table 14.1.2.5.

- On Day 3 two (8%) subjects did not receive the second dose of dutogliptin + filgrastim and one subject did not receive the second dose of placebo
- On Day 4 one (4.3%) subject did not receive the second dose of dutogliptin + filgrastim
- On Day 11 one subject did not receive the second dose of placebo

11.2. Treatment-Emergent Adverse Events

11.2.1. Brief Summary of Treatment-Emergent Adverse Events

An overview of all TEAEs reported during the study in the Safety Population is presented in Table 22. No TEAEs led to withdrawal of dutogliptin, filgrastim or placebo.

Table 22 Treatment-Emergent Adverse Events Overview

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any TEAE	17 (68.0) 39	17 (77.3) 54	34 (72.3) 93
Any severe TEAE	2 (8.0) 2	3 (13.6) 4	5 (10.6) 6
Any related TEAE	5 (20.0) 9	3 (13.6) 4	8 (17.0) 13
Any related severe TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any serious TEAE	5 (20.0) 6	4 (18.2) 6	9 (19.1) 12
Any related serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any serious AE	5 (20.0) 6	4 (18.2) 6	9 (19.1) 12
Any TEAE leading to withdrawal of any treatment	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any TEAE leading to withdrawal of dutogliptin	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any TEAE leading to withdrawal of filgrastim	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Any TEAE leading to withdrawal from study	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Related adverse events are events assessed as related or possibly related to investigational medicinal product
Source: Table 14.4.2.1.

11.2.2. Display of Treatment-Emergent Adverse Events

Non-serious TEAEs occurring in more than 5% of subjects are presented in Table 14.4.2.20. Treatment-emergent AEs information reported by more than one subject overall is presented in Table 23.

Treatment-emergent AEs were reported by fewer subjects in the active group than in the placebo group: 17 (68.0%) versus 17 (77.3%), respectively. Cardiac disorders were the most frequently reported TEAEs, reported by six (24.0%) subjects in the active group, compared with five (22.7%) subjects in the placebo group (Table 14.4.2.2).

Table 23 Treatment-Emergent Adverse Events (Safety Population)

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any TEAE	17 (68.0) 39	17 (77.3) 54	34 (72.3) 93
Cardiac disorders	6 (24.0) 7	5 (22.7) 8	11 (23.4) 15
Acute myocardial infarction	2 (8.0) 2	0 (0.0) 0	2 (4.3) 2
Atrial fibrillation	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Investigations	6 (24.0) 7	5 (22.7) 7	11 (23.4) 14
C-reactive protein increased	2 (8.0) 2	3 (13.6) 3	5 (10.6) 5
Hepatic enzyme increased	3 (12.0) 4	2 (9.1) 2	5 (10.6) 6
General disorders and administration site conditions	3 (12.0) 4	7 (31.8) 10	10 (21.3) 14
Pyrexia	2 (8.0) 2	2 (9.1) 3	4 (8.5) 5
Edema peripheral	0 (0.0) 0	2 (9.1) 2	2 (4.3) 2
Infections and infestations	4 (16.0) 4	4 (18.2) 4	8 (17.0) 8
Pneumonia	2 (8.0) 2	3 (13.6) 3	5 (10.6) 5
Psychiatric disorders	3 (12.0) 3	4 (18.2) 4	7 (14.9) 7
Insomnia	1 (4.0) 1	2 (9.1) 2	3 (6.4) 3
Gastrointestinal disorders	1 (4.0) 1	4 (18.2) 4	5 (10.6) 5
Diarrhea	1 (4.0) 1	2 (9.1) 2	3 (6.4) 3
Metabolism and nutrition disorders	2 (8.0) 3	3 (13.6) 6	5 (10.6) 9
Nervous system disorders	3 (12.0) 3	2 (9.1) 2	5 (10.6) 5
Headache	2 (8.0) 2	1 (4.5) 1	3 (6.4) 3
Skin and subcutaneous tissue disorders	2 (8.0) 3	1 (4.5) 1	3 (6.4) 4
Blood and lymphatic system disorders	0 (0.0) 0	2 (9.1) 3	2 (4.3) 3
Thrombocytopenia	0 (0.0) 0	2 (9.1) 2	2 (4.3) 2
Injury, poisoning and procedural complications	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Renal and urinary disorders	0 (0.0) 0	2 (9.1) 2	2 (4.3) 2
Respiratory, thoracic and mediastinal disorders	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Vascular disorders	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Hypotension	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Subjects were counted only once per System Organ Class and Preferred Term
Source: Table 14.4.2.2.

11.2.3. Analysis of Treatment-Emergent Adverse Events

11.2.3.1. Treatment-Related Adverse Events Overall

Five (20%) subjects reported a total of eight TEAEs possibly related to filgrastim (Table 14.4.2.5). Two (8%) subjects reported three TEAEs of increased hepatic enzyme, and TEAEs of increased white blood cell count, headache, contusion, bone pain and skin mass were each reported by one (4%) subject. There were no notable differences between

groups in the frequency of related TEAEs. Treatment-emergent AEs judged to be related or possibly related to IMP are presented in Table 24.

Table 24 Related Treatment-Emergent Adverse Events (Safety Population)

	Active group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any related TEAE	5 (20.0) 9	3 (13.6) 4	8 (17.0) 13
Investigations	3 (12.0) 4	1 (4.5) 1	4 (8.5) 5
Hepatic enzyme increased	2 (8.0) 3	1 (4.5) 1	3 (6.4) 4
White blood cell count increased	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Nervous system disorders	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Headache	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Syncope	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Gastrointestinal disorders	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Nausea	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
General disorders and administration site conditions	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Injection site hematoma	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Infections and infestations	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Gastroenteritis	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Injury, poisoning and procedural complications	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Contusion	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Musculoskeletal and connective tissue disorders	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Bone pain	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Skin and subcutaneous tissue disorders	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Skin mass	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Subjects were counted only once per System Organ Class and Preferred Term
Source: Table 14.4.2.4

When the relationship to the individual study drugs dutogliptin and filgrastim was considered, three (12%) subjects reported a total of seven TEAEs possibly related to dutogliptin (Table 14.4.2.6). Two (8%) subjects reported three TEAEs of increased hepatic enzyme, and TEAEs of increased white blood cell count, gastroenteritis, contusion and skin mass were each reported by one (4%) subject. No subjects reported TEAEs that were considered “related” to dutogliptin. Frequencies of possibly related and related TEAEs were similar between the active and placebo groups. Note: Relationship was judged while treatments were blinded. Treatment-emergent AEs by relationship to IMP are presented in Table 25.

Table 25 Treatment-Emergent Adverse Events by Relationship (Safety Population)

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any TEAE related to filgrastim			
Related	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Possibly related	4 (16.0) 7	2 (9.1) 3	6 (12.8) 10
Unlikely related	1 (4.0) 4	0 (0.0) 1	1 (2.1) 5
Not related	11 (44.0) 27	14 (63.6) 49	25 (53.2) 76
Any TEAE related to dutogliptin			
Related	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Possibly related	3 (12.0) 7	2 (9.1) 3	5 (10.6) 10
Unlikely related	1 (4.0) 3	0 (0.0) 1	1 (2.1) 4
Not related	13 (52.0) 29	14 (63.6) 49	27 (57.4) 78

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Subjects were counted only once in highest grading category, events were counted in each reported grading category
Source: Table 14.4.2.17.

11.2.3.2. Treatment-Emergent Adverse Events by Severity

There were no notable differences between groups in the frequency of TEAEs by severity. Treatment-emergent AEs by severity are presented in Table 26.

Table 26 Treatment-Emergent Adverse Events by Severity (Safety Population)

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any TEAE			
Severe	2 (8.0) 2	3 (13.6) 4	5 (10.6) 6
Moderate	7 (28.0) 14	3 (13.6) 6	10 (21.3) 20
Mild	8 (32.0) 23	11 (50.0) 44	19 (40.4) 67

N=number of subjects with events, percentages based on N, Obs=number of events; TEAE=treatment-emergent adverse event. Subjects were counted only once in highest grading category, events were counted in each reported grading category
Source: Table 14.4.2.12.

Treatment-emergent AEs judged to be related to IMP, by severity, are presented in Table 14.4.2.13 (overall), Table 14.4.2.14 (related to filgrastim) and Table 14.4.2.15 (related to dutogliptin). No TEAEs judged to be related to IMP were of severe intensity. Three (12%) subjects reported four TEAEs of maximum moderate intensity and two (8%) subjects reported four TEAEs of mild maximum intensity that were judged to be related to filgrastim (Table 14.4.2.14). Three (12%) subjects reported five TEAEs of maximum moderate intensity that were judged to be related to dutogliptin (Table 14.4.2.15).

Numbers of subjects with SAEs by maximum severity are summarized in Table 14.4.2.16. One (4%) subject in the active group and three (13.6%) subjects in the placebo group experienced one and four maximum severe SAEs, respectively. Four (16%) subjects in the active group experienced five SAEs of maximum moderate intensity, compared with one (4.5%) subject (two events) in the placebo group. Further details are presented in Section 11.2.4. Two (8.0%) subjects in the active group experienced a TEAE of maximum severe intensity, compared with three (13.6%) subjects in the placebo group (Table 14.4.2.3). No severe TEAE was experienced by more than one subject. Treatment-emergent AEs judged to be of severe intensity are presented in Table 27.

Table 27 Treatment-Emergent Adverse Events of Severe Intensity (Safety Population)

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any severe TEAE	2 (8.0) 2	3 (13.6) 4	5 (10.6) 6
Cardiac disorders	1 (4.0) 1	2 (9.1) 2	3 (6.4) 3
Atrioventricular block complete	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Cardiogenic shock	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Myocardial infarction	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Infections and infestations	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Pneumonia	1 (4.0) 1	1 (4.5) 1	2 (4.3) 2
Renal and urinary disorders	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Acute kidney injury	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Subjects were counted only once per System Organ Class and Preferred Term
Source: Table 14.4.2.3.

11.2.4. Deaths, Serious Adverse Events and Other Significant Treatment-Emergent Adverse Events

11.2.4.1. Listing of Deaths, Other Serious Adverse Events and Other Significant Treatment-Emergent Adverse Events

Deaths

Subject 0201-004 died during the study due to an SAE of pneumonia of severe intensity, which started on Day 4 after first dose of IMP. He had received placebo on Day 1, Day 2, Day 3, Day 5 and Day 15 and the SAE was judged to be unrelated to dutogliptin or filgrastim (Listing 16.2.4.5.1 and Listing 16.2.4.5.2).

Other Serious Adverse Events

Serious TEAEs are presented in Table 28. No subject experienced SAEs that were judged to be related to dutogliptin or filgrastim (Table 14.4.2.8, Table 14.4.2.9, Table 14.4.2.10

and Table 14.4.2.19). The only SAEs experienced by more than one subject were pneumonia (4 [8.5%] subjects) and acute myocardial infarction (2 [4.3%] subjects).

Table 28 Serious Treatment-Emergent Adverse Events (Safety Population)

	Active Group (N=25) n (%) Obs	Placebo Group (N=22) n (%) Obs	Safety Population (N=47) n (%) Obs
Any serious TEAE	5 (20.0) 6	4 (18.2) 6	9 (19.1) 12
Cardiac disorders	4 (16.0) 4	3 (13.6) 3	7 (14.9) 7
Acute myocardial infarction	2 (8.0) 2	0 (0.0) 0	2 (4.3) 2
Angina pectoris	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Cardiac failure acute	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Cardiogenic shock	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Coronary artery stenosis	1 (4.0) 1	0 (0.0) 0	1 (2.1) 1
Myocardial infarction	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Infections and infestations	2 (8.0) 2	2 (9.1) 2	4 (8.5) 4
Pneumonia	2 (8.0) 2	2 (9.1) 2	4 (8.5) 4
Renal and urinary disorders	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1
Acute kidney injury	0 (0.0) 0	1 (4.5) 1	1 (2.1) 1

N=number of subjects with events, percentages based on N, Obs=number of events, TEAE=treatment-emergent adverse event. Subjects were counted only once per System Organ Class and Preferred Term
Source: Table 14.4.2.7 and Table 14.4.2.11.

Other Significant Treatment-Emergent Adverse Events

Subject 0201-015, who was in the placebo group, was withdrawn from the study due to a TEAE of psychotic disorder of moderate severity, which began on Day 5 and was judged not recovered/not resolved at the last visit (Listing 16.2.4.1.1 and Listing 16.2.4.1.2).

Three subjects experienced AST or AST values at least 3 times the upper limit of normal concomitantly with pre-specified TEAEs (Listing 16.2.5.6):

- Subject 0201-004, who was in the placebo group, had an ALT value of 56 U/L (upper limit: 45 U/L) and an AST value of 203 U/L (upper limit: 35 U/L) on Day 3, with a TEAE of fever of 38.5°C. On Day 4 the subject had an ALT value of 47 U/L and an AST value of 116 U/L
- Subject 0201-009, who was in the placebo group, had an ALT value of 100 U/L (upper limit: 35U/L) and AST value of 195 U/L (upper limit: 30 U/L) at Screening, with a TEAE of nausea. On Day 3 the subject had an ALT value of 103 U/L and an AST value of 108 U/L, with a TEAE of fever
- Subject 0201-012, who was in the active group, had ALT values of 51, 85, 64 and 54 U/L (upper limit: 45 U/L), and AST values of 496, 487, 251 and 130 U/L (upper limit: 35 U/L) at Screening, Day 1, Day 2 and Day 3, respectively, while experiencing a TEAE of fever at the same time points

11.2.4.2. Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Treatment-Emergent Adverse Events

Serious AEs are presented by subject in Listing 16.2.4.5.1 and Listing 16.2.4.5.2 presented below.

Active group:

- Subject 0201-005 experienced an SAE of acute myocardial infarction of moderate intensity. The SAE started on Day 8, resolved after 6 days and was judged not related to dutogliptin or filgrastim
- Subject 0201-012 experienced an SAE of pneumonia of severe intensity. The SAE started on Day 1, resolved after 7 days and was judged not related to dutogliptin or filgrastim
- Subject 0703-003 experienced an SAE of acute cardiac failure of moderate intensity, which began on Day 54, resolved after 18 days and was judged not related to dutogliptin or filgrastim. The subject also experienced an SAE of pneumonia of moderate intensity, which began on Day 1, resolved after 21 days and was judged not related to dutogliptin or filgrastim
- Subject 0704-004 experienced an SAE of acute myocardial infarction of moderate intensity, which began on Day 76 and resolved on the same day
- Subject 0706-008 experienced an SAE of coronary artery stenosis of moderate intensity, which began on Day 3, resolved on the same day and was judged not related to dutogliptin or filgrastim

Placebo group:

- Subject 0201-004 experienced a fatal SAE of pneumonia of severe intensity (see Section 12.3.1.1). The SAE started on Day 4
- Subject 0201-008 experienced SAEs of acute kidney injury and cardiogenic shock, both of severe intensity, starting on Day 85 and recovering/resolving at last visit. The subject also experienced an SAE of pneumonia of moderate intensity. The SAE started on Day 0 and was judged to be resolved after 3 weeks
- Subject 0201-015 experienced an SAE of myocardial infarction of severe intensity. The SAE started on Day 1 and resolved on the same day
- Subject 0706-002 experienced an SAE of angina pectoris of moderate intensity, which began on Day 51 and resolved after 3 days

11.2.4.3. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Treatment-Emergent Adverse Events

Numbers of subjects reporting SAEs were similar in the placebo and active groups: four (18.2%) subjects and five (20.0%) subjects, respectively. No subject was withdrawn from

drug treatment or from the study following administration of dutogliptin + filgrastim. No subject died following administration of dutogliptin + filgrastim. No SAE was judged to be related to dutogliptin or filgrastim.

11.2.4.4. Clinical Laboratory Evaluation

Absolute values by parameter and time point for the Safety Population are presented in Table 14.5.2.1, Table 14.5.2.4 and Table 14.5.2.7 for clinical chemistry, hematology and quantitative urinalysis, respectively.

Absolute changes by parameter and time point for the Safety Population are presented in Table 14.5.2.2, Table 14.5.2.5 and Table 14.5.2.8 for clinical chemistry, hematology and quantitative urinalysis, respectively.

Values outside normal range by time point for the Safety Population are presented in Table 14.5.2.3, Table 14.5.2.6 and Table 14.5.2.9 for clinical chemistry, hematology and quantitative urinalysis, respectively.

Qualitative urinalysis results by parameter and time point for the Safety Population are presented in Table 14.5.2.10.

Line graphs for median (interquartile range) of ALT, AST and bilirubin at scheduled study visits are presented in Figure 14.7.1, Figure 14.7.2 and Figure 14.7.3, respectively.

Laboratory Values over Time

There were no evident patterns in absolute values or change from baseline in either group.

Individual Clinically Significant Abnormalities

Percentages of subjects with quantitative and qualitative urinalysis values outside normal range were similar in both groups at Screening, Day 15 and Day 90 (Table 14.5.2.9 and Table 14.5.2.10).

Percentages of subjects with hematology and clinical chemistry values outside normal range at Screening and Day 1, Day 2, Day 3, Day 5, Day 15 and Day 90 were similar in both groups at all time points (Table 14.5.2.3 and Table 14.5.2.6).

Subjects who experienced AST or AST values at least 3 times the upper limit of normal and pre-specified TEAEs are presented in Section 11.2.4.3

Subject 0706-008, who was in the active group, had an ALT value of 194 U/L, more than 3 times the upper limit of normal (upper limit: 40 U/L), an AST value of 620 U/L, more than 3 times the upper limit of normal (upper limit: 37 U/L) and a bilirubin value of 53.1 mg/dL (upper limit: 21 mg/dL) at Day 2 (Listing 16.2.5.5).

Seven subjects in the active group and nine subjects in the placebo group had AST or ALT values greater than 8 times the upper limit of normal (Listing 16.2.5.4).

11.2.4.5. Vital Signs

Vital signs values by parameter (systolic blood pressure, diastolic blood pressure, heart rate, temperature, height and weight) and time point for the Safety Population are presented in Table 14.6.2.1. Absolute changes for vital signs parameters are presented in Table 14.6.2.2.

Clinically relevant vital signs values by parameter and time point for the Safety Population are presented in Table 14.6.2.3.

Placebo group:

- One subject had a clinically relevant heart rate finding at Day 2
- One subject had a clinically relevant temperature finding at Day 3 and Day 5

Active group:

- One subject had a clinically relevant temperature finding at Day 1

11.2.4.6. Twelve-Lead Electrocardiogram

Twelve-lead ECG findings are presented by time point in Table 14.6.2.6. All ECGs were abnormal at Screening. Subjects with abnormal 12-lead ECG findings decreased over the course of the study: numbers of subject after PCI and at Day 1, Day 15 and Day 90, were 39 (83%) subjects, 38 (80.9%) subjects, 31 (77.5%) subjects and 23 (57.5%) subjects of ECGs, respectively in the Safety Population.

Clinically relevant 12-lead ECG findings are presented in Table 29. More subjects had clinically relevant findings at Screening and on Day 1 in the placebo group than in the active group. No subject had clinically relevant findings on Day 15 or Day 90.

Table 29 Clinically Relevant Twelve-Lead Electrocardiogram Findings by Time Point (Safety Population)

Any clinically relevant result	Active Group (N=25) n (%)	Placebo Group (N=22) n (%)	Safety Population (N=47) n (%)
Screening – before PCI			
No	12 (50.0)	6 (27.3)	18 (39.1)
Yes	12 (50.0)	16 (72.7)	28 (60.9)
Total	24	22	46
Screening – after PCI			
No	19 (95.0)	12 (63.2)	31 (79.5)
Yes	1 (5.0)	7 (36.8)	8 (20.5)
Total	20	19	39
Day 1			
No	19 (100)	16 (84.2)	35 (92.1)
Yes	0 (0.0)	3 (15.8)	3 (7.9)
Total	19	19	38
Day 15			
No	17 (100)	14 (100)	31 (100)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Total	17	14	31
Day 90			
No	12 (100)	11 (100)	23 (100)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Total	12	11	23

N=number of subjects with events, percentages based on total, PCI=percutaneous infusion
Source: Table 14.6.2.7.

11.2.4.7. Physical Examination

Physical examination findings by parameter and time point for the Safety Population are presented in Table 14.6.2.4. Clinically relevant physical examination findings are presented in Table 14.6.2.5.

Placebo group:

- One subject had a clinically relevant general inspection finding at Day 15 and Day 90
- One subject had a clinically relevant cardiac examination finding at Day 90
- One subject had a clinically relevant lung auscultation finding at Screening, Day 15 and Day 90
- One subject had a clinically relevant musculoskeletal finding at Day 90

Active group:

- One subject had a clinically relevant injection site/draining node finding at Day 15

11.3. Safety Conclusions

- Treatment-emergent AEs were seen in similar frequencies in the active and placebo group (overall, related, or serious AEs)
- Treatment with dutogliptin in co-administration with filgrastim was well tolerated and no safety issues were detected. There were no clinically or statistically significant differences in safety between active and placebo groups
- There were no deaths or withdrawals in the active group. There was one death in the placebo group

12. DISCUSSION AND OVERALL CONCLUSIONS

12.1. Discussion

The primary objective of this Phase 2, randomized, double-blind, placebo-controlled study was to assess the safety and tolerability of 60 mg dutogliptin (subcutaneous injection, twice daily for 14 days) in co-administration a 5-day course of subcutaneous injections of 10 µg/kg filgrastim (Neupogen) in subjects with STEMI who were successfully re-vascularized following PCI. The placebo group received dutogliptin injections (14 days) in co-administration with filgrastim placebo (5 days) injections.

The primary objective of this Phase 2, randomized, double-blind, placebo-controlled study was to assess the safety and tolerability of 60 mg dutogliptin (twice daily for 14 days) in co-administration with 10 µg/kg filgrastim (5 days), or matching dutogliptin placebo (14 days) in co-administration with matching filgrastim placebo (5 days) subcutaneous in subjects with STEMI who were successfully re-vascularized following PCI and stent implantation. The secondary objective of the study was to explore the efficacy of dutogliptin in co-administration with filgrastim in subjects with STEMI, compared with placebo, based on cMRI assessments, clinical endpoints and biomarkers.

Due to the COVID-19 pandemic, the study had to be closed-out early and therefore the sample size was smaller than planned and clinically meaningful efficacy differences between treatment groups may not have reached statistical significance. A total of 48 subjects (98.0%) were randomized and 47 (95.9%) of these received treatment. The ITT Population was predominantly male and white, with a mean age of 56.1 years. All subjects with STEMI who were successfully re-vascularized following PCI and stent implantation, received study treatment.

Safety:

During the study period, frequencies of TEAEs were similar in both treatment groups (active group: 17 [68.0%] subjects, placebo group: 17 [77.3%] subjects), five subjects had severe TEAEs (active group: 2 [8.0%] subjects, placebo group: 3 [13.6%] subjects), eight subjects had related TEAEs (active group: 5 [20.0%] subjects, placebo group: 3 [13.6%] subjects), and nine subjects had serious TEAEs (active group: 5 [20.0%] subjects, placebo group: 4 [18.2%] subjects). No subjects experienced related severe TEAEs or related serious TEAEs. In addition, no TEAEs led to withdrawal of any treatment (dutogliptin, filgrastim or placebo). There were no statistically significant TEAE differences between treatment groups. No TEAEs were considered “related” to dutogliptin. Frequencies of possibly related and related TEAEs were similar between the active and placebo groups. No TEAEs judged to be related to IMP were of severe intensity.

Furthermore, no subject experienced SAEs that were considered related to dutogliptin or filgrastim. The only SAEs experienced by more than one subject were pneumonia (4 [8.5%] subjects/ 2 in each group) and acute myocardial infarction (2 [4.3%] subjects in

the active group). No subject was withdrawn from drug treatment or from the study following administration of dutogliptin + filgrastim. No subject died following administration of dutogliptin + filgrastim treatment.

One subject in the placebo group had a clinically relevant heart rate finding on Day 2, and another subject had temperature findings on Day 3 and Day 5. One subject in the active group had a clinically relevant temperature finding at Day 1. All 12-lead ECGs were abnormal at Screening. The number of subjects with abnormal 12-lead ECG findings decreased over the course of the study. One subject in the active group had a clinically relevant physical examination of injection site/draining node finding at Day 15. One subject in the placebo group had a clinically relevant general inspection finding at Day 15 and Day 90; a cardiac examination finding at Day 90; a lung auscultation finding at Screening, Day 15 and Day 90, and a clinically relevant musculoskeletal finding at Day 90. All isolated out of range values in laboratory findings, vital signs and ECGs were not considered clinically significant by the Investigator. There were no clinically relevant differences between treatment groups regarding physical examinations, ECGs, or vital signs.

All laboratory safety tests were within acceptable limits, and there were no statistical differences between treatment groups. There were no evident patterns in absolute values or changes from Day 3 (baseline) against Day 90 on any of the assessment days regarding clinical chemistry, hematology and quantitative urinalysis in either treatment group.

Two subjects in the placebo group (ALT values: 56 U/L and 100 U/L respectively, vs first subject upper limit: 45 U/L and second subject upper limit: 35 U/L; AST values: 203 U/L and 195 U/L respectively, vs first subject upper limit: 35 U/L and second subject upper limit: 30 U/L) and one in the active group (ALT values: 51, 85, 64 and 54 U/L vs upper limit: 45 U/L; AST values: 496, 487, 251 and 130 U/L vs upper limit: 35 U/L) experienced ALT or AST values at least 3 times the upper limit of normal concomitantly with pre-specified TEAEs, which were judged to be unrelated to dutogliptin + filgrastim and placebo. Elevated liver enzyme values at the start of the treatment returned rapidly to normal following the PCI and they were judged unrelated to dutogliptin or filgrastim.

Efficacy:

Cardiac Magnetic Resonance Imaging Assessments – Left Ventricular Parameters

More subjects in the active group experienced changes in left and right ventricular parameters over time compared with the placebo group. Increases in mean change from Day 3 (baseline) against Day 90 values were seen for EDV (placebo group: 13.7, active group: 15.7), EDVI (derived; placebo group: 8.4, active group: 7.7), and EF (placebo group: 5.7, active group: 5.9) left ventricular parameters in both treatment groups. Decreases in mean change from baseline values were seen for mass (placebo group: -16.1, active group: -15.1) and mass index (derived; placebo: -8.3, active group: -7.9). No statistically significant difference was found between treatment groups in change from baseline for left ventricular parameters EDVI (derived; p=0.9303), ESVI (derived;

p=0.8201), and EF (p=0.9860) over time. P-values were not calculated for other left ventricular parameters.

Cardiac Magnetic Resonance Imaging Assessments – Right Ventricular Parameters

In ITT population similar increases were seen in both treatment groups in the mean changes from baseline against Day 90 for EDV (placebo group: 16.2, active group: 22.7), EDVI (derived; placebo group: 9.3, active group: 11.4), ESV (placebo group: 7.0, active group: 6.7), and ESVI (derived; placebo group: 0.1, active group: 3.4), in both treatment groups. There were no statistically significant differences between treatment groups.

Cardiac Magnetic Resonance Imaging Assessments – Tissue Characterization Parameters

Tissue characterization parameters over time were reported by a higher number of subjects in the active group compared to the placebo group. Decrease in mean change from Day 3 against Day 90 was observed for the following tissue characterization parameters: FWHM LGE mass (INF; placebo group: -12.7, active group: -19.9), relative FWHM LGE mass (INF/VV; placebo group: -6.6, active group: -12.7), 2SD LGE mass (placebo group: -15.3, active group: -19.0), relative 2SD LGE mass (placebo group: -8.2, active group: -11.1), 5SD LGE mass (placebo group: -15.5, active group: -18.7), and relative 5SD LGE mass (placebo group: -9.2, active group: -11.1). Mean change from Day 3 against Day 90 values for border zone mass (2SD-5SD) were very small for both treatment groups. There were no statistically significant differences between treatment groups in change from baseline for FWHM LGE mass (INF; p=0.2320), and relative FWHM LGE mass (INF/VV; p=0.2411). P-values were not calculated for any other tissue characterization parameters.

Clinical Endpoints

Twenty-three subjects (100%) in the active group and 20 subjects (100%) in the placebo group did not experience any of the following clinical endpoints: non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death), during the study period. Recurrent non-fatal myocardial infarction occurred in one case and hospitalization due to chronic heart failure also in one case (both in the active group). No statistically significant difference between the treatment groups for any of the clinical endpoints observed was found: recurrent non-fatal myocardial infarction (p=0.4906; two (8.7%) in the active group versus no subjects in the placebo group), hospitalization due to chronic heart failure (p=1.0000; one (4.3%) subject in the active group versus one (5.0%) subject in the placebo group), death due to any (other) cause (p=0.4651; no subject in the active group versus one (5.0%) subject in the placebo group), combined clinical endpoints (p=0.6105; three (13%) subjects in the active group versus one (5.0%) subject in the placebo group); up to Day 15, p-values were calculated for recurrent non-fatal myocardial infarction (p=1.0000; one (4.3%) subject in the active group versus no subject in the placebo group), death due to any (other) cause (p=0.4651;

no subject in the active group versus one (5.0%) subject in the placebo group), and combined clinical endpoint (p=1.0000; one (4.3%) subject in the active group versus no subject in the placebo group).

None of the subjects experienced any of the following clinical endpoints: non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death). Recurrent non-fatal myocardial infarction occurred in one case and hospitalization due to chronic heart failure also in one case (both in active treatment group).

Biomarkers

Also, quartiles of time to cardiovascular event were not calculable due to too few events. Sample sizes were low for NT-proBNP and high sensitivity troponin biomarkers assessments at various time points. Decreases in mean change from baseline values were seen for NT-proBNP (placebo group: -3048.3, active group: -1740.0) and high sensitivity troponin (placebo group: -9837.8, active group: -3399.0). Measurements were performed infrequently; results were variable and no statistically significant difference between the treatment groups was seen.

Sample sizes for biomarker assessments at various time points were low. Decreases in mean change from baseline values were seen for NT-proBNP in both treatment groups over the course of the study. The mean decrease in NT-proBNP from Day 1 to Day 90 was -1740.0 for the treatment group and -3048.3 for placebo. Mean values for high sensitivity troponin biomarker showed decreases over the course of the study. Change from Day 1 to Day 90 was -3399.0 for treatment and -9837.8 for placebo, although by Day 90 only one and four subjects provided data for the two groups, respectively.

12.2. Overall Conclusions

Due to the COVID-19 pandemic, the study had to be closed-out early and therefore the sample size is smaller than planned and clinically meaningful differences between treatment groups may not have reached statistical significance. One should however keep in mind that this is an exploratory and not a confirmatory trial.

The two treatment groups were comparable regarding baseline characteristics and concomitant treatments.

Safety:

- Treatment-emergent AEs were seen in similar frequencies in the active and placebo group (overall, related, or serious AEs)
- Treatment with dutogliptin in co-administration with filgrastim was well tolerated and no safety issues were detected. There were no clinically or statistically significant differences in safety between active and placebo groups

- There were no deaths or withdrawals in the active group. There was one death in the placebo group

Efficacy:

- Cardiac function and tissue characterization parameters assessed by cMRI show similar positive trends in both treatment groups; no statistically significant differences between groups were detected, possibly due to the smaller sample size
- Especially in the right ventricular parameters multiple positive non-significant trends are seen for the active group compared to placebo revealing a strong trend to more potential effect size in larger MIs, which is of prognostic value for DCM [Doesch, 2014].
- Only two cardiovascular events were observed and therefore no further analysis could be performed
- Biomarkers assessments were optional and infrequently performed, showing improvements with large variability in both treatment groups; no significant differences between groups could be demonstrated

Forty-eight (48) subjects were enrolled; 47 subjects were randomized, and 47 subjects received the study injections (25 in the active group arm, and 22 in the placebo group). More subjects in the active group (experienced positive changes in left and right ventricular parameters over time compared with the placebo group. Increases in mean change from Day 3 (baseline) against Day 90 values were seen for EDV (placebo: 13.7, treatment: 15.7), EDVI (derived; placebo: 8.4, active: 7.7), and EF (placebo: 5.7, active: 5.9) left ventricular parameters in both groups. Decreases in mean change from baseline values were seen for mass (placebo: -16.1, active: -15.1) and mass index (derived; placebo: -8.3, active: -7.9). Decreases in mean change from baseline values were seen for NT-proBNP (placebo: -3048.3, active: -1740.0) and high sensitivity troponin (placebo: -9837.8, active: -3399.0).

The use of dutogliptin was very safe. None of the subjects in this study experienced non-fatal stroke, stent thrombosis, and cardiovascular death (due to acute MI, CHF, stroke, sudden cardiac death), and there was no statistically significant difference between the active and placebo groups for recurrent non-fatal myocardial infarction (p=0.4906), hospitalization due to chronic heart failure (p=1.0000), death due to any (other) cause (p=0.4651), combined clinical endpoints (p=0.6105). Similar number of subjects reported SAEs in the active and placebo groups, and there were no subjects withdrawn from drug treatment or from the study following administration of the study injections.

Improvement in cardiac tissue health over time were noted in more subjects in the active group than in the placebo group: FWHM LGE mass (INF; placebo: -12.7, active: -19.9), relative FWHM LGE mass (INF/VV; placebo: -6.6, active: -12.7), 2SD LGE mass (placebo: -15.3, active: -19.0), relative 2SD LGE mass (placebo: -8.2, active: -11.1), 5SD LGE mass (placebo: -15.5, active: -18.7), and relative 5SD LGE mass (placebo: -9.2, active: -11.1). NT-proBNP and high sensitivity troponin biomarkers improved more in the active group than in the placebo group (NT-proBNP, active: -1740.0 vs placebo: -

3048.3; and high sensitivity troponin, active: -3399.0 vs. placebo: -9837.8). All together, these data are suggestive of a slowing down of the negative consequence's ischemia and reperfusion injury and of negative remodeling of the LV post MI.

Especially in the right ventricular parameters multiple positive non-significant trends are seen for the active group compared to placebo revealing a strong trend to more potential effect size in larger MIs, which is of prognostic value for DCM [Doesch, 2014].

Considering the morbidity and quality of life years lost post-STEMI and the excellent safety profile of dutogliptin along with data suggesting potential positive effects on cardiac function post administration, study of this therapeutic approach in a large, powered NDA enabling study is warranted.

13. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

13.1. Patient Overview and Baseline Data

Table 14.1.0.2	Patients by Site and Country (All Patients)
Table 14.1.0.3	Screening Failures and Reasons (All Patients)
Table 14.1.0.4	Inclusion/Exclusion Criteria not Met (All Patients)
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15. APPENDICES

15.1. Study Information

15.1.1. Protocol and Protocol Amendments

15.1.2. Sample Case Report Form (Unique Pages Only)

15.1.3. List of Independent Ethics Committees or Institutional Review Boards (plus the Name of the Committee Chair if Required by the Regulatory Authority) - Representative Written Information for Subjects and Sample Consent Forms

15.1.4. List and Description of Investigators and Other Important Participants in the Study, Including Brief Curricula Vitae or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

15.1.5. Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer, Depending on the Regulatory Authority's Requirement

15.1.6. Listing of Subjects Receiving Test Drug(s) / Investigational Product(s) from Specific Batches, where more than one Batch was used

15.1.7. Randomisation Scheme and Codes (Subject Identification and Treatment Assigned)

15.1.8. Audit Certificates (if Available) - NA

15.1.9. Documentation of Statistical Methods

15.1.10. Documentation of Inter-Laboratory Standardisation Methods and Quality Assurance Procedures if Used - NA

15.1.11. Publications Based on the Study - NA

15.1.12. Important Publications Referenced in the Report - NA

15.2. Subject Data Listings

15.2.1. Patient Overview and Baseline Listings

15.2.2. Efficacy Listings

15.2.3. Safety Listings

Listing 16.2.4.1.1	Treatment Emergent Adverse Events (TEAEs) Part I (ITT Population)
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15.3. Case Report Forms - Available on request

15.3.1. Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

15.3.2. Other Case Report Forms Submitted

15.4. Individual Subject Data Listings (United States Archival Listings) - Available on request