CLINICAL STUDY PROTOCOL

Study Title:	Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS (ERASe-Trial) – a phase III Study
Protocol Number:	DvL–2020-01
Product:	Ertugliflozin
Sponsor:	Medical University of Graz (to be announced)
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, regulatory authorities and members of the Research Ethics Committee.
Trials Sponsor: Medical University of Graz, Auenbruggerplatz 2-4, 8036 Graz

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Abbreviations

AESI	Adverse events of Special Interest
ALAT	Alanine-Aminotransferase
ASAT	Aspartate-Aminotransferase
BASG	Bundesamt für Sicherheit im Gesundheitswesen
BMI	Body mass index
CHF	Congestive Heart Failure
CLTR	Department for Clinical Trials
CRF	Case Report Form
CRT	Cardiac resynchronisation therapy
CV	Cardiovascular
DCM	Dilative cardiomyopathy
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl-Transferase
HDL	High Density Lipoprotein
HFmrEF	Heart Failure with Mid-Range Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ICD	Internal Cardioverter Defibrillator
IMI	Institute of Medical Informatics, Statistics and Documentation
ISF	Investigator Site File
INS	Institute Surveillance
KKS	Koordinierungszentrum für Klinische Studien

LBBB	Left bundle branch block
LDL	Low Density Lipoprotein
LPLV	Last Patient Last Visit
MCI	Myocardial Infarction
nsVT	Non sustained ventricular tachycardia
nt-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
pH	Pondus Hydrogenii
QoL	Quality of life
RR	Riva Rocci Blood Pressure Measurement
SGLT-2	Sodium-dependent glucose cotransporter 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
sVT	Sustained ventricular tachycardia
T2DM	Type 2 Diabetes Mellitus
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VF	Ventricular fibrillation
VT	Ventricular tachycardia
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection

AMENDMENT HISTORY

Amendment No.	Protocol Version	Date	Details of Changes made
EC Submission	1.16	25-May-2020	-
Supplemental EC submission	1.17	17-Jul-2020	Data analysis was changed
1	1.18	04-Nov-2020	Study Sites were added
2	1.19	09-Aug -2021	Clarification of inclusion criterion 2 eCRF (HybridForms®) Time schedule
3	1.20	22-Dec-2021	Study site (Uniklinikum St. Pölten) was added Additional Information about SAE Reporting Timeframe correction of secondary outcomes

Synopsis

Sponsor	Medical University of Graz Auenbruggerplatz 2-4 8036 Graz, Austria
Coordinating Investigator	Dirk von Lewinski, MD, Associate Professor
Indication	Patients with HFrEF or HFmrEF, and ICD±CRT therapy
Study design and phase	Randomized, prospective, placebo-controlled, double blind, multicenter, phase III study in patients with HFrEF or HFmrEF, and ICD±CRT therapy
Study Short Title	Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS
Keyword	SGLT-2 inhibition, heart failure, ICD, CRT, VT
Aims of the trial	The primary objective is to investigate the impact of Ertugliflozin on total burden of ventricular arrhythmias. Further objectives will be number of therapeutic interventions of implanted devices, atrial fibrillation, heart failure biomarker and changes in physical function quality of life, stress and anxiety.
Outcome measures of the trial	*Primary outcome measures:* Difference in number of sVT/VF episodes between treatment groups from randomization to week 52 *Secondary outcomes measures:* Difference in nsVT episodes between treatment groups from randomization to week 52 Difference in number of appropriate therapeutic ICD therapies between treatment groups from randomization to week 52 Difference in the change of nt-proBNP levels between treatment groups from randomization to week 52 Difference in the change of HbA1c between treatment groups from randomization to week 52 (in subjects with known T2DM) Difference in the number of hospital re-admissions due to heart failure between the treatment groups from randomization to week 56 Difference in the duration of hospital stay between the treatment groups after initiation of the study treatment from randomization to week 56 Difference in cardiovascular mortality between treatment groups from randomization to week 56
Number of patients	402 patients
Time schedule	*With reference to the trial:* EC Submission: NOV/2020 Local Authority Submission: SEP/2020 First Patient First Visit (FPFV): JUN/2021

	Last Patient First Visit (LPFV): JAN/2023 Last Patient Last Visit (LPLV): JAN/2024 Data Base Lock: APR/2024 First Results available: JUN/2024 Clinical Study Report: JUN/2024 *With reference to patients:* Duration of the treatment: 12 months
Main inclusion criteria	1) HFrEF or HFmrEF, and ICD±CRT therapy > 3 months 2) At least 10 documented VT episodes (either nsVT or sVT ± ICD treatment) within the last 12 months plus: - nt-proBNP > 500pg/mL or - LV-EF < 35% or - hospitalization for heart failure within the last 12 months or - >100nsVTs within the last 12 months ->1 sVT/VF within the last 12 months 3) Informed consent has to be given in written form. 4) eGFR > 30 ml/min/1.73m^2 5) Blood pressure before first drug dosing: $RR_{systolic}$ >100mmHg 6) Blood pressure before first drug dosing: $RR_{diastolic}$ >60mmHg 7) 18 – 80 years of age
Main exclusion criteria	1) Any other form of diabetes mellitus than type 2 diabetes mellitus, history of diabetic ketoacidosis 2) Ongoing ventricular arrhythmia 3) Known allergy to SGLT-2 inhibitors 4) Haemodynamic instability as defined by intravenous administration of catecholamine, calciumsensitizers or phosphodiesterase inhibitors 5) >1 episode of severe hypoglycaemia within the last 6 months under treatment with insulin or sulfonylurea 6) Planned catheter ablation for ventricular arrhythmia 7) Planned explantation of ICD, or planned up/downgrade to/from CRT-D device
Study medication	Active substance: Ertugliflozin Commercial name: Steglatro Manufacturer: MSD
Treatment plan	Ertugliflozin, 5mg once daily orally administered or matched placebo

1. INTRODUCTION AND RATIONALE

Sodium-dependent glucose cotransporter 2 (SGLT2) is mainly expressed in human kidneys and small intestinal cells. In the proximal tubule of the nephron SGLT2 is responsible for the reabsorption of approximately 90% of the filtrated glucose. Inhibition of SGLT2 was shown to increase renal glucose excretion and to lower glucose. Subsequently, a number of SGLT-2 inhibitors were developed and are currently approved for the treatment of type 2 diabetes. CV outcome trials, required by the European Medicines Agency (EMA) and Federal Drug Administration (FDA) have proven additional beneficial effects on cardiovascular outcome in various compounds of that class. Empagliflozin could even show significant positive effects on mortality(1). More consistent and most pronounced was the effect of reducing heart failure hospitalisation. Most recently, data of dapagliflozin was published (DAPA-HF)(2) extending these beneficial effects to non-diabetic heart failure patients, significantly reducing the primary endpoint of CV death and worsening heart failure as well as CV-mortality alone and even all course mortality.

As dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE) in patients with type 2 diabetes mellitus, providing 87% and 96% of maximal inhibition, respectively (product information Steglatro), the lower dose can be expected to be comparably efficient and will therefore be used in this study. This is also confirmed by the data of a recent pooled analysis of previous phase III trials with ertugliflozin showing a reduction in HbA1c of only 0.1% (3).

Ventricular arrhythmias are a typical feature of advanced heart failure with reduced ejection fraction (HFrEF) or heart failure with mid-range ejection fraction (HFmrEF), and account for a large proportion of cardiac death in this population. Implantation of an ICD is a class IA recommendation in the ESC heart failure guidelines both in secondary prevention and primary prevention (IB for DCM patients)(4). Additional CRT function is a class IA recommendation in all of these patients with QRS duration >150ms in sinus rhythm(4). Since arrhythmias occur independent of the type of cardiomyopathy (ischemic, dilative, idiopathic) the unifying phenotype of altered contractility and elevated diastolic pressure and potentially increased systemic inflammation itself must be regarded as the trigger of these arrhythmias(5).

Therefore, every improvement of heart failure should result in a reduction of ventricular arrhythmias. This has been shown extensively for beta-blockers(6), aldosterone-antagonists(7; 8), and ARNIs(9; 10). Large outcome studies with ACE inhibitors did only give limited insight in the type of arrhythmic events, their causes, and the effect of the treatments(11; 12), while studies analysing the rate of ventricular arrhythmias did show a significant reduction in these events(13).

Previous data showed that SGLT-2 inhibitor dapagliflozin (DAPA-HF) improved primary outcome in a HFrEF population comparable to sacubitril/valsartan in the PARADIGM trial(9) (both trials with a NNT of 21). Therefore, a comparable impact on heart failure morbidity and ventricular arrhythmias can be assumed for both drugs. Moreover, Martens et al. reported on a highly significant reduction of ventricular arrhythmias after initiation of sacubitril/valsartan in a retrospective analysis of 151 patients with an observation period of 6 months. The number of VT/VF episodes declined by more than two thirds(10).

Mortality in patients on ICD therapy is high despite optimal medical treatment. The study by Martens is a retrospective analysis of data of patients that were followed throughout the observation period of 364 days.

Therefore, severely ill patients and at least those who died within these 12 months were not analysed. Obviously, these patients tend to have the highest burden of ventricular arrhythmias. Therefore, event rate in the Martens study is underestimated.

More reliable data on event rates derive from prospective randomized trials such as the RAFT study. They report a rate of VTs of ~2 per year (11278 appropriate ICD detections in 5953.6 patient-years of follow-up) in a cohort of patients with severely reduced left ventricular ejection fraction (<30%).

Within another increased-risk population treated in the SHIELD trial 58% of the placebo-group experienced "all-cause shocks plus symptomatic tachyarrhythmias terminated by ATP". The overall number of episodes was 1595 in 214 patients (average of ~7.5/patient and year).

1.1 Aim of the study

The aim of this mechanistic study is to investigate the impact of ertugliflozin on the ventricular arrhythmic burden, physical function, quality of life and biomarkers in heart failure in patients with ICD±CRT therapy.

1.2 Study hypothesis

Treatment with the SGLT-2 inhibitor ertugliflozin will reduce sVT/VF episodes more effectively than placebo within 12 months.

2. OBJECTIVES AND OUTCOMES

2.1 Primary and Secondary Objectives

The primary objective is to investigate the impact of ertugliflozin on ventricular arrhythmia burden. Further objectives will be the number of therapeutic interventions of implanted devices, atrial fibrillation, heart failure biomarker and changes in physical function, quality of life, stress and anxiety.

2.2 Safety objectives

- All-cause mortality
- Number of serious adverse events
- Number of hypoglycaemic events
- Number of genital infections
- Number of ketoacidotic events
- Number of ventricular electric storm episodes
- Changes in liver function parameters (AST, ALT, GGT)
- Changes in renal function parameters (creatinine, eGFR)

2.3 Primary outcome

Difference in number of sVT/VF episodes between treatment groups from randomization to week 52

2.4 Secondary outcomes

Secondary outcomes measures:

Difference in nsVT episodes between treatment groups from randomization to week 52

Difference in number of appropriate therapeutic ICD therapies between groups from randomization to week 52

Difference in the change of nt-proBNP levels between treatment groups from randomization to week 52

Difference in the change of HbA1c between treatment groups from randomization to week 52 (in subjects with known T2DM)

Difference in the number of hospital re-admissions due to heart failure between the treatment groups from randomization to week 56

Difference in the duration of hospital stay between the treatment groups after initiation of the study treatment from randomization to week 56

Difference in cardiovascular mortality between treatment groups from randomization to week 56

3. STUDY DESCRIPTION

3.1 Design

This is a randomized, double-blind (patients and physicians), placebo controlled multi-center study to evaluate the effect of ertugliflozin 5mg once daily (p.o.) for 52 weeks on the ventricular arrhythmic burden and markers of physical and mental well-being as well as biomarker for heart failure in HFrEF and HFmrEF patients with ICD±CRT therapy. The study will be conducted in 8 experienced sites in Austria with an aim to enrol 402 patients (Figure 1) to evaluate the overall study hypothesis.

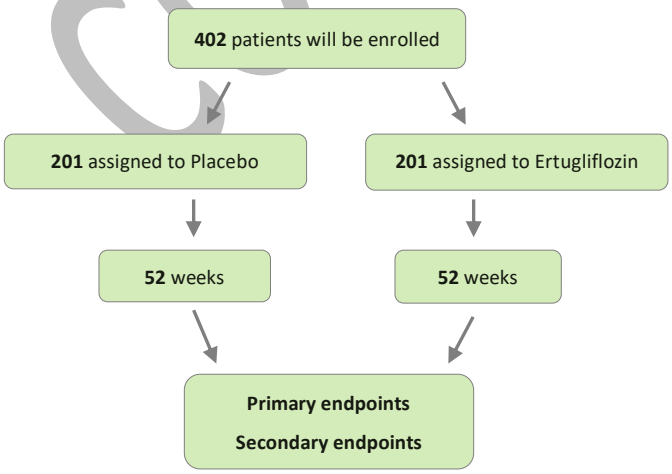

Figure 1 Study Flow Chart

3.2 Duration of study

It is anticipated that the study will run for 30 months.

4. STUDY POPULATION

We will study subjects with HFrEF or HFmrEF and ICD±CRT therapy with ≥10 episode of non-sustained VT within the last 12 months before enrolment. We aim to recruit >30% of subjects with established type 2 diabetes mellitus.

4.1 Inclusion criteria

1) HFrEF or HFmrEF and ICD±CRT therapy > 3 months

2) At least 10 documented VT episodes (either nsVT or sVT ± ICD treatment) within the last 12 months plus

- nt-proBNP > 500pg/mL or

- LV-EF < 35% or

- hospitalization for heart failure within the last 12 months or

- >100nsVTs within the last 12 months- > 1 sVT/VF within the last 12 months

3) Informed consent has to be given in written form.

4) eGFR > 30 ml/min/1.73m^2

5) Blood pressure before first drug dosing: $RR_{systolic}$ >100mmHg

6) Blood pressure before first drug dosing: $RR_{diastolic}$ >60mmHg

7) 18 – 80 years of age

4.2 Exclusion criteria

1) Any other form of diabetes mellitus than type 2 diabetes mellitus, history of diabetic ketoacidosis

2) Ongoing ventricular arrhythmia

3) Known allergy to SGLT-2 inhibitors

4) Hemodynamic instability as defined by intravenous administration of catecholamine, calcium-sensitizers or phosphodiesterase inhibitors

5) >1 episode of severe hypoglycaemia within the last 6 months under treatment with insulin or sulfonylurea

6) Planned catheter ablation for ventricular arrhythmia within upcoming 12 months

7) Planned explantation of ICD, or planned up/downgrade to/from CRT-D device within upcoming 12 months

8) Existing therapy with SGLT-2 inhibitors

4.3 Withdrawal criteria

Subjects may be withdrawn from the study at the discretion of the Investigator or Sponsor due to a safety concern or if judged non-compliant with trial procedures. A subject must be withdrawn from treatment of the following applies:

- Subject chooses to withdraw from the study at any time
- Adverse event requires unblinding of the study medication

- Pregnancy or intention of becoming pregnant
- Intolerable adverse effects
- Major violation of the study protocol
- Occurrence of an exclusion criterion
- Other circumstances that would endanger the health of the subject if he/she were to continue his/her participation in the trial.

Reasons for withdrawals and discontinuation of any subject from the protocol have to be recorded.

4.4 Termination of the entire trial

Premature termination of the clinical trial will be considered when the risk-benefit ratio changes markedly for the patient, the use of the study medication is no longer justifiable, the sponsor believes it is necessary to terminate the clinical trial for safety reasons, when early evidence of the superiority or inferiority of a treatment group is obtained by an interim analysis after 25 and 50% of patients completed the trial, or by other research results, or when the clinical trial proves to be impracticable.

4.5 Unblinding

In the case of a requirement to unblind study medication, one of the chief investigators needs to be informed to discuss the unblinding. The unblinding list is held by the Institute of Medical Informatics, Statistics and Documentation (IMI), Medical University of Graz, which is not involved in study investigations.

5. VISIT PROCEDURES, MEASUREMENTS AND ASSESSMENTS

5.1 Recruitment and screening

Sites will recruit competitively and sites will receive compensation for their work based on a per-patient fee. The clinic staff of the EP/arrhythmia service informs patients about the possibility of being enrolled in this study. No study-related procedures are undertaken before obtaining informed consent. The study team in detail explains the study procedures and asks the participant about their willingness to participate in this research study. After informed consent is signed and obtained, participants are given a signed copy of the informed consent document and are assigned a screening identification number.

After obtaining informed consent at the screening visit, subject´s eligibility will be further assessed and documented by using a source data form with a list of inclusion and exclusion criteria, medical history (including all medications past and current) will be acquired and the following measurements will be performed: body weight, height, blood pressure, ECG and blood parameters (see Table 2). Laboratory results up to 14 days before screening can be used to test eligibility for the trial.

Subjects unable to provide written informed consent will not be included in the study.

5.2 Randomisation

After screening, all eligible patients for the trial will be randomised into one of the two arms of the study via Randomiser Software (Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, http://www.randomizer.at), which will be programmed with a randomisation schedule provided by an independent statistician. The randomisation will be stratified by site, by type 2 diabetes and by eGFR < 60 vs ≥ 60.

Only the subject number will be recorded in the case report form (CRF). The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

A summary of all visits and procedures has been outlined below (Table 1). A more detailed description of each visit and accompanying procedures can be found later in the protocol (5.4 - 5.5)

5.3 Visit schedule

	Visit 1 (V1) Screening / Baseline	Visit 2 (V2) (Week 52 ± 4)	Visit 3 (V3) (4 weeks ±1w after V2)
Informed Consent	X		
Inclusion/exclusion criteria	X		
Randomisation	X		
Demography, medical history	X		
Concomitant medication	X	X	
Vital signs	X	X	
Height	X		
Weight	X	X	
Physical examination	X	X	
ECG	X		
Cardiac ultrasound	X	X	
Biobank sampling	X	X	
ICD interrogation	X	X	
nt-proBNP (local)	X	X	
Blood sampling	X	X	
Liver function parameters (AST, ALT, GGT)	X	X	
Renal function parameters (creatinine, eGFR)	X	X	
Adverse Events		X	X
Dispense medication	X		
Drug accountability		X	
Safety assessment before discharge	X		

Table 1: visit schedule (visit 3 telephone visit only)

5.4 Visit procedures

Visit 1 - Screening/Enrolment Visit (Day 0)

- Obtain informed consent of potential participant verified by signature on study informed consent form (10.5)
- Collect blood for routine biochemistry and to check inclusion criteria (eGFR, nt-proBNP) (5.5.5)
- Collect and prepare blood samples for biobank (5.5.6)
- Obtain demographic information, medical history, medication history and tobacco use history (5.5.1)
- Perform ECG, echocardiography, ICD interrogation (5.5.2)
- Record vital signs (5.5.3)
- Measure body weight and body height (5.5.4)
- Verify inclusion/exclusion criteria (4.1 and 4.2)
- Randomize the subject (5.2)
- Dispense the study medication for trial period (9.4)
- Adjust concomitant antihyperglycaemic medication
- Assessment of side effects and patient safety before discharge

Visit 2 - Follow-up Visit (Week 52 ± 4 weeks)

- Record adverse events as reported by participant or observed by investigator (6.1 – 6.5)
- Perform echocardiography, ICD interrogation (5.5.2)
- Record vital signs (5.5.3)
- Measure body weight (5.5.4)
- Collect blood for routine biochemistry (5.5.5)
- Record changes in medication (5.5.1)
- Collect and prepare blood samples for biobank (5.5.6)
- Record participant's adherence to treatment program
- Drug accountability (9.5)

Visit 3 - Telephone assessment (4weeks ± 1week after V2)

- Record adverse events as reported by participant (6.1 – 6.6)

5.5 Description of procedures and measurements

5.5.1 Medical history and physical examination

A medical history will be performed at the screening visit to record illnesses, disorders and medications. This information needs to be updated on all follow-up visits.

Physical examination will be performed at the Screening visit (study visit 1) according to local procedure. During this visit the physician will perform a physical examination with the focus on cardiac, lung and abdominal examination. Any abnormal, clinical significant findings must be recorded in the SDF (Source Data Form) as well as in the eCRF (HybridForms®). Any changes in subsequent visits as compared to the screening visit which fulfils the criteria of an AE must be recorded as an AE. Any changes in concomitant illness will be recorded as changes in medical history. Any changes in medications will be recorded in the eCRF.

5.5.2 ECG, echocardiography, ICD interrogation

An ECG, echocardiography, and ICD interrogation will be performed at the screening visit. In our study, ICDs are interrogated both with telemedicine (home-monitoring) and during on-site ICD follow-ups.

Patients will be offered to be included in our home-monitoring program. Currently, already 80% of patients have a home-monitoring device and routinely (every 4 months) transmit their data. In case of an alarm (sustained VT/VF) the data is transmitted automatically. In addition, all patients, regardless if they have a home-monitoring device or not, will be checked in the outpatient clinic on a yearly basis.

All arrhythmic events are recorded in the patient database. For this study, the number of episodes recorded during the study period will be tallied up.

All tests will be interpreted, signed and dated by the investigator before randomisation.

5.5.3 Vital signs

Pulse should be recorded at all visits after resting for five minutes in a sitting position. Systolic and diastolic blood pressure will be measured in sitting position at all visits.

5.5.4 Body weight and height

Weight should be measured at all visits. The same and calibrated pair of scales should preferably be used throughout the trial. Height will be recorded at the screening visit. BMI (body mass index) will be calculated as follows: BMI = weight (kg)/height^2 (m^2).

5.5.5 Routine biochemistry

Blood samples will be obtained at all visits and processed by the local laboratory using standard methods' for routine tests. Patients can take their regular morning medications but are asked that they do not take any of their diabetes medications on the morning of their study visit. Patients should bring their regular medication along to their study visits to be further advised by the doctor. See table 2 below for a detailed description of blood collection at each visit:

Blood test	Visit 1	Visit 2
Haematology (full blood count)	X	X
HbA1c	X	X
Sodium, Potassium, Chloride	X	X
Calcium	X	X
Phosphate	X	X
Magnesium	X	X
Iron, Ferritin, Transferrin	X	X
Creatine Kinase	X	X
LDH (Lactatdehydrogenase)	X	X
AST (Aspartate-Aminotransferase)	X	X
CK MB	X	X
ALT (Alanine-Aminotransferase)	X	X
GGT (Gamma-Glutamyl-Transferase)	X	X
CRP (C-reactive Protein)	X	X
Creatinine	X	X
eGFR	X	X
Total cholesterol	X	X
Triglycerides	X	X
HDL (high density lipoprotein)	X	X
LDL (low density lipoprotein)	X	X
NT-pro BNP	X	X

Table 2: Summary of blood tests at each study visit

5.5.6 Blood sample collection and plasma extraction for biobanking

Blood will be collected via venous puncture into 16ml serum and 10ml EDTA vacutainers and centrifuged within 30 min of collection. Plasma should be transferred into Eppendorf tubes and stored at -80°C locally. In regular intervals these samples will be shipped on dry ice to the Biobank of the Medical University of Graz, where they will be stored at -80°C for future biomarker analyses. Additional biomarkers will be measured in batches from these stored biomarker samples.

5.6 Benefit-Risk Assessment

Ertugliflozin has been studied in subjects with type 2 diabetes as monotherapy as well as in combination with DDP-inhibitors as well as metformin. A cardiovascular safety study is ongoing(14). However, it has not been studied with respect to cardiac arrhythmias, yet. Other SGLT-2 inhibitors already finished the cardiovascular outcome trials(1; 15-17) demonstrating cardiovascular safety and beneficial effects, most prominent with respect to heart failure. A class effect can be assumed. Moreover, first data is published, demonstrating beneficial cardiovascular effects in non-diabetic patients with heart failure, too. As heart failure per se is a trigger for ventricular arrhythmias, every improvement in heart failure is likely to reduce ventricular arrhythmias, too.

With respect to diabetes it can to be taken as given that the drug is not causing hypoglycaemic events per se, hypoglycaemia appears not to be a major issue in subjects without diabetes, that are studied in this trial as well. When ertugliflozin is used together with sulfonylurea or insulin, hypoglycaemia might occur and therefore participants will be instructed to reduce concomitant antihyperglycemic medication accordingly.

Fungal genital infections are the most common side effect of ertugliflozin and participants will be informed about this and instructed on prevention measures.

6. ADVERSE EVENTS (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, including an exacerbation of a pre-existing condition, or disease temporally associated with the use of the trial device/procedure, whether or not considered related to the treatment.

All adverse events that occur during this study will be recorded on the adverse event case report forms.

6.1 Adverse Event description

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. AEs will be recorded throughout the study.

6.2 Severity of Adverse Events

Mild: Awareness of event(s) or sign(s) but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Incapacitating or causing inability to carry out usual activity

6.3 Causality of Adverse Events

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

6.4 Abnormal Laboratory Test Results

All clinically significant abnormal laboratory test results besides creatinkinase and NT-proBNP occurring during the study will be recorded as adverse events.

6.5 Adverse events of Special Interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the Pharmacovigilance Department of MSD within the same timeframe that applies to SAEs.

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per Investigator discretion.

The following are considered as AESIs:

6.5.1 Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters after randomisation:

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood sample
- an isolated elevation of ALT and/or AST ≥ 5 fold ULN

These laboratory findings constitute a hepatic injury alert and the patients showing these abnormalities need to be followed up according to medical judgement.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test.

6.5.2 Decreased renal function

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI “decreased renal function” the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgement.

6.5.3 Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA).

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration. Due to its mechanism of action, ertugliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in the table below.

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

Table 3: Diagnostic criteria for DKA

* Nitroprusside reaction method
** Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18
*** Calculation: (Na+) – (Cl- + HCO3-) (mEq/L)

6.5.4 Events involving lower limb amputation

This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb).

Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

6.6 Serious Adverse Events (SAE)

An SAE is defined as any event that

- Results in death;
- Is immediately life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site,). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the investigator.

6.6.1 Reporting of SAEs

The study sites shall report (i.e., from signing the informed consent onwards through the trial defined follow-up period) all SAEs and non-serious AEs which are relevant for a reported SAE and Adverse Events of Special Interest (AESI) by fax or other secure method using the FDA Safety Information Form to the MSD Unique Entry Point immediately (within twenty four (24) hours or next business day whichever is shorter)

Merck Sharp & Dohme Ges.m.b.H
The ICON Vienna
Wiedner Gürtel 9-13
Fax: 0800 809 802

The sponsor will report the SAE to the ethics committee and the local authorities.

A suspected unexpected serious adverse reaction (SUSAR) is designated as such according to Guideline 2001/20/EG. A serious adverse reaction is deemed unexpected when it is not listed in the corresponding basic document (Summary of Product Characteristics, IB, IMPD).

7. STATISTICAL ANALYSES

The sample size calculations and the primary statistical method are based on the primary endpoint, which is the number of VT/VF episodes from randomization to week 52. The primary objective is to compare the rate of VT/VF episodes across the two experimental arms. The number of VT/VF episodes within 52 weeks can be considered as a discrete variable with relatively few possible values (0, 1, 2, 3 …) per patient. This fact prevent us from using the most common statistical methods in clinical trials that assume normality, such as Student's t-test, linear regression or

analysis of variance. We, instead, will use the negative binomial regression model, which is most appropriate in the case of recurrent events (the current situation), allows investigation of the treatment effect and confounding variables, and adjusts for variable follow-up times by using time at risk as the offset. For more details on the arguments to use the negative binomial models in this kind of research, please see: (18). Furthermore, the negative binomial will be used instead of the Poisson distribution (also used for modelling count data) due to expected over-dispersion in the data.

7.1 Sample size and power considerations

Previous data showed that VT/VF episodes are decrease by two thirds within 6 months after initiation of sacubitril/valsartan in ICD±CRT patients (10). sVT/VF Episodes declined by 62.5% whereas nsVTs rate dropped by ~70%. Based on comparable effects on heart failure morbidity with either SGLT-2 inhibition or sacubitril/valsartan treatment we expect a profound reduction in sVT/VF in the treatment arm. Since data of the large SGLT2 outcome trials which did not focus on arrhythmias and their detection but only counted cases of sudden cardiac death have a signal of smaller effects we calculate with a decrease in the event rate of 30%. Moreover, the retrospective analysis by Martens et al provides a rather low event rate in their population. However, as pointed out in the Introduction other prospective randomized trials have considerably higher event rates. The sample size calculation is based on the mathematical formula provided by Zhu and Lakkis for comparing event rates of two negative binomial distributions (19). We used the function power.nb.test of the package MKmisc in R that implements the results of the paper cited above. According to that formula, the parameters needed to calculate the sample size are: The expected yearly rate of VT/VF episodes in the control group (r0), The minimal clinical relevant effect (RR) defined here as the ratio of expected VT/VF episodes rates (RR = expected rate in treated/expected rate in control = r1/r0), the average follow-up or treatment duration (duration), the negative binomial dispersion parameter (k), the Type I error probability (α) and the power (1 - β). To detect a 30% reduction in VT/VF episodes rate in the ertugliflozin group as compared to the placebo group (i.e. using RR = 0.70), with a power of 80% and an alpha-level of 0.05%, a sample size of 191 patients in each group is needed. In this sample size calculation, we assumed the dispersion parameter k to be 1.0, the expected yearly rate of VT/VF episodes in the control group (i.e. r0) to be 1.0 and an average follow-up of 11.4 months. To account for a dropout rate of about 5% in each group, we will need of 402 patients in each arm.

Out of the > 1000 patients with ICD±CRT being seen at our out-patients clinic >50% have experienced episodes of non-sustained VT within the last 12 months. In order to enrich the study population with higher risk patients at least on additional inclusion criterion has to be met (either nt-proBNP > 500pg/mL or LV-EF < 35% or hospitalization for heart failure within the last 12 months or >100nsVTs or > 1sVT/VF episode within the last 12 months).

About 5-10% of our patients are currently treated with ARNI. Expecting similar numbers in the other participating centers we feel confident to recruit patients for this trial within 18 months. Moreover, the recent DAPA-HF trial with 11% of patients on ARNI therapy revealed an unaltered benefit of SGLT-2 inhibition in these patients(2).

Taking into account that compared to the Martens-trial the expected reduction in the applied study is much lower, the observation period twice as long and the populations risk is enriched due to the inclusion criteria the calculation can be rated conservative.

7.2 Data analysis

Intention-to-treat (ITT) analyses will be applied as the primary analysis. Analysis of the primary endpoint is comparison of the number of sVT/VF episodes between treatment groups from randomization to week 52. The primary endpoint will be analysed using analysis of covariance (ANCOVA), with treatment as a fixed factor, the baseline number of sVT/VF episodes as a covariate and with adjustment for history of T2D and eGFR and site of randomization.

Normally distributed variables will be presented as mean ± standard deviation (SD) and skewed distributed variables as median and interquartile range [IQR]. Comparisons between treatment and placebo group will be performed by an unpaired two sample *t*-test, Mann–Whitney test, or χ^2 test as appropriate.

A two-tailed p-value ≤0.05 will be considered statistically significant. A detailed statistical analysis plan including pre-specified subgroup analyses will be finalized ahead of database lock.

8. DATA MANAGEMENT

Data Management is the responsibility of the Medical University of Graz, Department of Cardiology and the study Monitor. The subject and the biological material obtained from the subject will be identified by subject number, trial site and trial identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional and national requirements.

This study will capture and process data using an electronic Case Report Form. . Data and reports will be extracted from the database throughout the study to monitor progress and training will be provided to all study staff on use of the database. The study will be monitored by qualified employees of the research group of cardiovascular Diabetology based on a specific monitoring plan.

9. TREATMENT

9.1 Study medication

Ertugliflozin is a sodium-glucose cotransporter 2 (SGLT2)-inhibitor. It works by increasing the amount of sugar that leaves the body in the urine. The study dose is 5mg once daily in the morning, taken with or without food. Each tablet contains 5mg Ertugliflozin or Placebo. The pharmaceutical form is a 6.4 x 6.6 mm large triangular tablet debossed „701“ on one side Ertugliflozin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Ertugliflozin is used in combination with a sulfonylurea and/or insulin. Pharmacy (Anstaltsapotheke) at the University Hospital of Graz, Austria will pack the medication as 52 weeks supplies for study participants and label study medication according to current regulatory requirements.

9.2 Method of administration

The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

9.3 Special precautions for storage

The study drug must be kept locked in a secure area. No particular storage conditions are required.

9.4 Dispensing of Study Drug

The study team shall dispense the study drug only to subjects entered into the study, under the direction of the PI or sub-investigators authorized to receive or dispense it. The study drugs will not be dispensed or supplied to any person not authorized to receive it. Each time a study drug is dispensed; there must be documentation in the sponsor provided log (drug accountability log) as to the amount dispensed, to whom it is dispensed, and the date and signature or initials of the person dispensing the drug. Subjects should be advised to follow the study protocol and as appropriate to protocol return all used and unused containers to the site at study visit 2 (week 52). Any discrepancies between the amounts used by the subjects and the amount returned should be documented.

9.5 Return/Destruction of Study Drug

Assure that unused supplies of the study drug are returned to the sponsor in accordance with sponsor requirements. Obtain authorization from the sponsor if unused supplies of the study drug will be disposed of at the end of the study. Maintain records of the return or disposition of the unused study drug, including the unused study drug amount, lot numbers and quantity, method of return or disposition, and any documentation related to shipment or destruction. At the end of the study ensure that all documentation regarding receipt, storage, dispensing, return of used containers, and accountability is complete and accurate.

10. REGULATORY, ETHICAL AND LEGAL ISSUES

10.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions.

10.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

10.3 Independent Ethics Committee/ competent authority

10.3.1 Initial Approval

Prior to the enrolment of subjects, the Ethics Committee at the Medical University of Graz must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

10.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the Ethics Committee for approval as instructed by the Sponsor. Amendments requiring approval may be implemented only after a copy of the approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or the Ethics Committee approval. However, in this case, approval must be obtained as soon as possible after implementation.

10.3.3 Competent Authority

Clinical Trial Applications (EudraCT application and the documents required for the assessment) should be addressed to the Austrian Competent Authority, the Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen, BASG) under the following address:

Austrian Federal Office for Safety in Health Care (BASG)
Austrian Agency for Health and Food Safety (AGES)
Institute Surveillance (INS), Department for Clinical Trials (CLTR)
Traisengasse 5
A-1200 Vienna, Austria

10.4 Insurance

Participant insurance according to legal requirements will be contracted.

10.5 Informed Consent

The participation of a subject in this clinical trial is voluntary. The investigator or a member of the research team will approach the patient to obtain informed consent. The background of the proposed study, the procedure, the follow-up schedule and all potential benefits and risks will be carefully explained to each subject. The person obtaining the informed consent shall:

- Avoid any coercion or undue influence of subjects to participate
- Not waive or appear to waive subject's legal rights
- Use language that is non-technical and understandable to the subject
- Clarify the subject that his/her data are confidential and are encoded with a subject ID number during the investigation
- Provide plenty of time for the subject to consider his/her participation
- Include dated signatures of the subject and of the clinical investigator
- Ask whether the subject has any questions about the study

After a subject has received and read the patient information sheet and agrees to participate in the study, the informed consent form approved by the Ethics Committee must be signed by the subject prior to any study specific tests being performed. It will also be signed by the person responsible for collecting the informed consent. The original will be kept in the subjects study research notes (source documents), a copy will be given to the subject and a copy kept in their hospital notes.

10.6 Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator. The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and Ethic Committees.

10.7 End of Trial

The trial will end after the last subject has completed the follow-up telephone assessment (Study visit 3). All patients will be reviewed by a clinician at their last study visit in order to arrange return to appropriate routine clinical care pathways.

10.8 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and at least for 15 years after study completion, as per the Sponsor's requirements. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date, either in paper or electronically. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator.

11. ADMINISTRATIVE MATTERS

11.1 Source Data

Source documents comprise the CRF and hospital records, laboratory records and correspondence. All documents will be stored safely in a confidential manner at the performing site. The subject will be referred to by a unique study subject number/code, their initials and date of birth on all study-specific documentations. The only exceptions will be the signed Consent Forms, Subject Identification log and subject clinical file, all of which will be stored securely by the clinical site. Source data will be made available for internal and external audits or inspections by regulatory authorities to authorised personnel only. As a minimum requirement the following data must be source data verifiable in source documentation other than the eCRF:

- Existence of subject (subject identifier, subject number and date of birth)
- Confirmation of participation in the trial (subject identification number (ID), trial ID and signed and dated informed consent forms)
- Diagnosis/ indication under investigation
- Visit dates
- Data from AEs, safety information form and pregnancy forms
- Relevant medical history, concomitant illness
- Reason for exclusion or withdrawal

11.2 Language

CRFs will be in German. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

11.3 Data Collection

All data collected will be documented in the source documents and eCRF (HybridForms®).

11.4 Electronic Recording of data

This study will capture and process data using HybridForms® (electronic data capture) which will be built by Kapsch Business Com AG, Graz, Austria. HybridForms® is a fully validated high quality electronic data capture system, which has a full audit trail and controlled level of access. Data and reports will be extracted from the database throughout the study to monitor progress and training will be provided to all study staff on use of the database. The Investigator must ensure that the data is recorded in the eCRFs as soon as possible after the visit preferably within 7 working days.

11.5 Study Management Structure

11.5.1 Trial Steering Committee (TSC)

A Trial Steering committee (TSC) comprised by all principal investigators and chaired be the Chief investigator will be responsible for overseeing the progress of the trial. A TSC Charter will be devised to list the roles and responsibilities of the TSC members. TSC will be convened at least biannually either in person or by teleconference.

11.6 Monitoring

A monitoring plan will be devised based on risk analysis and described in detail in the monitoring manual. During the course of the trial the Monitor will visit the trial sites to ensure that the protocol is adhered to, that all issues have been recorded and to perform source data verification. The study will be monitored periodically by a Clinical Trial Monitor responsible for this study.

Initiation visits will be completed at all trial centres prior to the recruitment of participants, and will consist of review of protocol and trial documents, training with respect to trial procedures (informed consent, SAE reporting, inclusion and exclusion criteria), review of recruitment strategy, review of site facilities and equipment, review of GCP principles, essential document receipt, collection and filing, and archiving and inspection. Copies of the trial specific procedure manuals and related documents will be given to the investigators. The approved version of the protocol should be followed at all times, and any significant protocol deviations will be documented in a Protocol Deviation Form and any significant deviations will be recorded on a Protocol Violation Form submitted to the study coordination centre and Sponsor as soon as possible. The investigators will allow the monitors to:

- inspect the site, the facilities, device management and materials used for the trial
- meet all members of the team involved in the trial, and ensure all staff working on the trial are experienced and appropriately trained, and have access to review all of the documents relevant to the trial
- have access to the electronic case record forms and source data

- discuss with the investigator and site staff trial progress and any issues on a regular basis

The monitor will ensure that:

- A percentage of records will be inspected for confirmation of existence, eligibility based on the results of the Risk Assessment
- 100 % of consent forms will be reviewed along with all SAE's.
- there is adherence to the protocol, including consistency with inclusion/exclusion criteria
- there is GCP and regulatory compliance
- trial documentation is complete and up to date (e.g. correct versions of documents being used, source data captured) and relevant documents are collected for the Trial Master File (TMF)
- the monitored eCRFs have been completed correctly and accurately, and all entries correspond to data captured in source documents

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

All information dealt with during such visits will be treated as strictly confidential. At the end of the trial, close out visits will be performed by the monitor after the final participant visit has been completed and prior to database lock. During this visit the monitor will verify that all trial close out activities are completed – all queries resolved, missing data completed, monitoring completed, archiving arrangements in place, ISF completed and TMF documents collected, and end of trial notification. Each investigator will also be notified that an audit or inspection may be carried out - by the sponsor, sponsor's representatives or the host institution, or regulatory authorities - at any time, before, during or after the end of the trial. The investigator must allow the representatives of the audit or inspection team:

- to inspect the site, facilities and material used for the trial,
- to meet all members of his/her team involved in the trial,
- to have direct access to trial data and source documents, to consult all of the documents relevant to the trial. If an Investigator is informed of an impending audit or inspection, the trial coordination centre should be notified immediately.

11.7 Disclosure of data and publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only. Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor. Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigators is completed. Permission from the Trial Steering Committee is necessary prior to disclosing any information relative to this study outside of the Steering Committee.

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Appendix A Participating Study Centers

- **Study Center Universitätsklinikum Graz**

  PI: Univ.-Prof. Dr. Daniel Scherr

  Universitätsklinik für Innere Medizin

  Klinische Abteilung für Kardiologie

  Auenbruggerplatz 15

  8036 Graz

  Tel.: +43 316 385 12544

  E-Mail: daniel.scherr@medunigraz.at

Principal Investigator:

Assoc.-Prof. Dr. Daniel Scherr:

Signature Date

I have read the attached protocol entitled "Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS (ERASe-Trial) – a phase III Study", V 1.20 dated 22/12/21, and agree to abide by all provisions set forth therein.

- **Study Center Elisabethinen Linz**

PI: PD Dr. Martin Martinek

Ordensklinikum Linz GmbH Elisabethinen

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Principal Investigator:

PD Dr. Martin Martinek:

Signature Date

I have read the attached protocol entitled "Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS (ERASe-Trial) – a phase III Study", V V 1.20 dated 22/12/21, and agree to abide by all provisions set forth therein.

- **Study Center Klinikum Klagenfurt**

PI: Prim. PD Dr. Hannes Alber

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Signature Date

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➢ **Study Center Innsbruck**

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- **Study Center Landesklinikum Wiener Neustadt**

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➢ **Study Center Kepler Universitätsklinikum Linz**

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Signature Date

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