CTC North

Randomized, double-blinded, controlled trial of intravenous iron in patients with cardiovascular disease and concomitant iron deficiency

Clinical Study Report

EudraCT-No.	2015-005744-34
Protocol-No.	Sponsor: iCHF-2 / CRO: CTC151164
Version / Date	1.0 / 15-DEC-2022
Study Phase	Phase IV
Study Start and Completion Date	Study start (first patient firs visit, FPFV): 28-FEB-2019 Last patient last visit (LPLV): 15-DEC-2021; the study was terminated early due to poor recruitment, largely due to the COVID-19 pandemic.
Sponsor	University Medical Center Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
Coordinating Principal Investigator	Mahir Karakas, MD, MBA (LKP) University Heart Center Hamburg Department of General and Interventional Cardiology E-Mail: m.karakas@uke.de Phone: +49 (0) 40 7410 - 57975
Deputy	Dirk Westermann, MD University Heart Center Hamburg Department of General and Interventional Cardiology E-Mail: d.westermann@uke.de Phone: +49 (0) 40 7410 - 58206

2 SYNOPSIS

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Ferinject®		
Name of Active Ingredient: Ferric carboxymaltose (FCM)		
Study Title	Randomized, double-blinded, controlled trial of intravenous iron in patients with cardiovascular disease and concomitant iron deficiency	
Coordinating Principal Investigator	Mahir Karakas, MD	
Substantial Amendments to Study Protocol	No substantial amendments were made, therefore not applicable.	
Publication (reference)	NA	
Protocol No.	iCHF-2 (Sponsor), CTC151164 (CRO)	
EudraCT-No.	2015-005744-34	
Study Period	Date of FPFV: 28-Feb-2019 LPLV: 15-Dec-2021; the study was terminated early due to poor recruitment, primarily due to the COVID-19 pandemic.	
Phase of development	Phase IV	
Primary Objective	The primary objective of the iCHF-2 trial was to show that treatment of patients with cardiovascular disease and concomitant iron deficiency (ID) with i.v. iron (ferric carboxymaltose, FCM) versus control (i.v. NaCl) can improve functional status.	

Methodology	A prospective, multicenter, double-blind, parallel group, randomized, controlled, interventional clinical trial. After an initial screening period (up to 10 days for cohort A, and up to 60 days for cohorts B and C) eligible patients were randomized (1:1) to i.v. FCM or i.v. control (0.9 % NaCl-solution) administration on top of usual care. Randomization was performed electronically in the eCRF via SecuTrial according to an external list which was prepared and loaded into the eCRF by the unblinded statistician and data manger, respectively. Patients were planned to be followed-up until the last patient recruited had completed 12 months' (cohort A and cohort C) or 36 months' (cohort B) of follow-up. Cohort B was terminated early. Patients in cohort B dropped-out of the clinical trial after visit 6. They participated in the planned end-of-study visit. **Cardiac MRI protocol** MRI was only performed in cohorts A and C. MRI´s were performed on dedicated 1.5 or 3.0 Tesla scanners as locally available. The basic protocol included: • Standard SSFP short- and long axis cine-MRI for the assessment of cardiac volumes, mass and function. • Standard black-blood (BB) T2 weighted (T2w) MRI on end-diastolic LV short-axes using a fat suppressed (STIR) triple inversion-recovery turbo-spin-echo sequence to quantify myocardial edema in AMI patients. • Phase-Sensitive Inversion Recovery (PSIR) LGE imaging to assess myocardial viability on end-diastolic short-axes images. • T1-mapping (optional, if locally available), preferably by using a Modified Look Locker Inversion Recovery (MOLLI) sequence with a "5(3)3" scheme on three representative short-axis positions. Sufficient image quality of the trial sites was assessed by the core lab on anonymized test scans in order to ensure a standardized and high data quality. **Cardiac MRI analysis** All measurements were performed by a core lab with experienced observers (at least SCMR/ESC/DGK/DRG level 2 competence) who were blinded to all patient information by using the commercially available and well-established software cmr42 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The following MRI parameters were obtained in agreement with current post-processing recommendations (www.scmr.org): • LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), LV mass index (LVMi), LV stroke volume index (LVSVi) and LV ejection fraction (LVEF) as well as RV end-diastolic volume index (RVEDVi), RV end-systolic volume index (RVESVi), RV stroke volume index (RVSVi), RV ejection fraction (RVEF) and left atrial volume index (LAVi) by cine MRI. • Myocardial edema/area-at-risk (AAR) by using a semi-automated threshold method ("+2SD threshold" relative to remote myocardium).

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	• Infarct size as mass and its ratio to normal myocardium by using a semi-automated threshold method (“+5SD threshold” relative to remote myocardium). Presence of microvascular obstruction. Myocardial salvage index (MSI) calculated as “AAR” minus “infarct size” divided by “AAR”. If available, native myocardial T1 and extracellular volume fraction (ECV) in the infarct area, in remote myocardium and globally.	

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Number of patients	**Planned:** n = 240 (cohort A n = 70, cohort B n = 100, cohort C n = 70) **Assessed for eligibility:** n = 8 **Screened:** n = 8 **Randomized:** n = 7 **Dosed:** n = 7 **Completed:** n = 1 **Early terminated :** n = 3 **Discontinued:** n = 3	
Indication	Cardiovascular disease and concomitant iron deficiency	
Main criteria for inclusion	**Key inclusion criteria:** 1. Cohort A (CAYAN): AMI within 10 days (randomization / first iron supplementation / MRI had to be performed within 10 days after AMI), without prior heart failure (defined as any known previous report of LVEF ≤ 45 %) Cohort B (JOANNA): Paroxysmal AF or persistent AF; of these 100 patients Cohort C (SINAN): LVEF ≤ 45 % (documented within the last 12 months prior to screening), all NYHA classes allowed 2. Confirmed presence of ID (ferritin < 100 ng/mL or ferritin 100-299 ng/mL with transferrin saturation [TSAT] < 20 %) 3. Hemoglobin ≤ 15.5 g/dL 4. Written informed consent **Key exclusion criteria:** 1. Evidence of iron overload or disturbances in the utilization of iron 2. History of severe asthma, eczema or other atopic allergy 3. History of immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) 4. Use of renal replacement therapy 5. Treatment with an erythropoietin stimulating agent (ESA), any i.v. iron and/or a blood transfusion in the previous 4 weeks prior to randomization	

<table>
<tr><td>Name of Sponsor/Company:
University Medical Center Hamburg-Eppendorf</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Ferinject®</td><td></td><td></td></tr>
<tr><td>Name of Active Ingredient:
Ferric carboxymaltose (FCM)</td><td></td><td></td></tr>
<tr><td>Test product, dose and mode of administration, batch no.</td><td colspan="3">Test product: Ferric carboxymaltose (FCM)

The sites were provided with the test product. FCM was labelled in accordance with local study site regulations for investigational medicinal products.

Dose: On day 1, patients randomized to FCM received an initial single dose of 1000 mg iron as FCM. If the iron deficiency exceeded 1000 mg, which was expected in 50 % of eligible patients, FCM supplementation was repeated by an optional administration of 500-1000 mg within the first 4 weeks (up to a total maximum dose of 2000 mg) according to approved dosing rules.

Bolus dosing of investigational medicinal product dossier

<table>
<tr><th rowspan="2">Hb at inclusion</th><th colspan="2">Weight < 70 kg</th><th colspan="2">Weight ≥ 70 kg</th></tr>
<tr><th>Hb < 10 g/dL</th><th>Hb ≥ 10 g/dL</th><th>Hb < 10 g/dL</th><th>Hb ≥ 10 g/dL</th></tr>
<tr><td>Baseline</td><td>1000 mg</td><td>1000 mg</td><td>1000 mg</td><td>1000 mg</td></tr>
<tr><td>Week 4</td><td>500 mg</td><td>No dose</td><td>1000 mg</td><td>500 mg</td></tr>
</table>

This was followed by administration of 500 mg FCM, except when hemoglobin rose > 16.0 g/dL or ferritin rose > 600 µg/L.

Mode of administration: i.v.

Batch no: 7120112AVA</td></tr>
<tr><td>Duration of treatment</td><td colspan="3">The clinical trial was planned for 48 months. It included a pre-study screening period (10 days cohort A and 60 days cohort B and C), a double-blind treatment period which consisted of five visits (visit 1 at D1, visit 2 at week 4, visit 3 at month 4, visit 4 at month 8 and visit 5 at month 12) for all patients (cohort A, B and C) and four additional visits (visit 6 at month 18, visit 7 at month 24, visit 8 at month 30 and visit 9 at 36 months) only for patients in cohort B and a follow-up period. The follow-up period lasted until the last patient recruited had completed 12 months' (cohort A and C) or 36 months' (cohort B) follow-up.

The treatment duration of intervention per patient was in accordance to the product information of FCM (max. 15 min). Repetitive treatment was continued during the entire duration of follow-up.</td></tr>
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Reference product, dose and mode of administration, batch no.	**Reference product:** NaCal (normal saline) The sites used the reference product from own stocks, this was not provided by the sponsor. **Dose:** 0.9 % w/v NaCl as sterile solution in water for infusions (100 mL per administration). **Mode of administration:** i.v. **Batch no:** 1940002	

Criteria for evaluation Efficacy and Safety	Efficacy • Primary endpoints in the three study cohorts: **Cohort A (CAYAN):** Condition: Acute Myocardial Infarction (AMI); **C**omprehensive **A**ssessment of iron supplementation in m**Y**ocardi**A**l infarctio**N** • Change from baseline to week 16 in left-ventricular ejection fraction (LVEF) as determined by cardiac-myocardial infarction (MRI) **Cohort B (JOANNA)**: Condition: Atrial Fibrillation (AF); **J**oint evaluation **O**f mechanism of **A**actio**N** and efficacy of iro**N** in **A**trial fibrillation • Delta between treatment groups in burden of atrial fibrillation from day 90 to 365 as assessed by a routinely implanted event recorder **Cohort C (SINAN)**: Condition: Heart Failure with reduced Ejection Fraction (HFrEF); **S**upplementation of **I**ro**N** in he**A**rt failure with reduced ejection fractio**N** Change from baseline to week 16 in LVEF as determined by cardiac-MRI • Cohort-specific secondary endpoints: • **Cohort A (CAYAN):** Change from baseline to week 16 in myocardial salvage, extent of myocardial scar, and area at risk as determined by cardiac magnetic resonance imaging (MRI) • **Cohort B (JOANNA):** Burden of AF between day 90 and day 365, burden of AF between day 90 and day 730, burden of AF between day 90 and day 1,095 (or maximum day of event recording). Disease burden. Arrhythmic burden other than AF between day 90, day 365, day 730 and day 1,095 (or maximum day of event recording) • **Cohort C (SINAN):** Change from baseline to week 16 in myocardial salvage, extent of myocardial scar, and area at risk as determined by cardiac MRI • General secondary endpoints, stratified for each cohort: 1. Change in ventricular and atrial diameters, and change of mass index from baseline to follow-up cardiac MRI (only **cohorts A and C**) 2. Change of glomerular filtration rate (as determined by Cystatin C-based calculation) from baseline to week 16, and from baseline to week 52 3. Change of New York Heart Association (NYHA) class from baseline to week 16, and from baseline to week 52 4. Change of distance walked at 6-minute walk test from baseline to week 16, and from baseline to week 52 5. Change of cardiometabolic and transcriptomic biomarkers (troponin T, N-terminal pro-brain natriuretic peptide [NT-proBNP]) from baseline to week 16, from baseline to week 52 and year 3 in **cohort B** 6. Change from baseline to week 16, and from baseline to week 52 regarding quality of life (QoL) questionnaire (EQ-5D), patients' global assessment (PGA)

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questionnaire, questionnaire for sleep quality (Pittsburgh Sleep Quality Index; PSQI), questionnaire for cognitive impairment (mini-mental state exam; MMSE), and questionnaire for depression (Becks depression inventory; BDI)

7. Percentage of patients meeting key safety endpoints defined as time to death, hospitalization for worsening heart failure, myocardial infarction, unscheduled coronary revascularization, atrial fibrillation (only **cohort A and cohort C**), ventricular fibrillation, cardiac arrest, stent thrombosis, stroke, cardiac death, or death

The above-mentioned primary results were pre-specified. The database was locked and analyzed. Nevertheless, all patients were planned to be followed until month 12 (cohorts A and C) or month 36 (cohort B).

Safety was ascertained via the assessment of key safety endpoints.

<u>Safety endpoints for tolerability included:</u>

- All adverse events (AEs)
- All serious adverse events (SAEs; including deaths and hospitalizations with date-change – all had to be adjudicated)
- Observation of episodes of anaphylactoid reactions or symptomatic hypotension after i.v. iron infusions

Planned Statistical Methods	**Efficacy / test accuracy:** The statistical analysis of the primary endpoint was planned to be performed using an ANCOVA model adjusted for baseline. The primary analysis was planned to be adjusted for the stratification factors of the randomization. Randomization was carried out centrally using a computerized system. A block randomization procedure was applied with stratification by sex and type of AF (only in cohort B: lone AF versus all-comer AF). **Description of the primary efficacy / test accuracy analysis and population:** The primary analysis population was planned for intention-to-treat. **Effect size assumed for power calculation:** Cohort A (CAYAN) and Cohort C (SINAN): The sample size calculation was based to evaluate an effect of an expected delta between the means of 3.5 % LVEF by a t-test. The standard deviation was given by 4.3 % LVEF (American College of Cardiology statement on vascular imaging with cardiac MRI, JACC 2007). Using a two-sided significance level of 5 % and a power of 80 % 25 patients per group would have been required. Compensating some drop-outs and variability between the centers 35 patients per group / per cohort for recruitment were chosen. Cohort B (JOANNA): The primary objective was to evaluate the burden of AF. AF burden is defined as total time in AF divided by the total time in sinus rhythm as assessed by 9 months' continuous rhythm monitoring. Endpoint definition: Only adjudicated episodes were planned to use for the analysis. An AF episode was defined as an AF event lasting more than 30 seconds. Atrial flutters were not be considered as primary endpoints. Analysis methods: AF burden was planned to be compared between the two treatment arms using a permutation test. Only adjudicated AF episodes was planned to use for analysis. Since this was the first analysis of its kind, exploratively 50 patients per group were chosen. A blinded sample size review was planned to be performed once 4-months data (day 120) were available in 40 patients. **Safety:** Adverse event data was planned to be summarized by treatment group using standard procedures. The primary analysis population was planned to for intention-to-treat. All details on the analyses, including the definition of the analysis populations, were detailed in a statistical analysis plan, which was finalized prior to database lock and unblinding. **Secondary endpoints:** The analysis of the secondary endpoints followed the same lines of analyses of the primary outcome assessment. The time to first event outcomes should be analyzed using the Cox proportional hazards model.

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	Due to recruitment problems, it was decided to terminate the clinical trial prematurely. Therefore, the planned statistical analysis according to the current version of the protocol (Version 5.0 from 14 Dec 2018) was not possible. Tables of safety events were provided and only descriptive analysis was performed.	

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Efficacy Results	The primary objective of the iCHF-2 trial was to show that treatment of patients with cardiovascular disease and concomitant iron deficiency (ID) with i.v. iron (FCM) versus control (i.v. NaCl) can improve functional status. The primary and secondary endpoints were planned to be analyzed based on the intention-to-treat (IIT) population. The efficacy analysis of the clinical trial was based on 240 enrolled patients. The primary objective was not met and the primary and secondary endpoints were not reached, due to poor recruitment rates mostly due to the COVID-19 pandemic and early termination. In addition, due to slow recruitment the scientific question was outdated as in the meantime four significantly larger clinical trials started to evaluate the efficacy of FCM in patients with cardiological diseases. Proceeding with this reported clinical trial would have been unethical, thus it was terminated. An efficacy analysis based on the protocol was not possible.	

Safety Results

The clinical trial was performed without any major safety issues in 7 patients. The study medication was well tolerated. No deaths occurred during the trial.

An overview of the number of observed SAEs and AEs is shown in the Table below.

Characteristic	CAYAN (Cohort A), N = 1	JOANNA (Cohort B), N = 4	SINAN (Cohort C), N = 2
Number of observed SAE	0	5	2
Number of observed AE	0	7	1
Patients with SAE	0 (0%)	4 (100%)	1 (50%)
Patients with AE	0 (0%)	4 (100%)	1 (50%)

In this trial, a total of 7 SAEs were reported in 5 patients. Five SAEs were reported for Cohort B (4 patients, 100%) and 2 SAEs were reported for Cohort C (1 patient, 50%). None of the reported SAE was documented for patients from Cohort A.

In total, 8 AEs were reported in 5 patients. In the Cohort B a total of 7 AEs occurred in 4 patients (100%), in the Cohort B a total of 1 AE occurred in 1 (50%). None of the reported AE was documented for patients from Cohort A.

All of the reported SAEs were considered to be “not related” to the IMP. Relationship, severity and outcome of SAEs are shown in the Table below. Of the reported SAEs, 4 SAEs belonged to the System Organ Class (SOC) *Cardiac disorders*, 2 to *Neoplasms benign, malignant, and unspecified*, and 1 to *Renal and urinary disorders*. The SAEs “Atrial fibrillation”, “Cardiac failure”, “Myocardial infarction” and “Cardiac failure acute” belonged to the SOC *Cardiac disorders*. The SAE “Skin cancer” and “Basal cell carcinoma” belonged to the SOC *Neoplasms benign, malignant, and unspecified* and the SAE “Acute kidney injury” belonged to the SOC *Renal and urinary disorders.*

Of the AEs, which met the criteria of an SAE, 3 AEs were of moderate severity and 4 AEs were of severe intensity.

Most of the reported SAE(s) could been recovered within the study (Cohort B: 4 AEs, 80%; Cohort C: 2 AEs, 100%). One AE (20%, Cohort B) was recorded as recovering.

SAEs per Cohort			
Characteristic	CAYAN (Cohort A), N = 0	JOANNA (Cohort B), N = 5	SINAN (Cohort C), N = 2
Relationship between Event and IMP FCM			
Not related (no reasonable possibility)	0	5 (100%)	2 (100%)
AE severity			
Moderate	0	3 (60%)	0 (0%)
Severe	0	2 (40%)	2 (100%)
Outcome:			
Recovered/resolved	0	4 (80%)	2 (100%)

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Recovering/resolving	0	1 (20%)	0 (0%)

All of the reported AEs were considered to be “not related” to the IMP. Relationship, severity and outcome of AEs are shown in the Table below. Of the reported AEs, 2 AEs belonged to the SOC *Cardiac disorders* (“Atrial fibrillation”), 2 to *Respiratory, thoracic and mediastinal disorders* (“Epistaxis” and “Pleural effusion”), 2 to *Infections and infestations* (“Pneumonia” and “Urinary tract infection”), 1 to *Musculoskeletal and connective tissue disorders* (“Muscle spasms“)and 1 to *Ear and labyrinth disorders* (“Vertigo”).

Three AEs were of mild intensity and 5 AEs were of moderate severity.

Most of the reported AE(s) could been recovered within the study (Cohort B: 4 AEs, 57%; Cohort C: 1 AE, 100%). Three AEs (43%, Cohort B) were recorded as ongoing.

AEs per Cohort			
Characteristic	CAYAN (Cohort A), N = 0	JOANNA (Cohort B), N = 7	SINAN (Cohort C), N = 1
Relationship between Event and IMP FCM			
Not related (no reasonable possibility)	0	7 (100%)	1 (100%)
AE severity			
Mild	0	3 (43%)	0 (0%)
Moderate	0	4 (57%)	1 (100%)
Outcome:			
Not recovered/not resolved/ongoing	0	3 (43%)	0 (0%)
Recovered/resolved	0	4 (57%)	1 (100%)

No episodes of anaphylactoid reactions or symptomatic hypotension after i.v. iron infusions were observed.

No safety concerns raised at any time during conduct of the clinical trial.

Conclusion	The aim of this phase IV, randomized, double-blinded, controlled trial was to show that treatment of patients with cardiovascular disease and concomitant ID with i.v. iron (FCM) versus control (i.v. NaCl) can improve functional status. Due to the premature termination and enrollment of only 7 patients, no efficacy analysis was performed in this clinical trial. Although the inclusion and exclusion criteria were determined in close cooperation with the involved study sites who are experienced in conducting clinical studies, the planned number of patients' recruitment was not achieved. The possible reasons might be: • Corona pandemic situation, which hindered patient recruitment and continuous conduct of the trial • The clinical trial was a functional study with a complex procedure (including serial cardio-MRI), which meant that the effort required under pandemic conditions had been disproportionately high. • There were other clearly larger endpoint studies to evaluate the efficacy of FCM in cardiology patients As the efficacy analysis was based on enrollment of 240 patients, due to poor recruitment and premature termination of this trial an analysis of the efficacy according to protocol was not possible. Hence, the primary and secondary objectives of the trial were not achieved. Overall, the safety evaluation revealed that the study medications were generally well tolerated in all 7 patients. The clinical trial was performed without major safety issues. The study medications were well tolerated and no deaths were reported. The reported 7 SAEs during the trial conduct were considered to be "not related" to the IMP, respectively. In total, 8 AEs were reported during the clinical trial, whereas the majority of the AEs occurred in the treatment group JOANNA Cohort B. The 'relationship between event and IMP FCM' were assessed as "not related" for all reported AEs. In total, the 'relationship between event and IMP FCM' was reported in zero patients (0 %). Otherwise, in most of the patients, physical examinations were reported as normal at all visits or the reported abnormal findings were evaluated as not clinically significant by investigator. However, some abnormal reported findings were evaluated as clinically significant. In all cases, no medical measures were required. There were no relevant clinically significant changes in clinical laboratory parameters and vital signs when comparing pre-study and post-study results. No safety concerns raised at any time during conduct of the clinical trial. In conclusion, the primary objective of this trial was not achieved due to the premature termination, poor recruitment and insufficient number of patients required for the efficacy analysis. The study medications were well tolerated and safe. However, further investigations with sufficient number of patients are needed to confirm this statement.

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Date of Report	15-DEC-2022	
Substantial Amendments	Change of Principal Investigator at Site 02 – Universitätsklinikum Ulm (new Principal Investigator: PD Dr. med. Dominik Buckert / former Principal Investigator: Dr. med. Sinisa Marcovic).	

3 LIST OF INVESTIGATORS

Coordinating Principal Investigator
Mahir Karakas, MD, MBA (LKP)
University Heart Center Hamburg
Department of General and Interventional Cardiology

Deputy:
Dirk Westermann, MD
University Heart Center Hamburg
Department of General and Interventional Cardiology
Investigator

Clinical CRO
CTC North GmbH
at the University Medical Center Hamburg-Eppendorf
Martinistr. 64, 20251 Hamburg
Germany

Steering Committee Head:
Mahir Karakas, MD, MBA
University Heart Center Hamburg
Martinistraße 52
20246 Hamburg, Germany

Further cohort-specific members of steering committee (alphabetical order):

Hamburg	Other sites
Stefan Blankenberg, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	Stefan Anker, MD Charite Berlin (CVK) Augustenburger Platz 1 13353 Berlin, Germany
Peter Clemmensen, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	Ulf Landmesser, MD Charite Berlin (CBF) Hindenburgdamm 30 12203 Berlin, Germany
Nils Gosau, MD University Heart Center Martinistraße 52	Alexander Lauten, MD Charite Berlin (CBF) Hindenburgdamm 30

20246 Hamburg, Germany	12203 Berlin, Germany
Gunnar Lund, MD University of Hamburg Martinistraße 52 20246 Hamburg, Germany	David Leistner, MD Charite Berlin (CBF) Hindenburgdamm 30 12203 Berlin, Germany
Christian Meyer, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	Sinisa Markovic, MD University of Ulm Albert-Einstein-Allee 23 89081 Ulm, Germany
Renate Schnabel, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	Wolfgang Rottbauer, MD University of Ulm Albert-Einstein-Allee 23 89081 Ulm, Germany
Enver Tahir, MD University of Hamburg Martinistraße 52 20246 Hamburg, Germany	
Dirk Westermann, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	
Stephan Willems, MD University Heart Center Martinistraße 52 20246 Hamburg, Germany	
Tanja Zeller, PhD University Heart Center Martinistraße 52 20246 Hamburg, Germany	

Sites and participating Investigators:

Site 01 **Universitätsklinikum Hamburg-Eppendorf**

Klinik für Allgemeine und Interventionelle Kardiologie
Universitäres Herzzentrum Hamburg
Martinistraße 52
20251 Hamburg

Principal Investigator: PD Dr. med. Mahir Karakas, MBA
Deputy: Prof. Dr. med. Dirk Westermann

Investigator:
Dr. Susanne Schmitt
Dr. Benedikt Schrage (FEB2019 – DEC2021)
Dr. Felix Stangl (FEB2019 – DEC2021)
Johannes Geng (FEB2019 – SEP2020)
Dr. Sarina Schäfer (FEB2019 – DEC2021)
Dr. Ulf Radunski (FEB2019 – MAR2020)
Prof. Dr. Gunnar Lund (FEB2019 – DEC2021)
Dr. Enver Tahir (FEB2019 – DEC2021)
Dr. Simon Winkelmann (JAN2020 – DEC2021)
Dr. Tobias Tönnis (JAN2020 – DEC2021)
Dr. Nina Fluschnik (JAN2020 – DEC2021)
Dr. Fabian Brunner (JAN2020 – DEC2021)

Site 02	**Universitätsklinikum Ulm**
	Klinik für Innere Medizin II Albert-Einstein-Allee 23 89081 Ulm
	Principal Investigator: Dr. med. Sinisa Markovic (JUL2020 – MAR2021) PD Dr. med. Dominik Buckert (APR2021 – JAN2022)
	Deputy: Dr. med. Mirjam Keßler
	Investigator: PD Dr. med Dominik Buckert (JUL2020 – MAR2021) Dr. med. Dr. univ. Leonhard-Moritz Schneider Dr. med. Karolina Weinmann Dr. med. Nicoleta Nita Matthias Gröger (APR2021 – JAN2022) Florian Schösser (APR2021 – JAN2022)