EU Clinical Trials Register

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

Summary

EudraCT number	2020-002581-14
Trial protocol	AT
Global end of trial date	23 June 2023

Results information

Result version number	v1 (current)
This version publication date	11 December 2024
First version publication date	11 December 2024

Trial information

Trial identification

Sponsor protocol code	DvL-2020-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz
Sponsor organisation address	Auenbruggerplatz 15, Graz, Austria,
Public contact	Dirk von Lewinski, Medical University of Graz, 43 316385 80684, dirk.von-lewinski@medunigraz.at
Scientific contact	Dirk von Lewinski, Department of Internal medicine, Division of Cardiology., 43 316385 80684, dirk.von-lewinski@medunigraz.at

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2023
Global end of trial reached?	Yes
Global end of trial date	23 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the impact of ertugliflozin on ventricular arrhythmia burden.

Protection of trial subjects:

The trial subjects were well informed about the treatment and its common side effects. Adverse reactions were immediately reported and treated according to the local practice. Fungal genital infections are the most common side effect of Ertugliflozin and subjects were informed about this and instructed on preventive measures. Ertugliflozin in combination with sulfonylurea or insulin might cause hypoglycemia, therefore subjects were instructed to reduce concomitant antihyperglycemic medication accordingly.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted between June 24, 2021 (1st visit of 1st patient) and June 23, 2023 (last visit of last patient) and patients were recruited from eight Austrian sites.

Pre-assignment

Screening details:

The patients with HFrEF/ HFmrEF and ICD and/or CRT therapy with >10 episodes of nsVT within the last 12 months were invited to participate in the study. After obtaining the informed consent, the willing participants were screened for further evaluation for the inclusion and exclusion criteria.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ertugliflozin group

Arm description:

The participants in this arm received ertugliflozin 5mg orally, once daily for 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Ertugliflozin
Investigational medicinal product code	SUB182716
Other name	Steglatro
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ertugliflozin is a sodium glucose co-transporter 2 (SGLT-2) inhibitor. The study dose is 5 mg orally, once daily in the morning, with or withour food, for 52 weeks.

Arm title	Placebo group

Arm description:

The participants in this arm received placebo drug 5 mg orally, once daily for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

The subjects received 5mg of Placebo drug once daily orally for 52 weeks

Number of subjects in period 1	Ertugliflozin group	Placebo group
Started	25	30
Completed	22	24
Not completed	3	6
Consent withdrawn by subject	3	5
Died without sufficient data	-	1

Number of subjects in period 1	Ertugliflozin group	Placebo group
Started	25	30
Completed	22	24
Not completed	3	6

Baseline characteristics

Reporting groups

Reporting group title	Ertugliflozin group
Reporting group description:	
The participants in this arm received ertugliflozin 5mg orally, once daily for 52 weeks	
Reporting group title	Placebo group
Reporting group description:	
The participants in this arm received placebo drug 5 mg orally, once daily for 52 weeks.	

Reporting group values	Ertugliflozin group	Placebo group	Total
Number of subjects	25	30	55
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
The age range of the study population is 18-80 years. This variable represents the average age of the subjects in the respective groups.			
Units: years			
arithmetic mean	65	66	
standard deviation	± 11	± 12	-
Gender categorical			
This variable represents the number of each Gender category in both study arms.			
Units: Subjects			
Female	3	3	6
Male	22	27	49

End points

End points reporting groups

Reporting group title	Ertugliflozin group
Reporting group description:	
The participants in this arm received ertugliflozin 5mg orally, once daily for 52 weeks	
Reporting group title	Placebo group
Reporting group description:	
The participants in this arm received placebo drug 5 mg orally, once daily for 52 weeks.	

Primary: Episodes of sustained ventricular tachycardia and ventricular fibrillation (sVT/VF)

End point title	Episodes of sustained ventricular tachycardia and ventricular fibrillation (sVT/VF)
End point description:	
The primary end point is the difference in number of sVT/VF episodes in the ertugliflozin and placebo group from randomization to week 52.	
End point type	Primary
End point timeframe:	
From randomization to week 52	

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of episodes	73	310		

Statistical analyses

Statistical analysis title	Negative binomial regression model
Statistical analysis description:	
The negative binomial regression model was used to analyze primary outcome. The dependent variable was the number of sVT/VF episodes during the follow up and the independent variable was the treatment category. We adjusted the results for the baseline values of the parameter and the exposure duration. The sample size calculation was based on the formula by Zhu and Lakkis for comparing event rates of two negative binomial distributions.	
Comparison groups	Ertugliflozin group v Placebo group
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Negative binomial reression model
Parameter estimate	Rate Ratio
Point estimate	0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.61

Notes:

[1] - To mitigate the effect of few extreme values we performed prespecified sensitivity analysis using robust estimation approaches for the negative binomial model. The robust methods applied weights on the response variable by applying Tukeys biweight function on the Pearson residuals and/or using the robust Mahalanobis distance for co-variate weighting. Due to early termination of the trial we had a small sample size and a complete-case analysis was used.

[2] - The yearly rate ratio, estimated from the negative binomial model, after adjusting for baseline sVT/VF episodes in the ertugliflozin group was less compared to placebo and this effect remained after adjustment for baseline NTproBNP levels.

Secondary: Number of nonsustained ventricular tachycardia episodes

End point title	Number of nonsustained ventricular tachycardia episodes

End point description:

The difference in the number of non-sustained ventricular tachycardia episodes between the two groups from randomization to week 52.

End point type	Secondary

End point timeframe:

Randomization to week 52

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of episodes	28	130		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of episodes of appropriate ICD therapies

End point title	Number of episodes of appropriate ICD therapies

End point description:

This represents the difference in the number of Implantable cardioverter-defibrillator therapies between the ertugliflozin and placebo group from randomization to week 52.

End point type	Secondary

End point timeframe:

randomization to week 52

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of episodes	5	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NTproBNP levels

End point title	Change in NTproBNP levels
End point description:	
The change in NTproBNP levels from randomization to week 52 in ertugliflozin and placebo groups.	
End point type	Secondary
End point timeframe:	
randomization to week 52	

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: ng/l				
median (inter-quartile range (Q1-Q3))	143 (-6 to 300)	101 (-103 to 322)		

Statistical analyses

Statistical analysis title	Multiple linear regression
Statistical analysis description:	
The confidence interval was not adjusted for multiple comparisons as no plan to control for multiple comparisons was prespecified.	
Comparison groups	Placebo group v Ertugliflozin group
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [3]
Method	Multiple linear regression model
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.69

Notes:

[3] - Multiple linear regression for the change in level from baseline to week 52 in log-NTproBNP levels, adjusting for baseline level, was similar between the ertugliflozin and placebo groups.

Secondary: Change in HbA1c levels

End point title	Change in HbA1c levels

End point description:

This represents the change in HbA1c levels from randomization to week 52 in the ertugliflozin and placebo groups.

End point type	Secondary

End point timeframe:

Randomization to week 52.

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: mmol/mol				
arithmetic mean (standard deviation)	0.9 (± 5.1)	-1.33 (± 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalizations

End point title	Number of hospitalizations

End point description:

This variable represents the mean number of all-cause hospitalizations in each group.

End point type	Secondary

End point timeframe:

Randomization to week 56

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of hospital stays				
arithmetic mean (standard deviation)	0.7 (± 1.0)	1.3 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aleast one hospitalization due to heart failure

End point title	Aleast one hospitalization due to heart failure

End point description:

This represents atleast one hospitalization due to heart failure in ertugliflozin and placebo groups.

End point type	Secondary

End point timeframe:

Randomization to week 56

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of hospitalization	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalizations due to heart failure

End point title	Number of hospitalizations due to heart failure

End point description:

This represents the number of hospitalizations due to heart failure in the ertugliflozin and the placebo group.

End point type	Secondary

End point timeframe:

Randomization to week 56

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of hospitalizations	1	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of hospital stay

End point title	Duration of hospital stay

End point description:

The average number of days of hospitalization in ertugliflozin and placebo group.

End point type	Secondary
End point timeframe:	

Randomization to week 56

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of days				
arithmetic mean (standard deviation)	3.6 (± 5.3)	10.4 (± 23.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiovascular death

End point title	Cardiovascular death
End point description:	

The total number of cardiovascular deaths in ertugliflozin and placebo group.

End point type	Secondary
End point timeframe:	

Randomization to week 56

End point values	Ertugliflozin group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Number of deaths	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

This study reported all serious (SAE) and non-serious adverse events (relevant for a reported SAE) and adverse events of special interest from randomization to week 56.

Adverse event reporting additional description:

The study sites reported all SAE and non-serious AEs and adverse events of special interest by fax or other secure method using the FDA Safety information Form to the MSD Unique entry point immediately.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Ertugliflozin group

Reporting group description:

This is the intervention group and 25 patients were initially enrolled in this group. They Received 5 mg of Ertugliflozin once daily orally from randomization to week 52. Among them, 3 withdrew their consent and 3 died with sufficient telemetric data.

Reporting group title	Placebo group

Reporting group description:

This is the control group. They received 5 mg of Placebo drug once daily orally from randomization to week 52. Initially 30 patients were randomized to this group. Among them, 5 withdrew their consent and 3 died.

Serious adverse events	Ertugliflozin group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 25 (60.00%)	29 / 30 (96.67%)	
number of deaths (all causes)	6	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular death			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 25 (4.00%)	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hospitalization due to cardiovascular event				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 25 (12.00%)	4 / 30 (13.33%)		
occurrences causally related to treatment / all	0 / 5	0 / 5		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nervous system disorders				
Seizure				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 25 (4.00%)	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
General disorders and administration site conditions				
Noncardiovascular death				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 25 (8.00%)	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hospitalization due to non-cardiovascular causes				
subjects affected / exposed	2 / 25 (8.00%)	7 / 30 (23.33%)		
occurrences causally related to treatment / all	0 / 2	0 / 9		
deaths causally related to treatment / all	0 / 0	0 / 0		
Any Hospitalization				
alternative assessment type: Non-systematic				
subjects affected / exposed	10 / 25 (40.00%)	21 / 30 (70.00%)		
occurrences causally related to treatment / all	0 / 12	0 / 33		
deaths causally related to treatment / all	0 / 0	0 / 0		
Death				
alternative assessment type: Non-systematic				

subjects affected / exposed	3 / 25 (12.00%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infectious disease			
subjects affected / exposed	1 / 25 (4.00%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Ertugliflozin group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	2 / 30 (6.67%)	
Blood and lymphatic system disorders			
Hypotension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	1 / 25 (4.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Genital fungal infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 30 (3.33%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2020	Addition of study sites (Wiener Neustadt and Medical University of Vienna)
11 August 2021	change of inclusion criterion (at least 10 documented VT episodes (either nsVT or sVT +/- ICD treatment within the last 12 months
22 December 2021	Addition of new study site (St.Pölten)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to early termination of the trial, we could not achieve the planned power. There is lack of generalizability as our study predominantly included White men. Additionally, 7 patients withdrew their consent.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35045327

http://www.ncbi.nlm.nih.gov/pubmed/39217453