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CLINICAL TRIAL PROTOCOL

Trial ID: EMPATICC (INCOR1)

Empower the Heart of Patients with Terminal Cancer using Cardiac Medicines Trial

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AGREEMENT ON THE PROTOCOL

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1. SYNOPSIS

Name of Sponsor: Universitätsklinikum Essen	Trial ID: EMPATICC (INCOR1)
Title of the trial: Empower the heart of patients with terminal cancer using cardiac medicines trial	
Trial design: This is a multi-center, prospective, controlled, double-blind, 1:1 randomised, 2-arm parallel, interventional clinical pilot trial. The intervention group will receive optimised heart failure (HF) therapy (incl. sacubitril/valsartan, ivabradine, ferric carboxymaltose and empagliflozin). The optimised therapy will be compared to usual care (1:1 randomisation). The treatment duration is 30 days (randomised phase) followed by an open-label extension phase with optimised therapy in all patients for additional 30 days.	
Trial centres: <ul style="list-style-type: none"> - Klinik für Kardiologie und Angiologie, Westdeutsches Herz- und Gefäßzentrum Essen, Universitätsklinikum Essen, Hufelandstrasse 54, 45147 Essen, Germany - Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany - Klinik für Kardiologie, Angiologie und Pneumologie, Medizinische Klinik Innere III, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 410. 69120 Heidelberg - Innere Medizin III, Universitätsklinikum des Saarlandes, Kirrberger Str. 100, 66421 Homburg/ Saar - Klinik und Poliklinik für Anästhesiologie und Intensivtherapie, Universitätsklinikum Leipzig, Liebigstr. 20, 04103 Leipzig 	
Coordinating investigator: Prof. Dr. Tienush Rassaf, Klinik für Kardiologie und Angiologie, Universitätsklinikum Essen, Germany Principal investigators: Dr. Markus Anker, Medizinische Klinik für Kardiologie (CBF), Charité Universitätsmedizin Berlin, Germany Prof. Dr. med. Lorenz Lehmann, Innere Medizin III/ Kardiologie, Universitätsklinikum Heidelberg, Germany Prof. Dr. Michael Böhm, Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/ Saar, Germany Prof. Dr. Sven Bercker, Klinik und Poliklinik für Anästhesiologie und Intensivtherapie, Universitätsklinikum Leipzig, Germany	
Trial population: Patients with terminal cancer in palliative care	
Key objectives: Primary objective: To improve the self-care ability and self-reported health care status of patients with terminal cancer in palliative care. Secondary objectives: To improve disease-specific measures of quality of life, symptom status and functional capacity of patients with terminal cancer in palliative care.	
Key endpoints: Primary endpoint: <ul style="list-style-type: none"> - Days alive and able to wash themselves since baseline during 30 days of follow-up [(definition of “washing themselves”: patient performed act of washing by him/her-selves 	

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without interference of staff (regardless of whether as shower or bath, on a sink, or using a “sponge bath” in the bed)]

Secondary endpoints:

- Days alive and able to wash themselves since baseline
- PGA of well-being on days 10, 20 and 30 vs baseline (7-point Likert scale & death)
- 4m-walking speed on days 10, 20 and 30 (minimum difference to declare superiority 0.3 sec) [walking ability & time are assessed starting in a still standing position – timing starts with the first foot movement and ends when one foot completely crossed the 4m-finishing line – times are used to calculate walking speed. Test is performed twice at each time point and the average time is calculated. The walking speed of patients not able to walk 4 m will be set to zero]
- Change in Eastern Co-operative Oncology Group (ECOG)-Performance-Status
- Change in Karnofsky-Performance-Status
- Change in Quality of life (QoL) overall status – assessed using the following questionnaires: EORTC-QLQ-C15-PAL, Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), Palliative Prognostic Score (PaP)
- Change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Change in left ventricular ejection fraction (LVEF)
- Change in glomerular filtration rate (eGFR)

Safety:

- All-cause mortality
- Reported AEs and SAEs (including, but not limited to acute kidney injury, hypoglycaemia, hyperkalaemia, symptomatic hypovolaemia and hypotension)

Key inclusion and key exclusion criteria:

Inclusion criteria:

Basic Criteria:

- Patients with solid cancer in Union internationale contre le cancer (UICC) stage 4 (in palliative care)
- 3-6 months expected survival (minimum 4 weeks) as assessed according to local standards
- Patients under optimised analgetic therapy

Group 1 Criteria:

- Heart rate >70 bpm
- NT-proBNP >600 pg/ml
- Elevated high-sensitive troponin (>99th percentile of respective test)
- LVEF <55%
- Heart failure with preserved ejection fraction (HFpEF) likelihood medium or large
- Evidence of left ventricular (LV) mass reduction >15% since start of cancer
- Iron deficiency (ID) with transferrin saturation (TSAT) <20%

Group 2 Criteria:

- 4 m walking time (≥ 6.0 secs for 4m - test will be performed twice and the average time is calculated) or not able to walk 4m at all.
- Not being able to wash oneself in at least 3 of the last 7 days
- Presence of shortness of breath (SoB) (NYHA IV)

Requirement for inclusion:

At least two fulfilled criteria of Group 1 PLUS at least one fulfilled criterion of Group 2

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Exclusion criteria:

- Previous participation in this trial. Participation is defined as randomised
- Ongoing haemodialysis
- Patients currently on intravenous iron
- Acute sepsis with at least 2 points at the quick sequential organ failure assessment (qSOFA) score. The use of i.v.-antibiotics is permitted in patients with a lower qSOFA score.
- Ongoing acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Acute ST elevation myocardial infarction (STEMI) or severe pulmonary embolism (PE) or severe deep vein thrombosis (DVT) (currently or in last 4 weeks)
- Current uncontrolled cerebral metastasis
- Impaired neurological status, precluding the ability to walk
- Unable or unwilling to give written informed consent
- Participation in other interventional trials using investigational products in randomised settings

Sample size:

72 subjects are planned to be randomised.

Optimised medical treatment (in addition to usual cancer therapy in the palliative care setting):

All medication in the optimised treatment will be given as per label and at approved doses. Patients with contraindications to any medication of the optimised treatment will not receive the respective treatment.

The optimised treatment consists of:

1. Sacubitril/valsartan: The starting dose will be 24/26mg sacubitril/valsartan twice daily. The target dose will be at the discretion of the unblinded cardiology team physician, but will not exceed 97/103mg sacubitril/valsartan twice daily. Patients already receiving ACE-inhibitors or Angiotensin-Renin-Blockers will be changed to sacubitril/valsartan.
2. Ivabradine: Ivabradine will be given to all patients with a heart rate ≥ 75 per minute. The starting dose will be 5 mg ivabradine twice daily. The target dose will be at the discretion of the unblinded cardiology team physician, but will not exceed 7.5 mg Ivabradine twice daily.
3. Ferric carboxymaltose (FCM): FCM will be given in all patients with iron deficiency defined as TSAT $< 20\%$. As per label, the individual iron need for repletion will be determined based on the patient's body weight and haemoglobin (Hgb) level:

Hgb		Patient body weight		
g/dL	mmol/L	below 35 kg	35 kg to <70 kg	70 kg and above
<10	<6.2	500 mg	1,500 mg	2,000 mg
10 to <14	6.2 to <8.7	500 mg	1,000 mg	1,500 mg
≥ 14	≥ 8.7	500 mg	500 mg	500 mg

Ferinject will be administered by intravenous infusion (diluted in 0.9% m/V sodium chloride solution). The maximum single dose is 20 mg iron/kg body weight, but will not exceed 1,000 mg iron. The FCM dose will be split in patients with an iron need above 1,000 mg with a maximum dose of 1,000 mg at the first application and the remaining dose one week later.

4. Empagliflozin: will be given at a dose of 10 mg once daily. Patients with contraindications, in particular with regard to renal and hepatic impairment, will not receive empagliflozin.

Reference treatment:

- Placebo

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Duration of treatment:

- 30 days (randomised phase).
- Open-label extension phase: additional 30 days.

After the end of the study extension phase, the treating palliative care oncologists will be informed of the ongoing treatment scheme of patients alive and requested to continue this therapy as needed and as per the patients' wishes.

Assessments:

After informed consent is obtained, inclusion/exclusion-criteria will be checked, and baseline assessments will be performed. Patients will be randomised to one of two treatments (optimised/standard care), which will be followed for 30 days (randomisation phase). During this phase patients will undergo various assessments for outcome parameters on days 10, 20, and 30. The randomisation phase is followed by an open label extension phase with all patients receiving optimised heart failure therapy for additional 30 days, with assessments taking place on days 40, 50 and 60.

Statistical method(s):

It is planned to randomise 72 patients in a 1:1 fashion, i.e. 36 in the intervention group and 36 in the usual care (control) group.

This is a pilot study. Precise power calculations for this study are limited by the very restricted availability of prior data regarding test reproducibility and expected treatment effects. Data on mean/median effects and inter-subject variability are taken from a yet unpublished retrospective survey in terminally ill patients at Charité - Universitätsmedizin Berlin (Dr. Markus Anker, Prof. Dr. Stefan Anker).

Based on these data, a sample size of 58 completing patients would have a power of 85% to detect a difference of 5 days in the primary endpoint (days alive and able to wash themselves) between the two treatment groups using the Wilcoxon-Mann-Whitney-Test at a two-sided alpha level of 0.05 and assuming a standard deviation of 6 days in this parameter. 72 subjects will be included in the trial assuming a drop-out-rate of about 20% in this highly vulnerable population. Primary and secondary endpoints will be compared between the intervention and the control group using non-parametric tests (e.g., Wilcoxon signed-rank test). To minimise the impact of drop-outs that do not provide any data for the primary endpoint statistical procedures such as the win-ratio approach might be used in case of substantial numbers of drop-outs. The decision whether or not to use the win-ratio approach or other procedures will be made before database lock. Details will be given in the Statistical Analysis Plan.

If the study hypothesis holds true, a clinically meaningful and statistically significant improvement of self-care ability, self-reported quality of life, functional status and cardiac function of patients in the intervention group is to be expected.

Randomisation:

Balanced group characteristics are of key importance in such small studies. To this end, minimization with residual randomness (of 15%) will be used. The minimization approach via a dedicated randomisation tool will be used to ensure adequate balance between groups for the following variables: age, sex, body mass index, tumour aetiology, clinical status (ECOG, Karnofsky-Index, self-care ability), presence of co-morbidities (T2DM, anaemia, iron deficiency), screening NT-proBNP level and prior cardiovascular therapy.

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2. SCHEMATIC TRIAL OVERVIEW

The information given in this section are considered the master representation of the trial schedule. In case of (apparent) inconsistencies in the trial protocol the information provided in Sections 2.2 is the binding one.

2.1. Chronological Structure of the Trial

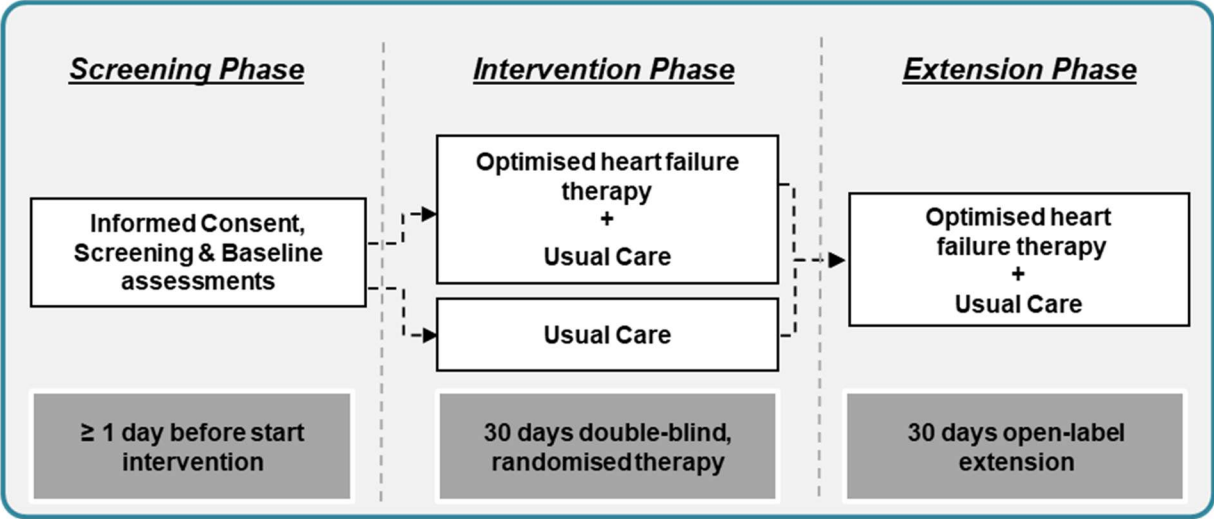


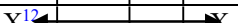



Figure 1 Schematic Overview of the Chronological Structure of the Trial

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2.2. Trial Flow Chart

Table 1 Trial Flow Chart

Description	Screening Phase	Base-line	Intervention Phase Day 1 to 30			Extension Phase Day 31 to 60			
Timing	1-4 days before baseline		± 2 days			± 2 days			
Day(s)	-4 to -1	1 ¹	10	20	30	31	40	50	60
Informed consent	X ²								
Inclusion/exclusion criteria	X								
Demographic data	X								
Concomitant illness and medical history ³	X								
Weight, height	X ⁴	X ⁵			X ⁵				X ⁵
Vital signs ⁶	X ⁴	X	X	X	X		X	X	X
ECG	X ⁴	X ⁴	X	X	X		X	X	X
4 meter walking test ⁷	X	X	X	X	X		X	X	X
Washing ability assessment	X	X	X	X	X		X	X	X
Laboratory tests ⁸	X ⁴	X	X		X		X		X
Echocardiography	X ⁴	X ⁴			X				X
Performance status and QoL questionnaires ⁹		X	X		X		X		X
PGA			X	X	X		X	X	X
Adverse event reporting ¹⁰									
Randomisation		X ¹							
Study treatment (optimised care/placebo)		X ¹¹				X			
Study treatment (optimised care)						X ¹²			
Recording of changes in concomitant medication ¹³	X								

- Baseline assessments will be done in the morning. Randomisation will be done and study medication will be administered immediately after completion of baseline assessments
- Informed consent has to be signed (with date and time) before any trial related activity
- Including, but not limited to UICC stage; expected survival time as assessed according to local standards; pain management; COPD status; SoB (NYHA IV); cerebral metastasis; neurological status; sepsis assessment (qSOFA), DVT, PE, tumour aetiology
- Assessments done within the last 7 days before screening for which results are available do not have to be repeated. Screening ECG and echocardiography, if available, will be used for baseline assessment. If ECG or echocardiography are not available from screening or the last 7 days before screening, these assessments must be done at baseline before first dosing of study medication.
- Weight only
- Blood pressure, pulse rate, in ear temperature
- Test for walking ability and speed. The speed of patients not being able to walk 4 meters will be set to zero
- NT-proBNP, high-sensitive troponin T/I, iron, transferrin, ferritin, blood cell count, Hgb (g/dl), TSAT (%), C-reactive protein (mg/dl), electrolytes (potassium, sodium, chloride), creatinine, eGFR, albumin, glucose, HbA1c, additional sample for later analysis in particular of cardiovascular and metabolic biomarkers. Blood loss will be about 30 mL per sampling
- To be filled out by subject (with or without help from physician): EORTC-QLQ-C15-PA (on days with PGA, PGA will be answered first). To be filled out by physician in the given order: ECOG-Performance-Status, Karnofsky-Performance-Status, Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), Palliative Prognostic Score (PaP).
- Adverse events will be reported from randomisation until the last visit
- Optimised care or placebo will be administered from Day 1 to Day 30
- Optimised care will be administered to all patients from Day 31 to Day 60
- Changes in concomitant medication from screening will be recorded from baseline until the last visit of each individual. Only newly started or stopped medication will be documented. Dose changes will not be documented.

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3. INTRODUCTION

3.1. Background Information

The pathophysiological implications of various cancer diseases and anti-cancer therapies is the occurrence of a cardiac disease-like phenotype with cardiac dysfunction, cardiac wasting, and cardiac homeostasis changes (incl. fibrosis and apoptosis) in end-stage cancer patients, causing heart failure like syndrome with development of congestion, dyspnoea and severely reduced physical functioning (1).

Unpublished data from 95 consecutive, prospectively included end-stage cancer patients with median survival 2 months (50 males/45 females; age 66 ± 11 years, BMI 23 ± 5 kg/m²). Most common cancer diagnoses included: lung, pancreatic, colorectal, breast, kidney, and prostate cancer, as well as non-Hodgkin-lymphoma (each approx. 10%). 68% of cancer patients had hs-Troponin T >14 ng/L (i.e. above the upper limit of normality, ULN); and 38% of cancer patients had a NT-proBNP >900 ng/L. 9% of these cancer patients presented with a left ventricular ejection fraction (LVEF) $<50\%$. Valvular heart disease \geq Grade 1 was frequent in these cancer patients (92%), of which the most prevalent were: tricuspid insufficiency (80%), mitral insufficiency (81%), and aortic insufficiency (43%). Pericardial effusion ≥ 3 mm was found in 37%. Shortness of breath (\geq NYHA II) was reported in 93% of patients.

Cardio-oncology is gaining increasing relevance with the advancement of medical therapy for cancer patients. This is reflected by the current ESC and DGK position paper on cardio-oncology (2, 3). It has been estimated that deaths due to cardiovascular illness are the 2nd most frequent cause of death after infection (4). Precise estimates are difficult, as there is rarely event adjudication in studies of patients with cancer, but it has been estimated that 20-30% of patients with cancer die due to cardiovascular co-morbidities. Clinically, it is a frequent observation that end-stage cancer patients very often show dyspnoea, reduced physical endurance, and die suddenly.

It is also known that cardiac wasting occurs in advanced cancer which has been documented in preclinical models (5) and humans (6). This is due to local wasting processes involving inflammatory cytokines and local neurohormonal activation. Changes in the interstitial cardiac milieu resulting in mitochondrial and myocardial cell death may be one important substrate of cardiac wasting in cancer patients. In addition, in animal models, onco-metabolites have been shown to cause cardiac dysfunction (7). Such mechanisms could also trigger cardiac dysfunction (via increases of left ventricular wall stress) in patients suffering from malignant carcinomas independent of chemotherapy related toxicity. Lastly, it is well known, that some anti-cancer therapies (e.g. anthracyclines, immunotherapies, antibodies, alkylating agents, and tyrosine kinase inhibitors (2, 8, 9) can cause additional damage to cardiomyocytes resulting in cardiotoxicity.

No studies, yet, have focused on improving dyspnea and physical functioning in end-stage cancer patients with very low life expectancy in the palliative care setting using therapies that are typically indicated for heart failure.

3.2. Rationale for the Trial

It is known that cardiac wasting occurs in advanced cancers (5, 6). Many contributing factors have previously been discussed (7). No studies have focused on alleviating these patho-mechanisms to reduce cardiac dysfunction and dyspnoea in cancer patients. As compared to usual care, optimised medical treatment with a therapeutic scheme that includes sacubitril/valsartan, ivabradine, i.v. iron (ferric carboxymaltose), and/or the SGLT2-inhibitor empagliflozin could reduce dyspnoea and

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increase physical functioning in end-stage cancer patients which would result in better self-care ability and better self-reported health care status.

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4. OBJECTIVES AND ENDPOINTS

4.1. Objectives

4.1.1. Primary Objective:

- To improve the self-care ability and self-reported health care status of patients with terminal cancer in palliative care.

4.1.2. Secondary Objective:

- To improve disease-specific measures of quality of life, symptom status and functional capacity of patients with terminal cancer in palliative care.

4.2. Endpoints

4.2.1. Primary Endpoints:

- Days alive and able to wash themselves since baseline during 30 days of follow-up
[(definition of “washing themselves”: patient performed act of washing by him/her-selves without interference of staff (regardless of whether as shower or bath, on a sink, or using a “sponge bath” in the bed)]

4.2.2. Secondary Endpoints:

- Days alive and able to wash themselves since baseline (analysed if win-ratio approach will be used for the primary endpoint, see Section [13.4.1](#))
- PGA of well-being on days 10, 20 and 30 (7-point Likert scale & death)
- 4m-walking speed on days 10, 20 and 30 (minimum difference to declare superiority 0.3 sec) [walking ability & time are assessed starting in a still standing position – timing starts with the first foot movement and ends when one foot completely crossed the 4m-finishing line – times are used to calculate walking speed. Test is performed twice at each time point and the average time is calculated. The walking speed of patients not able to walk 4 m will be set to zero]
- Change in Eastern Co-operative Oncology Group (ECOG)-Performance-Status
- Change in Karnofsky-Performance-Status
- Change in Quality of life (QoL) and overall status – assessed using the following questionnaires: EORTC-QLQ-C15-PAL, Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), Palliative Prognostic Score (PaP)
- Change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Change in left ventricular ejection fraction (LVEF)
- Change in glomerular filtration rate (eGFR)

4.2.3. Safety Endpoints:

- AEs
- All-cause mortality
- Reported SAEs (including, but not limited to acute kidney injury, hyperkalaemia, hypoglycaemia, symptomatic hypovolemia & hypotension)

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5. TRIAL DESIGN

5.1. Type of Trial

This is a multi-centre, prospective, controlled, double-blind, 1:1 randomised, 2-arm parallel, interventional clinical pilot trial in patients with terminal cancer in palliative care.

A schematic trial overview is given in Section 2, [Figure 1](#).

5.2. Randomisation

This is a randomised trial. Assignment of treatment allocation (1:1) will take place via the minimization approach using a dedicated randomisation tool. The minimization approach will be used to ensure adequate balance between groups for the following 8 variables: age, sex, body mass index, tumour aetiology, clinical status (ECOG, Karnofsky-Index, self-care ability), presence of co-morbidities (T2DM, anaemia, iron deficiency) and screening NT-proBNP level and prior cardiovascular therapy.

There will be 2 randomisation groups. One group will be assigned to the optimised treatment, the other group to standard care.

A patient will only be randomised if he/she complies with a combination of specific inclusion/exclusion criteria. At least 72 and no more than 108 subjects will be randomised in this trial.

Randomisation numbers will start with 8001, 8002, 8003.... and will be allocated in ascending order.

5.3. Blinding and Code Breaking Procedures

This is a double-blind randomised trial. Unblinded persons involved in the prescription and application of the optimised therapeutic scheme / application of placebo pills will not be involved in any other trial activities after randomisation during the double-blind intervention phase. During this period, all trial activities other than application of study medication will be done by blinded staff. . The unblinded study team at each site will include a certified cardiologist who will decide about start/stop and doses of the IMPs in the optimised heart failure therapy arm.

Treatment assignment will be kept strictly confidential and accessible only to authorised persons until after the time of un-blinding.

Seven sets of sealed codes with the subject randomisation number containing information about the treatment will be prepared for each subject. One set will be kept at each trial site in the office of the physician on duty (during the entire trial period), the other set will be kept under the responsibility of the sponsor and are to be used in case of code break need.

The code for a particular subject may be broken by an investigator in a medical emergency if knowing the identity of the treatment allocation could influence the treatment of the subject. The investigator may break the code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial subject. Consequently, the investigator has unrestricted and immediate access to break the treatment code. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents and on the code

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envelope. The breaking of blinded codes in case of medical emergency for one subject should not unblind the trial personnel to the treatment information of other subjects. The person performing the unblinding should inform as few people as possible about the result of the unblinding. All persons unblinded for a specific subject should be documented.

5.4. Investigational Treatment of Subjects

Each patient will be randomly allocated to either the optimised treatment or standard care for 30 days, followed by an open-label extension phase with all patients receiving optimised treatment for another 30 days.

The standard care of the patient population also includes diuretics. During the study diuretics therapy might be adapted. Diuretics (furosemide i.v./p.o., torasemide p.o., xipamide p.o., hydrochlorothiazide p.o.) might be given as needed at approved doses by the investigator to reduce peripheral oedema and lung congestion.

All medication in the optimised treatment will be given as per label and at approved doses. Patients with contraindications to any medication of the optimised treatment will not receive the respective treatment.

The optimised treatment consists of:

1. Sacubitril/valsartan: The starting dose will be 24/26mg sacubitril/valsartan twice daily. The target dose will be at the discretion of the unblinded cardiology team physician, but will not exceed 97/103mg sacubitril/valsartan twice daily. Patients already receiving ACE-inhibitors or Angiotensin-Renin-Blockers will be changed to sacubitril/valsartan.
2. Ivabradine: Ivabradine will be given to all patients with a heart rate ≥ 75 per minute. The starting dose will be 5 mg ivabradine twice daily. The target dose will be at the discretion of the unblinded cardiology team physician, but will not exceed 7.5 mg Ivabradine twice daily.
3. Ferric carboxymaltose (FCM): FCM will be given in all patients with iron deficiency defined as TSAT $< 20\%$. As per label, the individual iron need for repletion will be determined based on the patient's body weight and haemoglobin (Hgb) level:

Hgb		Patient body weight		
g/dL	mmol/L	below 35 kg	35 kg to <70 kg	70 kg and above
<10	<6.2	500 mg	1,500 mg	2,000 mg
10 to <14	6.2 to <8.7	500 mg	1,000 mg	1,500 mg
≥ 14	≥ 8.7	500 mg	500 mg	500 mg

Ferinject will be administered by intravenous infusion (diluted in 0.9% m/V sodium chloride solution). The maximum single dose is 20 mg iron/kg body weight, but will not exceed 1,000 mg iron. The FCM dose will be split in patients with an iron need above 1,000 mg with a maximum dose of 1,000 mg at the first application and the remaining dose one week later.

4. Empagliflozin: will be given at a dose of 10 mg once daily. Patients with contraindications, in particular with regard to renal and hepatic impairment, will not receive empagliflozin.

Dose administration will be performed by the unblinded study team. The unblinded certified cardiologist at each site will decide on the start and stop and on doses of the IMPs in each individual. Control group (standard care) patients will receive 1–3 different “placebo pills” and/or iv administration of saline (as placebo to FCM) at the discretion of the unblinded study team to keep blinding intact.

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After the end of the study extension phase, the treating palliative care oncologists will be informed of the ongoing treatment scheme of patients alive and continuation of therapy will be requested as needed and as per the patients' wishes.

5.5. Duration

The total trial duration for a subject will be up to 67 days.

Planned date for First subject first visit (FSFV): November 2022

Planned date for LSLV: September 2024

The end of the clinical trial is defined as last subject last visit (LSLV).

Actual time-lines may vary.

5.6. Stopping Rules

No specific stopping rules are applicable for this trial.

5.7. Rationale for the Trial Design and Treatment

The primary objective of this trial is to improve the self-care ability and self-reported health care status of patients with terminal cancer in palliative care.

As compared to usual care, optimised medical treatment with a therapeutic scheme that includes sacubitril/valsartan, ivabradine, i.v. iron (ferric carboxymaltose), and/or the SGLT2-inhibitor empagliflozin is supposed to reduce dyspnoea and increase physical functioning in end-stage cancer patients which results in better self-care ability and better self-reported health care status. To eliminate any safety concerns, all these therapies will be given at approved doses. Patients will be under close supervision and will mostly be treated in palliative care wards at the clinical sites. Patients who are in ambulatory care will be visited by the study team for study visits to avoid travel burden for these patients.

This is a randomized controlled trial (RCT), as this is the most definitive tool for evaluating the effectiveness of an intervention and establishing a cause-and-effect relationship between an intervention and an improved disease outcome. Randomisation and blinding avoid a possible bias introduced through an association between allocation of treatment schemes and subject characteristics.

A parallel design was chosen to limit the study duration for each patient and in turn have an acceptable time period (30-60 days) to ensure an appropriate evaluation of the trial endpoints.

In order to provide optimised medical treatment to all study participants an open-label extension was added to the double-blind randomized treatment period. In this extension, all study participants including those who were initially randomized to usual care will receive the optimised medical treatment.

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6. TRIAL POPULATION

6.1. Number of Subjects to be Studied

Planned number of subjects to be randomised: 72

Expected number of subjects to complete the trial: 60

6.2. Inclusion Criteria

1. Signed and dated informed consent obtained before any trial-related activities. Trial-related activities are any procedures that would not have been done during normal management of the subject.
2. Age ≥ 18 years
3. Male or female subject with solid cancer in UICC stage 4 (in palliative care).
4. Three-six months expected survival (minimum 1 month) as assessed according to local standards.
5. Patients under optimised pain management.
6. Patients must be able to swallow tablets.

Group 1 criteria for inclusion:

7. Heart rate at rest ≥ 75 bpm
8. NT-proBNP ≥ 600 pg/mL
9. Elevated Troponin (>99 th percentile of respective high-sensitive test)
10. LVEF $< 55\%$
11. HFpEF likelihood medium or large
12. Evidence of LV mass reduction $> 15\%$ since start of cancer
13. Iron deficiency with transferrin saturation (TSAT) $< 20\%$

Group 2 criteria for inclusion:

14. 4 m gait speed (≥ 6.0 secs for 4m) or not able to walk 4m at all
15. Not being able to wash themselves in at least 3 of the last 7 days
16. Presence of SoB at rest (NYHA IV)

Requirement for inclusion:

Fulfilled criteria 1-6 and at least two met criteria of Group 1 PLUS at least one met criterion of Group 2.

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6.3. Exclusion Criteria

Note: Subjects with contraindications to any medication of the optimized treatment will not receive the respective treatment.

1. Previous participation in this trial. Participation is defined as randomised.
2. Ongoing haemodialysis
3. Patients currently on intravenous iron
4. Acute sepsis with at least 2 points at the quick sequential organ failure assessment (qSOFA) score. The use of i.v.-antibiotics is permitted in patients with a lower qSOFA score.
5. Ongoing acute exacerbation of chronic obstructive pulmonary disease (COPD)
6. Acute ST elevation myocardial infarction (STEMI) or severe pulmonary embolism (PE) or severe deep vein thrombosis (DVT) (currently or in last 4 weeks)
7. Current uncontrolled cerebral metastasis
8. Impaired neurological status, precluding the ability to walk
9. Unable or unwilling to give written informed consent
10. Participation in other interventional trials using investigational products in randomised settings within the last 30 days

6.4. Discontinuation Criteria

1. At the discretion of the investigator due to safety concerns
2. Adverse event (AE): Subject reports symptoms or detection of clinical abnormalities, which are considered unacceptable by the investigator (i.e., allergic reactions, diabetic ketoacidosis)
3. A patient may withdraw his/ her consent at his/ her own request at any time.

6.5. Subject Replacement

A total of 72 subjects should complete the trial. If too many patients drop out of the study before completion of the intervention period on day 30, additional subjects might be enrolled. The decision whether or not to enrol additional patients will be made by the Steering Committee.

As mortality is an endpoint of this study patients who die before completion of the intervention period will not be regarded as drop-out. The maximum number of subjects enrolled into the study will not exceed 108 patients.

6.6. Rationale for Trial Population

Cardiac wasting and dysfunction is a hallmark of advanced cancer conditions. No studies have previously assessed whether an optimised heart failure therapy can alleviate these patho-mechanisms to improve dyspnoea and quality of life in advanced cancer patients.

The study will therefore be done in patients with terminal cancer as this is the target population for testing the study hypothesis.

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7. TRIAL MATERIALS

7.1. Investigational Medicinal Products

The IMPs listed in [Table 2](#) will be used (for further information please refer to the SmPC):

Table 2: Specification of medicinal products used in the trial

IMPs	Strength	Pharmaceutical dosage form	Administration route
Sacubitril /valsartan	24/26 mg 49/51 mg 97/103 mg	Tablet	Oral
Ivabradine	5 mg 7.5 mg	Tablet	Oral
Ferric carboxymaltose	50 mg/mL	Solution for injection or infusion	Intravenous
Empagliflozin	10 mg	Tablet	Oral

All investigational medicinal products used in this clinical trial are already approved and will be purchased from the national market.

Placebo pills (P-Tabletten blau Lichtenstein, P-Tabletten weiss 8 mm Lichtenstein, P-Dragees rosa Lichtenstein, all manufactured by Zentiva Pharma, Berlin) will be used for blinding in this trial. Physiological saline solution will be used as placebo for ferric carboxymaltose.

7.1.1. Packaging and Labelling Medicinal Products

Labelling will be in accordance with local regulations and trial requirements. Each site will provide the investigational medicinal products and placebo pills which will be purchased from the German market.

IMPs and placebo pills will remain in the original primary and secondary packages before distribution to the patients. IMP-tablets or placebo pills will be distributed without any further packaging into tablet boxes with the right amount of tablets per day and time (morning/midday/evening) for each individual. Doses and dosing frequency (once daily, twice daily, etc.) will be decided by the unblinded study team. Likewise, the unblinded study team will decide on the number of placebo pills (1-3) that the patients in the control arm will receive.

The unblinded study team will also decide on the administration and the dose of ferric carboxymaltose in accordance with the dosing instructions of Ferinject® in the SmPC. Patients in the control arm fulfilling the criteria for iron supplementation will receive saline infusions or injections.

As labelling of study medication in the tablet boxes will not be possible, patients will receive a leaflet with all relevant information on the IMPs or placebo pills. Individual information (dose, dosing frequency) will be added by the unblinded study team.

7.1.2. Storage and Drug Accountability of Investigational Medicinal Products

All IMPs will be stored and handled in accordance with the manufacturer instructions at the investigator's site.

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The investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. The investigator must inform the monitor immediately if any IMP has been stored outside specified conditions (e.g. outside temperature range). IMP that has been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use. The investigator must take appropriate action to ensure correct storage.

For all IMPs, the investigator must keep an accurate record of all IMPs provided to each subject in a Drug Accountability Record. Storage locations, batch numbers and expiry dates are also documented in this form.

The drug accountability has to be performed in a timely manner.

7.1.3. Dispensing and Return of Investigational Medicinal Products

No IMPs may be dispensed to any person not enrolled in the trial.

7.1.4. Retention Samples

No retention samples will be stored for this trial.

7.1.5. Preparation and Application of IMP

IMP administration will be in accordance with the randomisation list.

As the IMPs differ from placebo pills in their outer appearance, it has to be ensured that the blinded study team will not have access to the medication provided to patients. It is expected that patients will not have the knowledge to distinguish between IMPs and placebo pills.

The unblinded study team involved in the preparation/administration process must not disclose any information to any other persons in order to ensure the double-blind design of the trial. The randomisation list, any preparation documents as well as any accountability forms will be kept in a way that it is only accessible to the persons involved in preparation.

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8. ASSESSMENTS

8.1. Procedures

Please refer to the information given in Section 2 for a general overview of the trial assessments and procedures. The following sections describe details of the assessments and procedures.

The investigator must keep a subject screening and identification log.

8.2. Informed Consent

Prior to any trial-related activities, potential subjects will be provided with oral and written information about the trial course, the employed therapies and the visit procedures. The subjects will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They have the opportunity to discuss all open questions and will have ample time to consider participation. Subjects who wish to participate in the trial will be asked to personally date and sign (incl. time) an informed consent form prior to any trial-related activities. Trial-related activities are any procedures that would not have been performed during normal management of the subject. Likewise, the investigator must also personally date and sign the informed consent form prior to any trial related activities. All subjects will be provided with a copy of their own signed and dated informed consent form.

8.3. Screening phase: Screening and Baseline Assessments

Subjects will receive a screening number with the first figure being specific to the study site and following two figures being in ascending order starting with 01 (for site 1: 101, 102, 103...; for site 2: 201, 202, 203...; for site 3: 301, 302, 303...etc.).

Activities performed in the screening phase are listed in the trial flow chart, see Section 2.2. Relevant information on the subject's demographic data, concomitant illness, medical history and concomitant medication will be obtained from the patient hospital file or from the patient directly, in particular information on UICC stage, expected survival time as assessed according to local standards, pain management, COPD status, SoB (NYHA4), cerebral metastasis, neurological status, sepsis assessment (qSOFA-score), DVT, PE, and tumour aetiology. Body weight and height will be determined as well as vital signs (blood pressure, pulse, temperature (in ear)) and laboratory assessments. An ECG and an echocardiography will be performed. Assessments done within the last 7 days before screening for which results are available in the patient file do not have to be repeated.

Subjects will undergo a 4 m walking test, if feasible. The ability to walk 4 m (yes/no) and the speed for the 4 m walking test will be recorded in the CRF.

Screened subjects who do not meet or comply with the specific combination of inclusion and exclusion criteria are excluded (screening failures), and their data will be recorded on a screening failure form. The reason for exclusion must be recorded on the screening failure form. Detailed information about which data will be entered into the trial database will be described in the trial specific data management plan.

If subjects do not comply with a few inclusion and exclusion criteria only, they can be re-screened if changes in their clinical status might lead to full compliance with all inclusion and exclusion criteria. Each subject can only be re-screened once.

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Baseline assessments will further include: Performance status methods and QoL questionnaires. Please refer to the later sections in this chapter for a description of all assessments.

Results from screening must be available and assessed to be acceptable by the investigator before intervention phase procedures take place. The investigator should document if out of range results (vital signs, laboratory tests, ECG, echocardiography) are clinically significant or not clinically significant.

Subjects that comply with the specific combination of in- and exclusion criteria for continuation in the trial (see Sections 6.2, 6.3) will continue with randomisation and intervention.

8.4. Interventional Phase

8.4.1. Randomisation Phase (Day 1-30) and Open-Label Phase (Day 31-60)

Subjects that comply with the specific combination of in- and exclusion criteria for continuation in the trial (see Sections 6.2, 6.3) will be randomised (see Section 5.2) and continue with the trial procedures. Randomisation should occur on Day 1. Study-related IMP or placebo administration will start the same day.

Please refer to the Trial Flow Chart in Section 2 for the procedures and timing of assessments. Please refer to the later sections in this chapter for a description of the assessments.

8.5. Assessment of Treatment Compliance

Treatment compliance will not be formally assessed. Study participants will be hospitalised or under ambulatory care. They will receive study medication in a tablet box according to the instructions by the unblinded staff. The administered doses will be recorded in the Drug Accountability Form / CRF. Likewise, medication that was not taken and remained in the tablet box will be recorded.

8.6. Washing ability assessment

According to the primary outcome of the trial it will be investigated whether the patient is able to wash him/her-self without the interference of staff (regardless of whether as shower or bath, on a sink, or using a “sponge bath” in the bed).

8.7. Walking ability and time measurement

Four (4) m-walking ability (yes/no) and time are assessed starting in a still standing position – timing starts with the first foot movement and ends when one foot completely crossed the 4m-finish line. Walking ability will be measured twice at each time point – both times will be recorded in the CRF. The average time will be calculated for evaluation of results.

8.8. PGA of well-being

PGA of well-being will be assessed by asking the patient "Since I began participating in this study, my health has?" Patients can respond on a 7-point Likert scale. The scale offers 7 different answer options: Very improved, (moderately) improved, slightly improved, not changed, slightly worsened, (moderately) worsened, very worsened.

8.9. ECOG-Performance-Status

The ECOG-Performance-Status describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) (10). It is divided

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in 6 different grades (**0**=fully active, able to carry on all pre-disease performance without restriction; **1**=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; **2**=Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; **3**=Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; **4**=Completely disabled; cannot carry on any selfcare; totally confined to bed or chair; **5**=Dead).

8.10. Karnofsky-Performance-Status

The Karnofsky-Performance-Status is another (besides the ECOG-Performance-Status) widely used method to assess the functional status / impairment of a patient (11, 12). The Karnofsky index ranges between 100 and 0 (100=Normal, no complaints; no evidence of disease; 90=Able to carry on normal activity; minor signs or symptoms; 80= Normal activity with effort, some signs or symptoms of disease; 70=Cares for self but unable to carry on normal activity or to do active work; 60=Requires occasional assistance but is able to care for most of personal needs; 50=Requires considerable assistance and frequent medical care; 40=Disabled; requires special care and assistance; 30=Severely disabled; hospitalization is indicated although death not imminent; 20=very ill; hospitalization and active supportive care necessary; 10=Moribund; 0=Dead).

8.11. Quality of Life (QoL)

QoL overall status is assessed using the following questionnaires: EORTC-QLQ-C15-PAL [15 questions] (13). All questionnaires are validated and available in German.

8.12. Echocardiography

A standard transthoracic echocardiography will be performed in accordance with current ESC recommendations (14) at screening or baseline (screening echocardiography will be used for baseline), and on days 30 and 60 to determine LVEF (biplan), E/A, E/e', left atrial (LA) volumen, LVMM, LVEDD, high-grade valvular heart disease. If patients are in ambulatory care, echocardiography will be performed with a mobile device. The same investigator will perform all echocardiographs in one individual, if feasible. Key echocardiographic variables will be measured by the study site and entered in the eCRF. In addition, echocardiographic images will be anonymously saved on a DVD and sent to the central study core-lab (Cardiovascular Imaging Laboratory, West German Heart and Vascular Center) for further assessment.

8.13. Laboratory assessments

Laboratory assessments will be done at the local laboratories of the investigational sites. The following parameters will be assessed:

- N-Terminal pro B-type natriuretic peptide (NT-proBNP, pg/mL)
- Troponin (high-sensitive troponin T or I, ng/L)
- Blood cell count (per µl blood)
- Hgb (g/dL)
- TSAT (%)
- Transferrin (g/L)

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- Ferritin
- C-reactive protein (mg/dl)
- Electrolytes (potassium, sodium, chloride), mmol/L
- Glucose (mg/dL)
- HbA1c
- Iron (µg/dL)
- Creatinine (mg/dL)
- Albumin
- Estimated glomerular filtration rate (eGFR, mL/min), using the formula of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (15).

In addition, serum and/or plasma will be stored for a potential later analysis of laboratory parameters, in particular for (new) metabolic and cardiovascular biomarkers. Patients who do not consent to these additional blood samples, will still be able to participate in the study.

Laboratory values will be transferred to the eCRF together with the normal ranges.

8.14. Assessments for Safety

8.14.1. Adverse Events

Adverse events (AEs) will be recorded in accordance with the procedures described in Section 9. Any clinically significant worsening of a previous finding must be reported as an AE.

As the subjects are in palliative care they are routinely asked about changes of their health status. This will be documented in the subject's medical record.

8.14.2. Concomitant Illness and Medical History

A concomitant illness is any illness that is present at the start of the trial (i.e. at the screening visit).

Medical history is an account of medical events that the subject has experienced in the past.

- Concomitant illnesses present at the start of the trial will be recorded in the CRF at screening.
- Relevant medical conditions/illnesses in the past will be recorded in the CRF at screening.

The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution or continuation.

Any change to a concomitant illness should be recorded during the trial, including end date, if applicable. A clinically significant worsening of a concomitant illness must be reported according to Section 9.

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8.14.3. Vital Signs

An examination of the following vital signs will be performed:

- Diastolic and systolic blood pressure (mmHg) are measured.
- Pulse (beats per min) is measured.
- In ear temperature (°C)

In addition to the pre-specified assessments in Sections 2.2, blood pressure, pulse and temperature may be assessed at any time during the trial at the discretion of the investigator.

8.14.4. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed as indicated in the trial flow chart (Section 2.2). Any abnormality will be recorded and described in the CRF including the investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Clinically significant findings at the screening visit should be recorded as concomitant illness. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

8.15. Other Assessments

8.15.1. Demography

- Age
- Sex
- Race

8.15.2. Concomitant Medication

A concomitant medication is any medication, other than the IMPs, which is taken during the trial, including screening and follow-up periods.

Details of any concomitant medication must be recorded at trial entry (i.e. at screening). Any changes in concomitant medication (only newly started or stopped medication (no dose changes) will be documented) must be recorded at each visit as they occur. The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation. A change in medication due to an AE must be recorded and reported according to Section 9. If the change in medication influences the subject's eligibility to continue in the trial, the sponsor and monitor must be informed.

8.15.3. Body Measurements

- Height (cm), without shoes
- Body weight (kg), only wearing light clothes or underwear (will be documented)

8.16. Volume and Storage of Blood Samples

8.16.1. Volume of Blood Sampled during Trial

A total amount of approximately 180 mL blood will be drawn from each subject during the trial.

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Additional blood samples may be drawn at the discretion of the investigator if deemed necessary for the safety of the subjects.

8.16.2. Blood Samples Storage

The samples for analysis of cardiovascular and metabolic biomarkers will be stored for up to two years after last patient last visit. All other samples will be destroyed after analysis.

8.16.3. COVID-19 related procedures/assessments

All study sites have established comprehensive standard procedures to minimize the risk of COVID-19 infections for study participants. These measures are also carefully implemented as part of the study procedures. The situation with regards to COVID-19 restrictions and regulations will be assessed by the Investigators on a regular basis and procedures might be adapted.

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9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a trial subject administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

AEs include:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory abnormality which is clinically significant, i.e. any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should not be recorded as AEs:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first dosing.
- Pre-existing conditions which had started prior to the first dosing. This also applies to previously unknown conditions which have been found as a result of assessments done as part of the trial procedures. Pre-existing conditions should be reported as medical history or concomitant illness.

9.1.2. Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,

or events that may require intervention to prevent one of the above listed outcomes.

9.1.3. Other Significant Adverse Events

Other significant adverse events will be defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events (16).

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9.1.4. Intensity of an Adverse Event

The maximum intensity (severity) of all AEs must be assessed by the investigator and documented. Severity should be graded when the AE outcome is known:

- **Mild:** A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A 'severe' reaction does not necessarily deem the AE as 'serious' and a SAE may not be 'severe' in nature.

9.1.5. Causality Relationship to IMP

The causality of each AE should be assessed by the investigator according to the following classification:

- **Probable:** Good reason and sufficient documentation to assume a causal relationship.
- **Possible:** A causal relationship is conceivable and cannot be dismissed.
- **Unlikely:** The event is most likely related to aetiology other than the trial product.

9.1.6. Outcome of an Adverse Event

The outcome of all AEs must be assessed by the investigator and documented by his/her staff. The following definitions should be used:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/ resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.

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9.2. Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported from first dosing of the IMP until the end of the extension phase. At each contact with the site (visit or telephone, excluding safety visits, where the subject is not seeing the investigator or his staff (e.g. visits to the laboratory)) the subject must be asked about AEs. All AEs, either observed by the investigator or reported by the subject, must be recorded by the investigator and evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (17).

The investigator should record the diagnosis, if possible. If no diagnosis can be made the investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the investigator. One single Adverse Event Form must be used per AE from start to resolution. For SAEs, the Serious Adverse Event Form must also be completed.

AE information should include the following:

- AE term
- Date and time of onset and resolution
- Date of investigator's first information on the (S)AE (will not be collected in the CRF)
- Seriousness
- Severity
- Causal relationship with IMP
- Interruption or withdrawal of treatment with IMP and other measures taken
- Outcome

The date and time of the last contact with a subject will be entered for any ongoing AE where outcome is "recovering/resolving" or "not recovered/not resolved".

The investigator must report initial information in writing (fax or email) on all SAEs to the Sponsor Representative immediately (without undue delay) after obtaining knowledge about the event.

The sponsor must inform the competent authorities and IRBs/IECs in accordance with the local requirements in force and ICH guideline for GCP. The trial monitor must be informed accordingly.

9.3. Follow-up of Adverse Events

Follow-up procedures may be different based on the nature (diagnosis, severity, seriousness) of the AE.

Non-serious AEs classified as severe or possibly/probably related to trial product will be followed until the subject has "recovered" or "recovered with sequelae" and all queries have been resolved.

Note: Cases of chronic conditions, cancer or AEs ongoing at time of death (i.e. a subject dies from another AE), can be closed with an outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering", when the subject has completed the post-trial follow-up period (1 week after last dosing) and is expected to recover as judged by the investigator.

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All other non-serious AEs will be followed up until the outcome of the event is “recovering”, “recovered”, “recovered with sequelae” or until the end of the post-treatment follow-up period (1 week after last dosing), whichever comes first, and until all queries related to these AEs have been resolved.

The investigator shall follow up on all SAEs until the outcome of the event is “recovered”, “recovered with sequelae” or “fatal” and until all queries have been resolved, even after trial completion (LSLV). Note: Cases can be closed with an outcome of “recovering” when the subject has completed the trial and is expected by the investigator to recover.

Follow-up actions for all SAEs will be determined after internal review and/or sponsor review.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the investigator’s signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up the AE Form and SAE Form have to be used and reporting timelines follow those of a SAE.

9.4. Precautions

Normal precautions taken for a human trial will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the subjects. A trained cardiologist or experienced cardiology fellow will decide on the IMPs that subjects in the optimised heart failure therapy arm are going to receive. During a subject’s participation in the trial, the investigator should ensure that adequate medical care is provided to the subjects for any AEs, including clinically significant laboratory values related to the trial. The investigator should inform the subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

For further information on safety precautions for all IMPs please refer to the SMPCs.

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10. RISK-BENEFIT ASSESSMENT

This study will investigate the hypothesis that optimised medical treatment with a therapeutic scheme that includes sacubitril/valsartan, ivabradine, i.v. iron (ferric carboxymaltose), and/or the SGLT2-inhibitor empagliflozin will reduce dyspnoea and increase physical functioning in end-stage cancer patients which may result in better self-care ability and better self-reported health care status.

Study participants will comprise of patients with late-stage solid cancer in palliative care with massively reduced life expectancy.

10.1. Potential Risks

Patients in the intervention arm receiving one, several or all IMPs are at risk of experiencing drug-related side effects. The risk for these side effects are described in the SmPCs of the respective IMPs and include, but are not limited to hyperkalaemia (but also hypokalaemia), hypoglycaemia, acute kidney injury, symptomatic hypovolaemia and hypotension, headache, syncope, vertigo, fatigue, asthenia, cough, diarrhoea (but also constipation), gastritis, nausea, vomiting, genital infections, pruritus, polyuria, bradycardia (but also tachycardia), ventricular extrasystoles, atrial fibrillation, hypertension, muscle cramps, muscle spasms, peripheral oedema, fever, and chills.

In order to reduce the risk of side effects, the start, dose and dose frequencies of all IMPs will be directed and supervised by a certified cardiologist as member of the unblinded study staff at each investigational site. All IMPs will be used in line with standard care guidelines and at approved doses and dosing frequencies. Particular attention will be paid to frequent and very frequent side effects of the IMPs used in this study. Patients will be frequently monitored by study staff allowing (dose) changes in the study medication (including stop of some IMPs in individual study participants).

Overall, subjects in the intervention arm are at risk of IMP-related side effects, but frequent observations of patients should reduce the frequency and/or severity of side effects.

Patients in the control arm will only be treated with placebo pills which should not lead to substantial additional risk in the high-risk study population to be included in this study during the intervention phase. However, these patients will receive the same treatment as the intervention arm in the optimised medical treatment arm in the extension phase of this trial.

Trial subjects will have been informed by the investigator of the potential risks of the used IMPs before they enter the trial.

Trial procedure-related risks are mainly associated with venous blood sampling. These risks are minimal, because the blood sampling techniques have been used as standard procedure for a long time, and numerous injections and infusions have been performed in human research subjects. In addition, the morbidly ill patients to be included in this study will have frequent blood sampling as part of their routine care.

10.2. Potential Benefits

If the study hypothesis is confirmed patients in the intervention arm will benefit from an optimised heart failure therapy through improved symptoms (i.e., less congestion, dyspnoea or other heart-failure associated symptoms) and better physical functioning resulting in better self-care ability

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and better health care status. Overall, heart failure therapy might enhance life quality in these patients.

Therefore, patients in the control arm will be offered to participate in the extension phase where they will also receive optimised heart failure therapy with the potential benefits.

10.3. Risk-Benefit Assessment

While there are potential risks from the intervention, in particular adverse drug effects of the used IMPs, these risks are reduced (but not completely abolished) by the study setting ensuring close monitoring of all study participants by certified cardiologists. On the other hand, patients might have a substantial benefit from the study intervention with improved physical functioning and thereby better quality of life. Improved life quality is a high priority in patients with end-stage cancer and severely reduced life expectancy.

To date, the benefit of optimised heart failure therapy in end-stage cancer patients has not been proven. It is therefore also possible, that the study hypothesis is not confirmed and patients will not benefit from optimised heart failure therapy. Nevertheless, in view of the relevance of the findings of this trial potentially improving medical care for persons with end-stage cancer and the attempts to minimise risks as much as possible, the overall risk-benefit ratio for subjects participating in this trial is believed to be acceptable.

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11. DATA MANAGEMENT

Data Management is the responsibility of Profil Institut für Stoffwechselforschung GmbH, Neuss Germany.

The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

11.1. Case Report Forms (CRFs)

For this trial an electronic CRF (eCRF) will be used.

The Data Management Department of Profil Institut für Stoffwechselforschung GmbH will provide the eCRF. Data will be transcribed from source data files into the eCRF. eCRF data will never be source, but only transcriptions. All further information regarding the CRF and the data flow will be described and agreed on in the Data Management Plan.

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12. MONITORING PROCEDURES

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial subjects are respected, (ii) that accurate, valid and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The monitor must be given direct access to the TIF and source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include to verify the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol and the progress in subject enrolment.

Because no information that could reveal the identity of subjects may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the investigator and monitor will be maintained as required through telephone calls and e-mail. The investigator and/or key members of staff involved in the trial must be available to assist the monitor during all visits.

12.1. Site Initiation Visit

During the Site Initiation Visit (SIV) the sponsor and/or monitor will review information on the IMP, the protocol, the CRFs and other key aspects of the trial with the investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the investigator. Sponsor's documentation on the SIV (e.g. power point presentation) should be filed by the investigator.

12.2. Source Data Verification

Details on source data verification are specified in the Monitoring Manual.

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13. STATISTICAL CONSIDERATIONS

Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany, will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines and Profil's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before data base lock. Any changes of the original statistical plan will be described and justified in an updated version of the SAP and/or in the final CSR, as appropriate. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or later.

13.1. Sample Size Calculation

This is a pilot study. Precise power calculations for this study are limited by the very restricted availability of prior data regarding test reproducibility and expected treatment effects.

Given a two-sided alpha level of 0.05, a planned power of 85% with 1:1 randomization, a sample size of 72 would be sufficient to assess the primary endpoint based on the following assumptions: Days alive and able to wash themselves during the last 4 weeks is 11 ± 6 days (mean \pm SD). This can be increased by 5 days over the treatment period of 28 days in the intervention group vs controls. Under the above assumptions and accounting for a drop-out rate of about 20%, the trial's power is calculated to be 85% with 72 enrolled patients and 58 completing patients using the Wilcoxon-Mann-Whitney test at a two-sided alpha level of 0.05 (G*Power, version 3.1.9.7). Using other software packages the power of the study under the same conditions will be 83.4% (nQuery) or 86.4% (SAS). A mean difference of 5 days and a standard deviation of 6 days results in a probabilistic index (i.e., the probability that the days alive and able to wash themselves are larger for a patient in the experimental group as compared to a patient in the control group) of 0.278. Note: If patients in the intervention group vs controls experience at least 6 days more of being alive and able to wash themselves during the treatment period of 28 days, then the power of the study for the primary endpoint increases to >90%.

13.2. Selection of Subjects for Analyses

The following analysis sets are defined in accordance with the ICH-E9 guidance:

- **Full Analysis Set (FAS)** is based on the intention-to-treat principle and includes all randomised subjects. In exceptional cases subjects from the FAS may be excluded (will be decided in the DBR meeting). In such cases the exclusion will be justified and documented. Subjects will contribute to the evaluation 'as randomised'.
- **Per-Protocol Population (PPP)** includes all subjects of the FAS who completed the trial without any major protocol violations. Subjects in the PPP will contribute to the evaluation 'as treated'.
- **Safety Analysis Set** includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation 'as treated'.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which study arm the subjects were assigned to. The blinding of the IMPs will be maintained for everyone involved in allocating subjects to the analysis sets until data are

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released for statistical analysis. Furthermore, outliers will be identified by data review according to ICH-E9 using a fake randomisation. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis.

Obviously erroneous data points may be excluded from the analyses or re-analysed (in case of e.g. serum concentrations). The decision to re-analyse or exclude data points from the statistical analysis is the joint responsibility of the sponsor, the investigators and the Trial Statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CSR.

13.3. Database Release Meeting

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which treatment the subjects were assigned to. The blinding will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Outliers will be identified by data review according to ICH-E9 (18). In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis.

Obviously erroneous data points may be excluded from the analyses. The decision to exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator and the Trial Statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

13.4. Statistical Methods

A statistical analysis plan (SAP) will be written, in addition to the protocol. The SAP will be finalised prior to database lock (DBL), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

Unless otherwise stated, all formal tests of hypothesis will be conducted at the two-sided 5% level of significance. No alpha adjustment will be done.

All analyses, listings, tables and plots will be performed using all available data unless otherwise stated. In general missing data will not be replaced, and obviously erroneous data points will be excluded from the analyses or re-analysed (as described in Section 13.2).

In general, descriptive statistics will be performed for all endpoints. Categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, standard deviation, coefficient of variances, minimum, median, maximum and the number of subjects with evaluable data.

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Data from clinical assessments will be presented in summary tables. Data will be summarised with respect to demographic and other baseline characteristics, efficacy and safety observations and other measurements.

Individual subject listings will be sorted by randomisation number, treatment group, and, if applicable, visit and/or time. Summary tables will be presented by treatment group.

Presentation of results from a statistical analysis will include the estimated median treatment effects for absolute values. Estimated median treatment differences will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically.

If not otherwise specified, the baseline measurement is defined as the latest available measurement at or prior to randomisation.

Subject disposition will be tabulated including the numbers of screened subjects, screening failures, randomised subjects, subjects exposed to trial product, withdrawals, subjects completing the trial and subjects in the FAS, efficacy analysis set and safety analysis set.

Subjects withdrawn from the trial will be listed including the primary reason for withdrawal.

The primary analysis is aimed to demonstrate that an optimised heart failure therapy will lead to significant improvements in self-care ability in patients with terminal cancer in palliative care. Secondary analyses are aimed to demonstrate that an optimised heart failure (HF) therapy will lead to significant improvements in functional status, cardiac function or self-reported quality of life of patients with terminal cancer in palliative care.

13.4.1. Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint of this study (days of patients being alive and able to wash themselves since baseline during 30 days of follow-up) describes the mortality and self-care ability of patients with terminal cancer in palliative care.

The primary endpoint will be analysed using the Wilcoxon-Mann-Whitney-Test or other non-parametric tests, e.g. using the win-ratio approach (see below). The difference in median between treatment groups and the corresponding p-value will be presented. In addition, the point estimate of Hodges and Lehmann and corresponding two-sided 95% CIs for the difference will be determined and presented. Alternatively, the win-ratio with 95% CIs will be used.

To minimise the impact of drop-outs that do not provide any data for the primary endpoint statistical procedures such as the win-ratio approach might be used in case of substantial numbers of drop-outs. The decision whether or not to use the win-ratio approach or other procedures will be made before database lock. The win-ratio approach would facilitate the incorporation of further components of clinical relevance such as PGA and 4 m walking ability.

Further details will be given in the Statistical Analysis Plan (SAP).

13.4.2. Analysis of the Secondary Efficacy Endpoints

Analysis of the secondary efficacy endpoints will be performed similarly to the analysis of the primary endpoint.

Findings of the PGA and quality of life questionnaires as well as of the ECOG-Performance-Status and the Karnofsky-Performance-Status will be summarised by treatment group and question using frequency tables. The overall scale will be summarised per treatment group.

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13.4.3. Safety Criteria

13.4.3.1. All-cause mortality

All-cause mortality will be analysed by means of the Kaplan–Meier method. A log-rank test will be used for hypothesis testing, and the hazard ratio and its 95% confidence interval (95% CI) will be estimated from the unadjusted Cox model. Additional multivariate Cox regression sensitivity analyses may be conducted. These will be described in the SAP. Cause of death adjudication will be performed as well.

13.4.3.2. Adverse Events

AEs will be listed by subject, IMP, system organ class and preferred term, seriousness, the time of onset and duration, the time of last IMP administration, the intensity, and relationship to the IMP, the outcome of the AE, the action taken on the trial product, and the action taken to treat the AE. Treatment emergent AEs (TEAEs) will be analysed by descriptive statistics separated by study arm. The summaries will include the number of subjects with event (N), the percentage of subjects exposed with event (%), and the number of events (E), TEAEs by MedDRA system organ class (SOC) and MedDRA preferred term (PT). Likewise, serious adverse events that might be associated with the use of IMPs (including, but not limited to acute kidney injury, hypoglycaemia, hyperkalaemia, symptomatic hypovolaemia and hypotension) will be analysed by descriptive statistics by study arm. Details will be given in the SAP.

A separate listing of deaths, serious and other important AEs will be presented.

13.5. Interim Analysis

No interim analysis is planned.

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14. INDEPENDENT ETHICS COMMITTEE AND COMPETENT AUTHORITY

The trial will be conducted according to the following relevant binding documents and standards

- the national Medicinal Products Act (AMG in Germany)
- the GCP ordinance (GCP-Verordnung in Germany)
- the Declaration of Helsinki (19)
- the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Guideline for Good Clinical Practice (ICH GCP) (20)

14.1. Independent Ethics Committee

Written favourable opinion must be obtained from the responsible independent ethics committee (IEC) prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect subject safety or the trial integrity (substantial amendments) must not be implemented before favourable opinion has been obtained, unless necessary to eliminate hazards to the subjects. Non-substantial amendments do not require favourable opinion by the IEC but the respective IEC will be notified according to local requirements.

The sponsor and investigator must approve any amendment in writing before its implementation.

The sponsor must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the sponsor's trial master file (TMF).

14.2. Informed Consent Process for Subjects

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline (20) and the requirements in the Declaration of Helsinki (19).

Prior to any trial-related activity, the investigator must give the subject oral and written information in a form that the subject can read and understand about all aspects of the trial that are relevant to the subject's decision to participate. The subject will be given ample time to decide whether or not to participate in the trial.

The subject must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by authorised monitors or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated Informed Consent Form must be obtained from the subject prior to any trial-related activity. The Informed Consent Form must also be signed and dated by the physician who conducted the informed consent procedure. All subjects will be

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provided with a copy of their own signed and dated informed consent form and with any additional subject information.

The responsibility for taking informed consent must remain with that of a physician.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the Informed Consent Form may need to be revised to reflect the changes to the protocol. It is the responsibility of the sponsor to ensure that an amended consent form is reviewed and has received favourable opinion from IEC, and the investigator has to ensure that the amended consent form is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the amendment.

14.3. Competent Authority

An implicit or explicit approval must be obtained from the competent authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the competent authority but will be notified according to local requirements.

The sponsor and investigator must approve the amendment in writing before its implementation.

The sponsor must maintain an accurate and complete record of all submissions made to the competent authority. The records should be filed in the sponsor's TMF.

14.4. Premature Termination of the Trial

The sponsor, investigator or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that will warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons.
- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical trial.
- A decision of the sponsor to suspend or discontinue investigation of the applied IMPs.

If a trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and assure appropriate therapy and follow-up. Furthermore, the sponsor should promptly inform the IEC and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IEC in case it will have an impact on the planned follow-up of the subjects who have participated in the trial. Necessary actions needed to protect the subjects should be described.

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15. ADMINISTRATIVE MATTERS

15.1. Deviations from the Protocol

A deviation from the protocol is in general an unplanned non-compliance with the protocol that is not implemented or intended as a systematic change. The investigator, or person designated by the investigator, should document and explain any deviation from the protocol and inform the sponsor and/or monitor. The deviation must be evaluated for its root cause and classification (important/non-important). Corrections (if possible) and/or corrective/preventive actions are to be documented and implemented. The documentation must be kept in the TIF and the sponsor's TMF. Each deviation is listed in a deviation log.

15.2. Essential Documents

Essential Documents, as outlined in ICH GCP Chapter 8, are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

Trial files should be established at the beginning of the trial, both at the investigator's site (for the TIF) and at the office of the sponsor's delegate for TMF management (for the TMF). A final close-out of a trial can only be done after it has been confirmed that all necessary documents are in the appropriate files.

15.3. Responsibilities

The trial related responsibilities are defined in the trial specific Responsibility Split List, which is an essential part of the trial contracts. In these documents the distribution of responsibilities between sponsor, investigational sites and the contract research organisation Profil is specified.

The investigator is accountable for the conduct of the trial according to the approved protocol, ICH-GCP (20) and Declaration of Helsinki (19). For responsibilities delegated, the investigator should maintain a list of appropriately qualified persons to whom he has delegated specified significant trial-related duties. The Coordination Investigator will discuss and approve the protocol and review and sign the Integrated CSR.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

15.4. Reports and Publications

The Coordinating Investigator of the trial will review and sign the CSR on behalf of the sponsor. A summary of the final CSR will be submitted to the IEC and competent authority.

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According to the Declaration of Helsinki (19) investigators and sponsors ‘have ethical obligations with regard to the publication and dissemination of the results of research’.

The trial design and results may be published as one or more original research manuscripts / abstracts and presented at a scientific meeting. The investigator and sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors (ICMJE) (21).

Participating subjects will not be identified by name in any published reports about the clinical trial.

15.5. Audits and Inspections

In the event of an audit, representatives of the sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the informed consent form signed by the subject.

15.6. Retention of Clinical Trial Documentation

The sites will maintain the subject’s medical file according to local regulations.

The investigational sites will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified.

The documentation includes all the raw data generated during the clinical trial, the TIF and a copy of the clinical report. The documents will be retained for a period of 25 years after the clinical trial has ended or been discontinued.

The sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

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17. APPENDICES

17.1. Appendix 1: List of Abbreviations

AE	Adverse event
BP	Blood pressure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CSR	Clinical study report
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FAS	Full analysis set
GCP	Good clinical practice
HFpEF	Heart failure with preserved ejection fraction
Hgb	Haemoglobin
ID	Iron deficiency
ICH	International council for harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
i.v.	Intravenous(ly)
LSLV	Last subject last visit
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal prohormone of b-type natriuretic peptide
PaP	Palliative Prognostic Score
PE	Pulmonary embolism
PGA	Patient global assessment
PPI	Palliative Prognostic Index
PPP	Per-protocol population
PPS	Palliative Performance Scale
QoL	Quality of life
qSOFA	Quick sequential organ failure assesement
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous(ly)
SIV	Site initiation visit
SmPC	Summary of product characteristics
SoB	Shortness of breath
SOP	Standard operating procedure
STEMI	ST elevation myocardial infarction
TIF	Trial investigator file
TMF	Trial master file
TSAT	Transferrin saturation
UICC	Union internationale contre le cancer