Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS (ERASe-Trial) – a phase III Study

Statistical Analysis Plan

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SAP Signatures

I give my approval for the attached SAP entitled: Ertugliflozin to Reduce Arrhythmic burden in ICD/CRT patientS (ERASe-Trial) – a phase III Study, dated 19/02/2024

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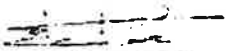
Signature: 

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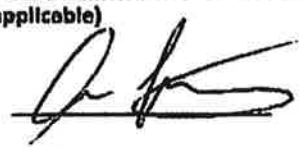
Signature: 

Date: 19/02/2024

Principal Investigator
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19/02/2024

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Abbreviations and Definitions

6MWT	6-minute walk test
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
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

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).

2 Study Objectives and Endpoints

2.1 Primary and secondary objectives

The primary objective of this study is to investigate the impact of Ertugliflozin on incident sustained ventricular tachycardia or ventricular fibrillation (sVT/VF) in patients with ICD±CRT therapy. Secondary objectives investigate the impact of Ertugliflozin on the number of therapeutic interventions of implanted devices, atrial fibrillation, and heart failure biomarkers.

2.2 Primary, secondary and safety endpoints

2.2.1 Primary endpoint

The primary endpoint is the number of incident sustained (>30 seconds) ventricular tachycardia or ventricular fibrillation (sVT/VF) from randomization to week 52.

2.2.2 Secondary endpoints

Secondary endpoints are as follows:

- The number of incident non-sustained ventricular tachycardia (nsVT) from randomization to week 52
- The number of appropriate ICD-treatment episodes from randomization to week 52
- The number of hospitalization due to heart failure from randomization to week 52
- The total number of hospitalization days from randomization to week 52
- The change in NTproBNP from randomization to week 52.
- The change in HbA1c levels from randomization to week 52.
- Cardiovascular mortality from randomization to week 52.

2.2.3 Safety endpoints

- All-cause mortality
- Number of serious adverse events
- Number of hypoglycaemic events
- Number of genital infections
- Number of ketoacidotic events
- Changes in liver function parameters (AST, ALT, GGT)

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- Changes in renal function parameters (creatinine, eGFR)

3 Study Methods

3.1 General Study Design and Plan

This is a two arms randomized controlled multi-center, parallel-group, double-blinded trial. The control group is a placebo and the treated group is Ertugliflozin. The aim of the trial is to show superiority of Ertugliflozin over Placebo in HFrEF and HFmrEF patients with ICD±CRT therapy.

3.2 Inclusion-Exclusion Criteria and General Study Population

3.2.1 Inclusion criteria

1) HFrEF or HFmrEF and ICD±CRT therapy > 3 months
2) At least 10 documented non-sustained VTs 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
3) Informed consent has to be given in written form.
4) eGFR > 30 ml/min/1.73m2
5) Blood pressure before first drug dosing: RRsystolic >100mmHg
6) Blood pressure before first drug dosing: RRdiastolic >60mmHg
7) 18 – 80 years of age

3.2.2 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 hypoglycemia 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.

3.3 Randomization

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.

3.4 Study Assessments

Data is collected according to the following 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	
6min walk test	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		

4 Sample Size

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 (11). 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 1.3 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 total.

5 Statistical analysis

The Negative Binomial Regression model will be used to analyse the primary endpoint (number of sVT/VF episodes from randomization to week 52). These models are suitable when comparing recurrent event rates in different groups. They allow investigation of the treatment effect and confounding variables, and adjust for variable follow-up times by using time at risk as the offset11. They are a generalization of the more commonly used Poisson regression models (in case of over-dispersion) and are also superior to different Cox-regression methods12. We will model the expected number of sVT/VF episodes as follows:

$$\log(\mu_{ij}) = \log(t_{ij}) + \beta_0 + \beta_1 x_{ij}$$

Where tij. Is the exposure time of patient i in group j (j = 1 if control; j=2 if treated), μij is the expected number of sVT/VF episodes of patient i in group j during the exposure period tij and xij is the treatment indicator of patient i in group j (xij = 0 if j=1 (control) and 1 if j = 2 (treated)). It can be shown from the equation above that the yearly rate ratio between treated and controls is a direct function of the parameter β1 and can be derived as

RR = $e^{\beta 1}$. The efficacy of the drug, compared to placebo, will then be investigated by testing the following null and alternative hypotheses:

$$H_0: \beta_1 = 0 \quad \text{vs.} \quad H_A: \beta_1 \neq 0$$

The function glm.nb from the MASS package in R will be used for this reason and for fitting the negative binomial regression model. The model will also adjust for the baseline number of sVT/VF. Sensitivity analysis will be carried out by using methods robust to outliers.

The analysis of secondary endpoints will be as follows: The number of incident nsVT, the number of appropriate ICD-treatment episodes, the total number of hospitalization due to heart failure will be analysed using a beta binomial model. The change in NTproBNP and the change in HbA1c levels from randomization to week 52 will be analysed using a multiple linear regression model. Hospitalization days from randomization to week 52 will be compared between the two groups using mean and SD. Cardiovascular mortality will be analysed by comparing proportions across the two groups.

5.1 Covariates and subgroups

All analyses, including the primary analysis, will be adjusted for the variables used when stratifying the randomization if the sample size permits. Analysis may also be adjusted for baseline levels of the dependent variables if available. No subgroup analyses are planned.

5.2 Missing Data

Missing data will be imputed for the primary analyses if the sample size allows. Missing values will be imputed using Multiple Imputation with Chained Equation (MICE) approach. Ten imputed data sets with will be generated. The analysis will be performed on each of the 10 imputed datasets, which will produce estimates of treatment effect and the standard error of that estimate. Finally, the set of estimates and standard errors will be analysed by the *mice* R package to produce overall (pooled) estimates, confidence intervals, and p-values for the treatment effect.

5.3 Interim Analyses and Data Monitoring (as applicable)

No interim analyses are planned for this study

5.4 Multiple Testing

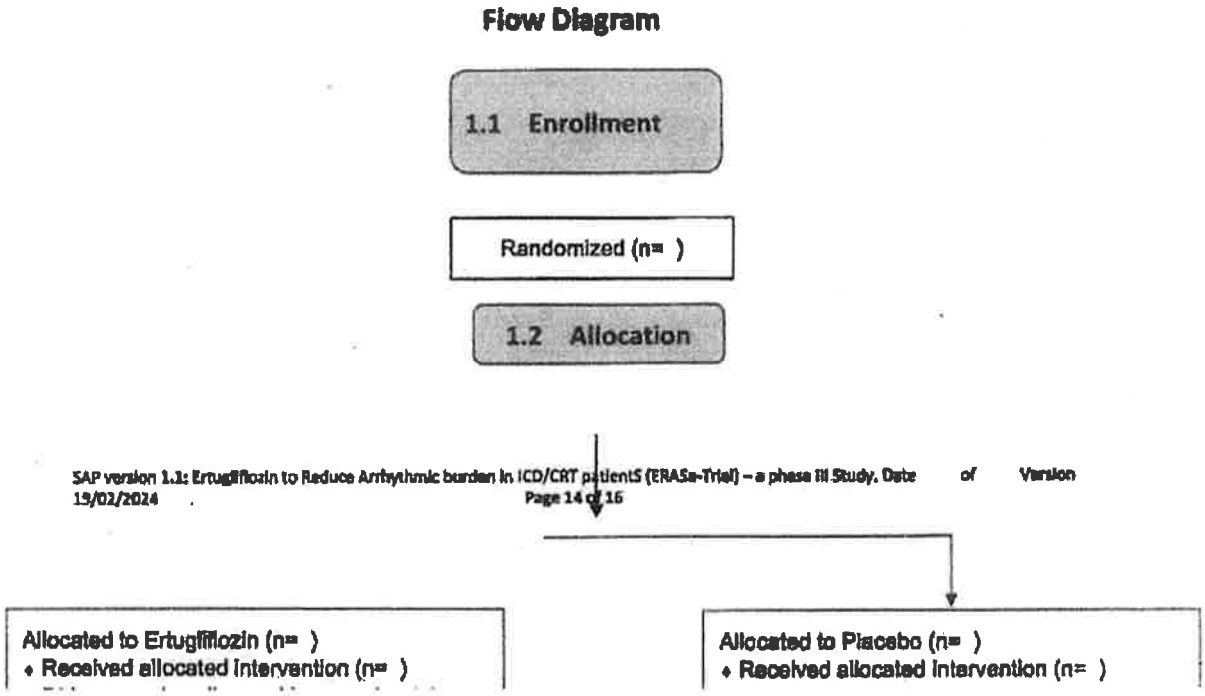
There is no need to control for the overall type 1 error using multiple testing procedure since we have one single primary efficacy endpoint. The overall type 1 error will also not be controlled for when analysing secondary endpoints.

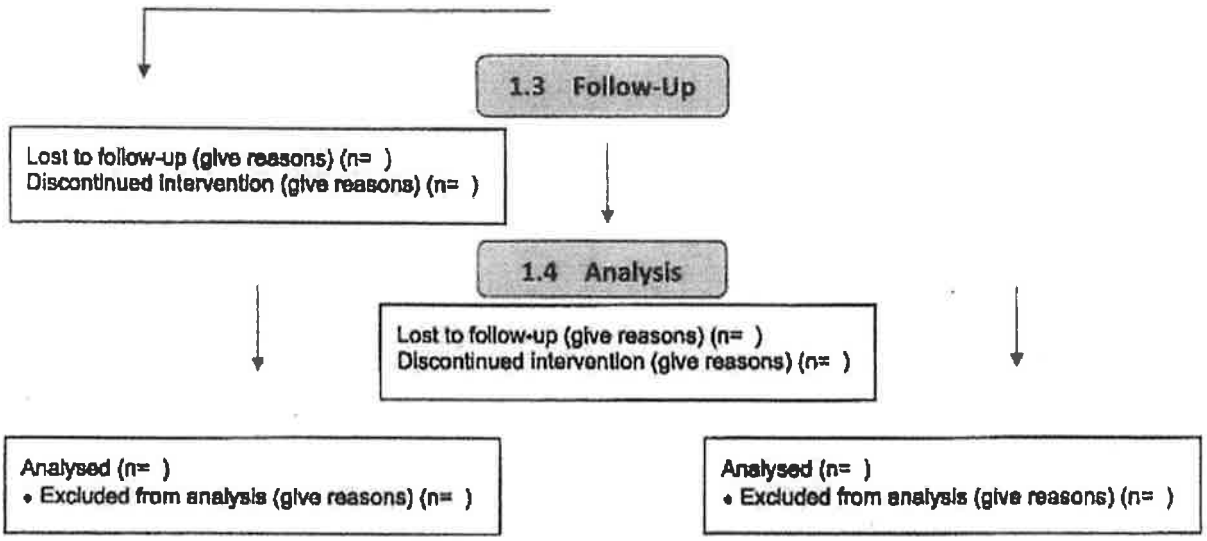
6 Summary of Study Data

All summary tables will be structured with columns for each treatment and overall in the order (overall, placebo, ertugliflozin) and will be annotated with the total population size relevant to that table, including any missing observations. All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables. Demographic and clinical characteristics to be summarized will include all relevant baseline variables.

6.1 Subject Disposition

A graphic showing an overview of the recruitment rate overall and by treatment groups will be provided. Also, a flow diagram will be provided as shown below:





7 Summary of Changes to the SAP

This is the revised version of the SAP. It was revised due to the early termination of the trial and the corresponding lower sample size.

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