Clinical trial results:
An International, Multicentre, Parallel-group, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the effect of Dapagliflozin on Exercise Capacity in Heart Failure Patients with Reduced Ejection Fraction (HFrEF)

Summary

EudraCT number	2018-003442-16
Trial protocol	SE DK
Global end of trial date	07 March 2020

Results information

Result version number	v2 (current)
This version publication date	20 June 2021
First version publication date	20 March 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D169EC00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03877237
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Forskargatan 18, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com

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	20 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2020
Global end of trial reached?	Yes
Global end of trial date	07 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and reduced ejection fraction (LVEF≤40%) [HFrEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity

Protection of trial subjects:

This study will be conducted in accordance with the protocol and with the following: 1) Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines 2) Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines 3) Applicable laws and regulations. The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Background therapy:

All HFrEF patients were treated according to locally recognised guidelines on standard of care treatment with both drugs and devices, as appropriate. Guideline-recommended medications were used at recommended doses unless contraindicated or not tolerated. Therapy have been individually optimised and stable for ≥ 4 weeks (this does not apply to diuretics) before Visit 1 and include (unless contraindicated or not tolerated): • an ACE inhibitor, or ARB or sacubitril/valsartan and • a beta-blocker and • if considered appropriate by the patient's treating physician; a mineralocorticoid receptor antagonist

Evidence for comparator:

Comparator was placebo

Actual start date of recruitment	08 April 2019
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	Brazil: 22
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Denmark: 37
Country: Number of subjects enrolled	Japan: 30
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	South Africa: 29
Country: Number of subjects enrolled	Sweden: 22
Country: Number of subjects enrolled	United States: 89

Worldwide total number of subjects	313
EEA total number of subjects	78

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)	116
From 65 to 84 years	187
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

A total of 313 patients were randomised in this international, multi-center study which was conducted at 77 centers in 9 countries between 09 April 2019 and 07 March 2020.

Pre-assignment

Screening details:

In DETERMINE-reduced, at the first visit, i.e. the enrollment visit 1, patients were evaluated regarding the protocol mandated inclusion and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapa 10mg

Arm description:

Dapagliflozin 10 mg, given once daily per oral use.

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

Dosage and administration details:

Dapagliflozin 10 mg tablets administered orally once daily

Arm title	Placebo

Arm description:

Placebo tablet to match dapagliflozin 10 mg, given once daily per oral use.

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:

Matching placebo for dapagliflozin 10 mg administered orally once daily

Number of subjects in period 1	Dapa 10mg	Placebo
Started	156	157
Completed	151	151
Not completed	5	6
Adverse event, serious fatal	3	2
Physician decision	1	-
Adverse event, non-fatal	1	2
Withdrawal by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Dapa 10mg
Reporting group description:	
Dapagliflozin 10 mg, given once daily per oral use.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet to match dapagliflozin 10 mg, given once daily per oral use.	

Reporting group values	Dapa 10mg	Placebo	Total
Number of subjects	156	157	313
Age Categorical Units: Subjects			
Adults (18-64 years)	56	60	116
Elderly (From 65-84 years)	95	92	187
Elderly 85 years and over	5	5	10
Age Continuous Units: years			
arithmetic mean	68.4	67.3	
standard deviation	± 9.84	± 10.95	-
Gender Categorical Units: Subjects			
Female	45	35	80
Male	111	122	233
Ethnicity (NH/OMB) Units: Subjects			
Hispanic/Latino	18	21	39
Not Hispanic/Not Latino	138	136	274
Race/Ethnicity customized Units: Subjects			
White	100	98	198
Black or Africian American	25	22	47
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Asian	19	27	46
Other	12	10	22

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients that were randomised, regardless of whether treated or not.	

Reporting group values	Full analysis set		
Number of subjects	313		
Age Categorical Units: Subjects			
Adults (18-64 years)	116		
Elderly (From 65-84 years)	187		
Elderly 85 years and over	10		
Age Continuous Units: years arithmetic mean standard deviation	 ±		
Gender Categorical Units: Subjects			
Female			
Male			
Ethnicity (NH/OMB) Units: Subjects			
Hispanic/Latino			
Not Hispanic/Not Latino			
Race/Ethnicity customized Units: Subjects			
White			
Black or Africian American			
Native Hawaiian or other Pacific Islander			
American Indian or Alaska Native			
Asian			
Other			

End points

End points reporting groups

Reporting group title	Dapa 10mg
Reporting group description:	
Dapagliflozin 10 mg, given once daily per oral use.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet to match dapagliflozin 10 mg, given once daily per oral use.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients that were randomised, regardless of whether treated or not.	

Primary: Change from baseline in Kansas-City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) at week 16 (higher scores represent less HF symptom frequency and burden).

End point title	Change from baseline in Kansas-City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) at week 16 (higher scores represent less HF symptom frequency and burden).
End point description:	
Change from baseline in KCCQ-TSS was defined as the endpoint value at week 16 minus the baseline value. KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. The KCCQ-TSS incorporates the symptom frequency (4 items) and symptom burden (3 items) domains into a single summary score. The score is transformed to a range of 0-100, in which a higher score reflects better health status. Baseline value is the last value on or prior to the randomisation visit. Deaths are treated as the worst outcome and ordering among deaths is based on last value while alive. In rank ANCOVA and HL estimation, multiple imputation was performed on missing values for patients who were alive at the visit at week 16 but did not have KCCQ-TSS values.	
End point type	Primary
End point timeframe:	
At baseline and at week 16 or death before week 16	

End point values	Dapa 10mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	157		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
Change from baseline at week 16	2.08 (-4.17 to 14.58)	0.00 (-10.42 to 9.38)		

Statistical analyses

Statistical analysis title	HL estimate of treatment diff. and rank ANCOVA

Statistical analysis description:

Rank ANCOVA model is used to analyse ranked data based on the hierarchical composite rank-based endpoint. The model includes baseline rank of outcome variable as a covariate, treatment group as a

factor, and is stratified by T2DM status at randomisation.

Comparison groups	Placebo v Dapa 10mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.02164 [2]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	4.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	8.22

Notes:

[1] - For the primary efficacy endpoint KCCQ-TSS, the following hypothesis was tested using the significance level 0.04990 • H0: m(r(A)) = m(r(C)) versus • H1: m(r(A)) ≠ m(r(C)) Where H0 and H1 are the null and alternative hypotheses, respectively, and m(r(A)) and m(r(C)) represent the median of the ranked changes in the primary efficacy endpoint, KCCQ-TSS, from baseline to week 16, among patients receiving dapagliflozin (Active) and placebo (Control) treatment, respectively.
[2] - To account for multiplicity, a pre-specified testing strategy was followed to control the overall type I error rate.

Primary: Change from baseline in Kansas-City Cardiomyopathy Questionnaire-Physical Limitation Score (KCCQ-PLS) at week 16 (higher scores represent less physical limitation due to HF)

End point title	Change from baseline in Kansas-City Cardiomyopathy Questionnaire-Physical Limitation Score (KCCQ-PLS) at week 16 (higher scores represent less physical limitation due to HF)

End point description:

Change from baseline in KCCQ-PLS was defined as the endpoint value at week 16 minus the baseline value. KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. The KCCQ-PLS incorporates the 6 physical limitation items into a single score. The score is transformed to a range of 0-100, in which a higher score reflects better health status. Baseline value is the last value on or prior to the randomisation visit. Deaths are treated as the worst outcome and ordering among deaths is based on last value while alive. In rank ANCOVA and HL estimation, multiple imputation was performed on missing values for patients who were alive at the visit at week 16 but did not have KCCQ-PLS values.

End point type	Primary

End point timeframe:

At baseline and at week 16 or death before week 16

End point values	Dapa 10mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	156		
Units: Score on the scale				
median (inter-quartile range (Q1-Q3))	4.17 (-4.17 to 12.50)	0.00 (-8.33 to 8.33)		

Statistical analyses

Statistical analysis title	HL estimate of treatment diff. and rank ANCOVA

Statistical analysis description:

Rank ANCOVA model is used to analyse ranked data based on the hierarchical composite rank-based endpoint. Model includes baseline rank of outcome variable as a covariate, treatment group as a factor, and is stratified by T2DM status at randomisation.

Comparison groups	Dapa 10mg v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.05842 [4]
Method	Rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	4.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	8.33

Notes:

[3] - For the primary efficacy endpoint KCCQ-PLS, the following hypothesis was tested at significant level of 0.04990 • H0: m(r(A)) = m(r(C)) versus • H1: m(r(A)) ≠ m(r(C)) Where H0 and H1 are the null and alternative hypotheses, respectively, and m(r(A)) and m(r(C)) represent the median of the ranked changes in the primary efficacy endpoint, KCCQ-PLS, from baseline to week 16, among patients receiving dapagliflozin (Active) and placebo (Control) treatment, respectively.

[4] - KCCQ-PLS was tested at the alpha level of 0.04990 because KCCQ-TSS had a statistically significant p-value, in accordance with the pre-specified testing strategy.

Primary: Change from baseline in 6-minute walk distance (6MWD) at week 16 (larger distances represent better functional capacity).

End point title	Change from baseline in 6-minute walk distance (6MWD) at week 16 (larger distances represent better functional capacity).

End point description:

Change from baseline in 6-minute walk distance (6MWD) (exercise capacity) at week 16 was defined as the distance walked in 6 minutes at week 16 minus the baseline value. Baseline value is the last value on or prior to the randomisation visit. Deaths are treated as the worst outcome and ordering among deaths is based on last value while alive. In rank ANCOVA and HL estimation, multiple imputation was performed on missing values for patients who were alive at the visit at week 16 but did not have 6MWD values.

End point type	Primary

End point timeframe:

At baseline and at week 16 or death prior to week 16

End point values	Dapa 10mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	157		
Units: meters				
median (inter-quartile range (Q1-Q3))	20.0 (-2.0 to 42.0)	13.5 (-12.5 to 46.5)		

Statistical analyses

Statistical analysis title	HL estimate of treatment diff. and rank ANCOVA

Statistical analysis description:

Rank ANCOVA model is used to analyse ranked data based on the hierarchical composite rank-based endpoint. The model includes baseline rank of outcome variable as a covariate, treatment group as a factor, and is stratified by T2DM status at randomisation.

Comparison groups	Dapa 10mg v Placebo
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.68626 [6]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	13

Notes:

[5] - For the primary efficacy endpoint 6MWD, the following hypothesis was tested using the significance level 0.00010: H0: m(r(A)) = m(r(C)) versus H1: m(r(A)) ≠ m(r(C)) Where H0 and H1 are the null and alternative hypotheses, respectively, and m(r(A)) and m(r(C)) represent the median of the ranked changes in the primary efficacy endpoint, 6MWD, from baseline to week 16, among patients receiving dapagliflozin (Active) and placebo (Control) treatment, respectively.

[6] - To account for multiplicity, a pre-specified testing strategy was followed to control the overall type I error rate.

Secondary: Change from baseline at the end of the study in the total time spent in light to vigorous physical activity, as assessed using a wearable activity monitor (accelerometer).

End point title	Change from baseline at the end of the study in the total time spent in light to vigorous physical activity, as assessed using a wearable activity monitor (accelerometer).

End point description:

Change from baseline at the end of the study in total time spent in light to vigorous physical activity (LVPA), as assessed using a wearable activity monitor, was defined as the total time [per day] spent in LVPA at the end of the study minus the baseline value. Baseline is the 7 day period starting on the day of enrolment and ending before randomisation. End of study is defined as the period starting on the day of week 14 and prior to the week 16 visit. Deaths are treated as the worst outcome and ordering among deaths is based on last value while alive.

End point type	Secondary

End point timeframe:

At baseline and at end of study or death before week 16.

End point values	Dapa 10mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[7]	34[8]		
Units: hours				
median (inter-quartile range (Q1-Q3))	-0.19 (-0.57 to 0.15)	-0.15 (-0.68 to 0.53)		

Notes:

[7] - 92 patients from device-sites had wearable activity monitor data collected in Dapa 10mg group

[8] - 83 patients from device-sites had wearable activity monitor data collected in Placebo group

Statistical analyses

Statistical analysis title	HL estimate of treatment diff. and rank ANCOVA

Statistical analysis description:

Rank ANCOVA model is used to analyse ranked data based on the hierarchical composite rank-based endpoint. Model includes baseline rank of outcome variable as a covariate, treatment group as a factor, and is stratified by T2DM status at randomisation.

Comparison groups	Dapa 10mg v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.19748 [10]
Method	rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.22

Notes:

[9] - For the secondary efficacy endpoint, total time spent in LVPA, the testing hypothesis is • H0: m(r (A)) = m(r(C)) versus • H1: m(r(A)) ≠ m(r(C)) Where H0 and H1 are the null and alternative hypotheses, respectively, and m(r(A)) and m(r(C)) represent the median of the ranked changes in secondary efficacy endpoint, total time spent in LVPA, from baseline to End of study among patients receiving dapagliflozin (Active) and placebo (Control) treatment, respectively.

[10] - Total time spent in LVPA was not tested for statistical significance and the p-value is considered nominal because the test for 6MWD was not statistically significant.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Includes data collected on or after date of first dose and up to (including) 30 days following last dose of randomized study drug, and no later than visit 5 (up to day 119). Deaths collected on or after first dose of randomized study drug,up to 119 days.

Adverse event reporting additional description:

For analysis of Adverse Events Safety analysis set is used. Safety analysis set : All randomised participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Dapa 10 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There was not any non-serious AEs occurring in greater than 5% of participants.

Serious adverse events	Dapa 10 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 156 (12.18%)	23 / 157 (14.65%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 156 (0.64%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 156 (0.64%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 156 (1.28%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 156 (1.92%)	6 / 157 (3.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 156 (0.64%)	4 / 157 (2.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 156 (0.00%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 156 (0.00%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 156 (1.28%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 156 (0.00%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 156 (0.00%)	2 / 157 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chagas' cardiomyopathy			

subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Dapa 10 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 156 (0.00%)	0 / 157 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2020	The main purpose of this amendment was to add 2 primary objectives to the study (ie, reduction in HF symptoms and reduction in physical limitation). The primary objectives are now to determine whether dapagliflozin is superior to placebo in reducing heart failure symptoms, reducing physical limitation, or improving exercise capacity in patients with chronic heart failure. The family of primary endpoints are KCCQ-TSS, KCCQ-PLS, and 6MWD. Some secondary objectives became exploratory objectives and other exploratory endpoints were revised. Clarifications were also made to text unrelated to the endpoints. The following details the key changes: Section 1.2 (Synopsis): Updated to reflect changes in the CSP text, including the changes to the objectives/endpoints as detailed in Section 3. Section 2: (INTRODUCTION) Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Section 3 (OBJECTIVES AND ENDPOINTS): Two additional primary efficacy objectives/endpoints were added (ie, KCCQ-TSS and KCCQ-PLS) to create a primary endpoint family. Some secondary objectives became exploratory and certain exploratory objectives/endpoints were reordered and rephrased. Section 4 (STUDY DESIGN): Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Explanation/clarification was added for the choice of primary endpoints. Section 6.3.1.2 (Capping): Updated to allow it on a level lower than the whole study. Section 7.4 (Discontinuation of the study): Reasons for the early closure of the study site were added as per more recent protocol template. Section 8.1 (Efficacy assessments): Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Section 9 (STATISTICAL CONSIDERATIONS): Updated to reflect changes in the objectives/endpoints as detailed in Section 3, including updated power calculations and methodology for type I error control. General:Minor editing corrections to improve clarity and consistency.

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.

Data collection from the wearable device worn by a subset of patients at home for 3 periods of 7 days was challenging and a substantial amount of data was missing. This limits the use of the data based on the wearable activity monitors.

Notes: