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 Preserved Ejection Fraction (HFpEF)

Summary

EudraCT number	2018-003441-42
Trial protocol	SE DK SK BG IT
Global end of trial date	09 July 2020

Results information

Result version number	v1 (current)
This version publication date	22 July 2021
First version publication date	22 July 2021

Trial information

Trial identification

Sponsor protocol code	D169EC00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03877224
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	02 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2020
Global end of trial reached?	Yes
Global end of trial date	09 July 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 preserved ejection fraction (LVEF>40%) [HFpEF] 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 HFpEF 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 before Visit 1 (this does not apply to diuretics) and include (unless contraindicated or not tolerated) treatment of co-morbidities (including high blood pressure, ischaemic heart disease, atrial fibrillation/flutter). Optimised and stable treatment applies also past Visit 1 and until patient is randomised.

Evidence for comparator:

Comparator was placebo

Actual start date of recruitment	04 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	Argentina: 23
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	Denmark: 43
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Slovakia: 58

Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	United States: 99
Worldwide total number of subjects	504
EEA total number of subjects	196

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)	102
From 65 to 84 years	371
85 years and over	31

Subject disposition

Recruitment

Recruitment details:

A total of 504 patients were randomised in this international, multi-center study which was conducted at 102 centers in 12 countries between 04 April 2019 and 09 July 2020.

Pre-assignment

Screening details:

In DETERMINE-preserved, 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 10 mg

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 10 mg	Placebo
Started	253	251
Completed	248	243
Not completed	5	8
Adverse event, serious fatal	3	2
Consent withdrawn by subject	1	6
Patient is alive, just unable to come for visits	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dapa 10 mg
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 10 mg	Placebo	Total
Number of subjects	253	251	504
Age categorical Units: Subjects			
Adults (18-64 years)	50	52	102
Elderly (From 65-84 years)	187	184	371
Elderly 85 years and over	16	15	31
Age Continuous Units: Years			
arithmetic mean	72.0	71.7	
standard deviation	± 9.1	± 9.7	-
Sex: Female, Male Units: Subjects			
Male	162	158	320
Female	91	93	184
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic/Latino	28	31	59
Not Hispanic/Not Latino	225	220	445
Race/Ethnicity, Customized Units: Subjects			
White	192	178	370
Black or African American	17	17	34
Asian	36	50	86
Native Hawaiian or other Pacific Islander	1	0	1
Other	7	6	13
American Indian or Alaska Native	0	0	0

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	504		
Age categorical Units: Subjects			
Adults (18-64 years)	102		
Elderly (From 65-84 years)	371		
Elderly 85 years and over	31		
Age Continuous Units: Years arithmetic mean standard deviation	 ±		
Sex: Female, Male Units: Subjects			
Male			
Female			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic/Latino			
Not Hispanic/Not Latino			
Race/Ethnicity, Customized Units: Subjects			
White			
Black or African American			
Asian			
Native Hawaiian or other Pacific Islander			
Other			
American Indian or Alaska Native			

End points

End points reporting groups

Reporting group title	Dapa 10 mg
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. KCCQ-TSS incorporates symptom frequency (4 items) and symptom burden (3 items) domains into a single score. The score is transformed to a range of 0-100 (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 alive at the week 16 visit but without KCCQ-TSS values. All the data for the endpoint, except for death, collected during COVID-19, are set as missing and imputed same way as pre-COVID-19 missing data.

End point type	Primary

End point timeframe:

At baseline and at week 16 or death before week 16

End point values	Dapa 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	251		
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))				
Change from baseline at week 16	5.21 (-3.13 to 12.50)	1.04 (-5.73 to 15.10)		

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 and weeks impacted by COVID-19 as covariates, treatment group as a factor, and is stratified by T2DM status at randomisation.

Comparison groups	Dapa 10 mg v Placebo
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.07905 [2]
Method	Rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	6.01

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. KCCQ-PLS incorporates 6 physical limitation items into a single score. The score is transformed to a range of 0-100 (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 week 16 visit but without KCCQ-PLS values. All the data for the endpoint, except for death, collected during COVID-19, are set as missing and imputed same way as pre-COVID-19 missing data.

End point type	Primary

End point timeframe:

At baseline and at week 16 or death before week 16

End point values	Dapa 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	250		
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))				
Change from baseline at week 16	0.00 (-4.17 to 12.50)	0.00 (-8.33 to 12.50)		

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 and weeks impacted by COVID-19 as covariates, treatment group as a factor, and is stratified by T2DM status at randomisation.

Comparison groups	Dapa 10 mg v Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.23215 [4]
Method	Rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	5.37

Notes:

[3] - For the primary efficacy endpoint KCCQ-PLS, the following hypothesis was tested at significant level of 0.00005 • 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] - To account for multiplicity, a pre-specified testing strategy was followed to control the overall type I error rate.

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 before week 16

End point values	Dapa 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	251		
Units: meters				
median (inter-quartile range (Q1-Q3))				
Change from baseline at week 16	9.0 (-15.0 to 37.0)	8.5 (-14.5 to 35.5)		

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 10 mg v Placebo
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.66801 [6]
Method	Rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	9

Notes:

[5] - For the primary efficacy endpoint 6MWD, the following hypothesis was tested using the significance level 0.00005: 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 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[7]	71[8]		
Units: hours				
median (inter-quartile range (Q1-Q3))				
Change from baseline at the end of the study	-0.06 (-0.63 to 0.44)	-0.07 (-0.67 to 0.13)		

Notes:

[7] - 165 patients from device-sites had wearable activity monitor data collected in Dapa 10mg group

[8] - 155 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 10 mg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.12523 [10]
Method	Rank ANCOVA
Parameter estimate	Hodges-Lehmann median diff. vs placebo
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.48

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 randomised study drug, and no later than visit 5 (up to day 119). Deaths collected on or after first dose of randomised study drug, up to 119 days.

Adverse event reporting additional description:

For analysis of Adverse Events Safety analysis set is used. Saftey 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	Placebo
Reporting group description: -	
Reporting group title	Dapa 10 mg
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: None of non-serious adverse vent meet 5% threshold cut-off for reporting. So there is no non-serious adverse event reported.

Serious adverse events	Placebo	Dapa 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 249 (7.63%)	26 / 252 (10.32%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	2	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
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			
subjects affected / exposed	2 / 249 (0.80%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 249 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 249 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			

subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 249 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 249 (0.40%)	2 / 252 (0.79%)	
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	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 249 (1.61%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 249 (0.80%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 249 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Conduction disorder			

subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 249 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridial infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 249 (1.20%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 249 (0.00%)	4 / 252 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Dapa 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 249 (0.00%)	0 / 252 (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 amendment was to add a primary objective to the study (ie, effect on 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. Most amendments were consequential to the change in primary objectives/endpoints. The secondary objective/endpoint was switched with one of the exploratory objectives/endpoints and exploratory endpoints were revised. The remaining amendments were intended to add clarity and correct minor errors. 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): A third primary efficacy objective/endpoint was added (ie, KCCQ-PLS). The secondary objective/endpoint (now 'total time spent in light to vigorous physical activity') was switched with an exploratory objective/endpoint (now 'movement intensity during walking'). The exploratory KCCQ endpoints and the description of the subset of patients to be assessed for certain exploratory measures were revised. Section 4 (STUDY DESIGN): Updated to reflect changes in the objectives/endpoints as detailed in Section 3. Further explanation/clarification was added for the choice of primary endpoints. 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. 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: