Clinical trial results:
Effects of empagliflozin on diuresis and renal function in patients with acute decompensated heart failure

Summary

EudraCT number	2018-003692-35
Trial protocol	DE
Global end of trial date	29 June 2021

Results information

Result version number	v1 (current)
This version publication date	20 December 2023
First version publication date	20 December 2023

Trial information

Trial identification

Sponsor protocol code	ZKSJ0109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04049045
WHO universal trial number (UTN)	-
Other trial identifiers	ZKS Protocol Code: ZKSJ0109_EMPAG-HF

Notes:

Sponsors

Sponsor organisation name	Friedrich-Schiller-Universität Jena
Sponsor organisation address	Am Klinikum 1, Jena, Germany, 07747
Public contact	Center for Clinical Studies, University Hospital, ZKS@med.uni-jena.de
Scientific contact	Department of Internal Medicine I, Division of Cardiology, Pneumology, Angiology and IMC, University Hospital, 0049 3641 9324101, christian.schulze@med.uni-jena.de

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	03 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2021
Global end of trial reached?	Yes
Global end of trial date	29 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of empagliflozin plus loop diuretics versus placebo plus loop diuretics in patients with ADHF on the increase of urine output

Protection of trial subjects:

The application of the Intervention (oral applicateion of investigational drug/matching placebo, one tablet per day)
is very similar to the one usually applied in clinical routine. Study specific measures were limited to a few general clinical examinations and additional laboratory parameters.

Background therapy: -

Evidence for comparator:

matching placebo used

Actual start date of recruitment	01 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	9
From 65 to 84 years	49
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

60 patients were recruited from 29Sep2019 to 30Apr2021.

Pre-assignment

Screening details:

59 patients treated, one screening failure

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, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum arm

Arm description:

Empagliflozin 25 mg film-coated tablets, for oral use

Arm type	Experimental
Investigational medicinal product name	Empagliflozin 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25mg Empagliflozin once daily for 5 days in addition to routinely administered (weight adjusted) intravenous furosemide

Arm title	Placebo arm

Arm description:

Placebo tablet, film-coated tablets, for oral use, matching to investigational product.

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

Dosage and administration details:

Placebo once daily for 5 days

Number of subjects in period 1[1]	Verum arm	Placebo arm
Started	30	29
Completed	30	29

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 60 patients were screened worldwide, for one patient later turned out that one inclusion criterion wasn`t met (before treatment).

Baseline characteristics

Reporting groups	
Reporting group title	Verum arm
Reporting group description:	
Empagliflozin 25 mg film-coated tablets, for oral use	
Reporting group title	Placebo arm
Reporting group description:	
Placebo tablet, film-coated tablets, for oral use, matching to investigational product.	

Reporting group values	Verum arm	Placebo arm	Total
Number of subjects	30	29	59
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			
Units: years			
median	76.5	80.0	
inter-quartile range (Q1-Q3)	66 to 81	71 to 82	-
Gender categorical			
Units: Subjects			
Female	11	12	23
Male	19	17	36

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients with intention to treat	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients without major protocol deviations	

Reporting group values	ITT	PP	
Number of subjects	59	55	

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	80	80	
inter-quartile range (Q1-Q3)	68 to 82	68 to 82	
Gender categorical Units: Subjects			
Female	36	34	
Male	23	21	

End points

End points reporting groups

Reporting group title	Verum arm
Reporting group description: Empagliflozin 25 mg film-coated tablets, for oral use	
Reporting group title	Placebo arm
Reporting group description: Placebo tablet, film-coated tablets, for oral use, matching to investigational product.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients with intention to treat	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: All patients without major protocol deviations	

Primary: Total urine output summed over 5 days

End point title	Total urine output summed over 5 days
End point description:	
End point type	Primary
End point timeframe: over 5 days	

End point values	Verum arm	Placebo arm	ITT	PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	29	57	53
Units: ml				
median (inter-quartile range (Q1-Q3))	10775 (9100 to 12925)	8650 (6450 to 10350)	9500 (7750 to 11400)	9500 (7750 to 11400)

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Verum arm v Placebo arm
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	2125

Confidence interval	
level	95 %
sides	2-sided
lower limit	840
upper limit	3550
Variability estimate	Standard error of the mean

Secondary: net urine output over 5 days

End point title	net urine output over 5 days
End point description:	
End point type	Secondary
End point timeframe: over 5 days	

End point values	Verum arm	Placebo arm	ITT	PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	29	57	53
Units: ml				
median (inter-quartile range (Q1-Q3))	3725 (2621.5 to 5829.5)	1480 (650 to 3825.7)	3100 (1200 to 5184)	3000 (1200 to 5184)

Statistical analyses

No statistical analyses for this end point

Secondary: net fluid output over 5 days

End point title	net fluid output over 5 days
End point description:	
End point type	Secondary
End point timeframe: over 5 days	

End point values	Verum arm	Placebo arm	ITT	PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	28	29	57	53
Units: ml				
median (inter-quartile range (Q1-Q3))	3925 (2825 to 6505)	1680 (850 to 4025.7)	3350 (1400 to 5384)	3300 (1400 to 5384)

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Verum arm v Placebo arm
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	2005
Confidence interval	
level	95 %
sides	2-sided
lower limit	700
upper limit	3300
Variability estimate	Standard error of the mean

Secondary: change in body weight	
End point title	change in body weight
End point description:	
End point type	Secondary
End point timeframe: day 5	

End point values	Verum arm	Placebo arm	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	25	53	
Units: kg				
arithmetic mean (standard deviation)	-4.19 (± 3.53)	-3.02 (± 2.97)	-3.64 (± 3.24)	

Statistical analyses

Statistical analysis title	Independent samples t-test
Comparison groups	Verum arm v Placebo arm

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.198
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	0.63
Variability estimate	Standard error of the mean

Secondary: cumulative dose of diuretics

End point title	cumulative dose of diuretics
End point description:	
End point type	Secondary
End point timeframe: over 5 days	

End point values	Verum arm	Placebo arm	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	30	29	59	
Units: mg Furosemide equivalent				
arithmetic mean (standard deviation)	313.04 (± 194.57)	351.41 (± 220.66)	331.9 (± 206.9)	

Statistical analyses

Statistical analysis title	indemendent samples t-test
Comparison groups	Verum arm v Placebo arm
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.481
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-38.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-176.7
upper limit	70
Variability estimate	Standard error of the mean

Secondary: diuretic efficiency

End point title	diuretic efficiency
End point description:	
End point type	Secondary
End point timeframe: over 5 days	

End point values	Verum arm	Placebo arm	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	29	57	
Units: mL/mg Furosemide equivalent				
median (inter-quartile range (Q1-Q3))	8.3 (-32.9 to 58.8)	-25.9 (-80.3 to 16.8)	1.0 (-58.6 to 32.5)	

Statistical analyses

Statistical analysis title	Mann-Whitney U Test
Comparison groups	Verum arm v Placebo arm
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	43.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	93
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to day 30	
Assessment type	Systematic

Dictionary used	
Dictionary name	Precoded terms
Dictionary version	1.0

Reporting groups	
Reporting group title	Treatment group
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Serious adverse events	Treatment group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	7 / 29 (24.14%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Hypotension			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac tamponade			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Transient ischaemic attack			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (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			
Death	Additional description: Heart failure		
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)	9 / 29 (31.03%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Cardiac disorders			
Worsening of heart failure			

subjects affected / exposed	1 / 30 (3.33%)	4 / 29 (13.79%)	
occurrences (all)	1	4	
Infections and infestations			
Covid-19 infection			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)	4 / 29 (13.79%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2020	Change of in- and exclusion criteria based on current research results and prolongation of planned study duration.

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.

Short observation period not sufficient to observe AEs after discharge. Study not powered for analysis of end points such as cardiovascular mortality. Focus was early decongestion, inclusion within 12 h of hospitalization.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35766022