Clinical trial results:
A Phase 2b, Randomised, Double-Blind, Active-Controlled, Multi-Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients with Heart Failure and Chronic Kidney Disease

Summary

EudraCT number	2020-003126-23
Trial protocol	BE LT HU DK SE CZ SK BG PL DE IT ES
Global end of trial date	22 September 2023

Results information

Result version number	v2 (current)
This version publication date	14 December 2024
First version publication date	06 October 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D6402C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04595370
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, 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 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on urinary albumin to creatinine ratio (UACR).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 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	Bulgaria: 38
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	144
EEA total number of subjects	91

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)	21
From 65 to 84 years	114
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 26-January-2021 (first subject first visit) to 22-September-2023 (last subject last visit). Study had 6 arms, however, AZD9977 monotherapy and placebo arms closed early due to change in Heart Failure (HF) treatment guidelines.

Pre-assignment

Screening details:

Subjects were enrolled after signing the Informed Consent Form (ICF). The study had an optional pre-screening visit. Study enrolled 153 subjects across 6 arms. Due to ERF limitations, subject disposition and baseline data were presented for only 144 subjects. Nine subjects were excluded from analysis due to site misconduct and GCP non-compliance.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD9977 15 mg + Dapagliflozin 10 mg

Arm description:

Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

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:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

Investigational medicinal product name	AZD9977
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received AZD9977 once daily for 12 weeks.

Arm title	AZD9977 50 mg + Dapagliflozin 10 mg

Arm description:

Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

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:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

Investigational medicinal product name	AZD9977
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received AZD9977 once daily for 12 weeks.

Arm title	AZD9977 150 mg + Dapagliflozin 10 mg

Arm description:

Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

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:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

Investigational medicinal product name	AZD9977
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received AZD9977 once daily for 12 weeks.

Arm title	AZD9977 150 mg

Arm description:

Subjects received AZD9977 150 mg orally once daily for 12 weeks.

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

Dosage and administration details:

Subjects received matching placebo to Dapagliflozin once daily for 12 weeks.

Investigational medicinal product name	AZD9977
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received AZD9977 once daily for 12 weeks.

Arm title	Dapagliflozin 10 mg

Arm description:

Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo to AZD9977 once daily for 12 weeks.

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

Dosage and administration details:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

Arm title	Placebo

Arm description:

Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.

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:

Subjects received matching placebo to dapagliflozin once daily for 12 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo to AZD9977 once daily for 12 weeks.

Number of subjects in period 1	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg
Started	34	31	35
Completed	32	23	26
Not completed	2	8	9
Withdrawal of Consent	1	1	1
Adverse event, non-fatal	-	4	3
Death	-	1	-
Subjects not treated, Withdrawal by subject	-	-	1
Subjects not treated, Protocol Deviation	1	-	-
Withdrawal by Subject	-	-	1

Protocol-Specified Withdrawal Criterion Met	-	-	1
Lost to follow-up	-	-	-
Discontinued treatment due to other reasons	-	2	2

Number of subjects in period 1	AZD9977 150 mg	Dapagliflozin 10 mg	Placebo
Started	6	33	5
Completed	5	27	4
Not completed	1	6	1
Withdrawal of Consent	-	-	-
Adverse event, non-fatal	1	1	1
Death	-	1	-
Subjects not treated, Withdrawal by subject	-	-	-
Subjects not treated, Protocol Deviation	-	-	-
Withdrawal by Subject	-	2	-
Protocol-Specified Withdrawal Criterion Met	-	-	-
Lost to follow-up	-	1	-
Discontinued treatment due to other reasons	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	AZD9977 15 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 50 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 150 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 150 mg
Reporting group description:	
Subjects received AZD9977 150 mg orally once daily for 12 weeks.	
Reporting group title	Dapagliflozin 10 mg
Reporting group description:	
Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.	

Reporting group values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg
Number of subjects	34	31	35
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	4
From 65-84 years	27	23	30
85 years and over	1	2	1
Age Continuous Units: Years			
arithmetic mean	70.9	72.4	73.7
standard deviation	± 7.1	± 8.4	± 8.1
Sex: Female, Male Units: Subjects			
Female	11	5	8
Male	23	26	27
Race Units: Subjects			
Asian	4	3	7

Black or African American	0	1	1
White	30	27	27

Reporting group values	AZD9977 150 mg	Dapagliflozin 10 mg	Placebo
Number of subjects	6	33	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	5	0
From 65-84 years	5	25	4
85 years and over	1	3	1
Age Continuous Units: Years			
arithmetic mean	77.0	72.2	77.2
standard deviation	± 8.7	± 9.4	± 5.8
Sex: Female, Male Units: Subjects			
Female	1	10	1
Male	5	23	4
Race Units: Subjects			
Asian	0	3	0
Black or African American	0	2	1
White	6	28	4

Reporting group values	Total		
Number of subjects	144		
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)	21		
From 65-84 years	114		
85 years and over	9		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		

Sex: Female, Male Units: Subjects			
Female	36		
Male	108		
Race Units: Subjects			
Asian	17		
Black or African American	5		
White	122		

End points

End points reporting groups

Reporting group title	AZD9977 15 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 50 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 150 mg + Dapagliflozin 10 mg
Reporting group description:	
Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	AZD9977 150 mg
Reporting group description:	
Subjects received AZD9977 150 mg orally once daily for 12 weeks.	
Reporting group title	Dapagliflozin 10 mg
Reporting group description:	
Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.	

Primary: Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12

End point title	Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12
End point description:	
Change from baseline in UACR at the end of 12 weeks of study treatment was calculated as the average of the UACR values at Week 12 and was analyzed by a mixed-effects model for repeated measures (MMRM). Due to early removal of arms (AZD9977 150 mg monotherapy and Placebo), the study objectives were revised and the MMRM analysis included the 4 remaining arms (AZD9977 15/50/150 mg + Dapagliflozin, and Dapagliflozin 10 mg). Since 2 arms were removed from the study resulting in fewer subjects only descriptive statistics are shown for those two arms without formal comparison. Here, -999.999 and 999.999 indicates that the lower and upper limits of the 95% CI were not calculated due to insufficient number of participants enrolled in this arm. FAS included all subjects who were randomized and either received or did not receive any study intervention.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) and Week 12	

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	23	25	5
Units: Percent change from baseline				
least squares mean (confidence interval	-56.391	-42.085	-58.047	-45.01

95%)	(-71.528 to -33.207)	(-64.174 to -6.376)	(-73.560 to -33.430)	(-999.999 to 999.999)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	3		
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-34.318 (-58.204 to 3.220)	230.32 (-999.999 to 999.999)		

Statistical analyses

Statistical analysis title	AZD9977 + Dapagliflozin v/s Dapagliflozin
Comparison groups	AZD9977 15 mg + Dapagliflozin 10 mg v AZD9977 50 mg + Dapagliflozin 10 mg v AZD9977 150 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3645
Method	F-Test
Parameter estimate	F test statistic
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-999.999
upper limit	999.999

Secondary: Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at 12 weeks to Assess Dose-Response Relationship

End point title	Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at 12 weeks to Assess Dose-Response Relationship

End point description:

Change from baseline in UACR at the end of 12 weeks of study treatment was calculated as the average of the UACR values at Week 12 and was analyzed by a mixed-effects model for repeated measures (MMRM). Due to early removal of arms (AZD9977 150 mg monotherapy and placebo), the study objectives were revised and the MMRM analysis included the 4 remaining arms (AZD9977 15/50/150 mg + Dapagliflozin, and Dapagliflozin 10 mg). Since 2 arms were removed from the study resulting in fewer subjects, only descriptive statistics was shown for those two arms without formal comparison.
Here, -999.999 and 999.999 indicates that the lower and upper limits of the 95% CI were not calculated due to insufficient number of participants enrolled in this arm.
FAS included all subjects who were randomized and either received or did not receive any study intervention.

End point type	Secondary

End point timeframe:
Baseline (Day 1) and Week 12

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	23	25	5
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-56.391 (-71.528 to -33.207)	-42.085 (-64.174 to -6.376)	-58.047 (-73.560 to -33.430)	-45.01 (-999.999 to 999.999)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	3		
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-34.318 (-58.204 to 3.220)	230.32 (-999.999 to 999.999)		

Statistical analyses

Statistical analysis title	AZD9977 15mg + Dapagliflozin v/s Dapagliflozin
Comparison groups	AZD9977 15 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1588
Method	Mixed models analysis
Parameter estimate	Percent difference between treatment
Point estimate	-33.606
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.53
upper limit	17.644

Statistical analysis title	AZD9977 150mg + Dapagliflozin v/s Dapagliflozin
Comparison groups	AZD9977 150 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1398
Method	Mixed models analysis
Parameter estimate	Percent difference between treatment
Point estimate	-36.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.85
upper limit	16.066

Statistical analysis title	AZD9977 50mg + Dapagliflozin v/s Dapagliflozin
Comparison groups	AZD9977 50 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6846
Method	Mixed models analysis
Parameter estimate	Percent difference between treatment
Point estimate	-11.826
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.195
upper limit	62.634

Secondary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)

End point description:

The safety and tolerability of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo was assessed.

Safety analysis set included all subjects who were randomized and received any study intervention.

End point type	Secondary

End point timeframe:

From baseline (Day 1) until Day 113

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	31	34	6
Units: Subjects				
Any AE	9	12	18	5
Any SAE	1	3	2	0
Any SAE with outcome death	0	2	0	0
Any AE leading to discontinuation of IP	0	4	3	1
Any AE leading to withdrawal from study	0	5	2	0
Any AE leading to dose interruption	1	1	1	0

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	5		
Units: Subjects				
Any AE	14	3		
Any SAE	4	2		
Any SAE with outcome death	1	0		
Any AE leading to discontinuation of IP	1	1		
Any AE leading to withdrawal from study	1	0		
Any AE leading to dose interruption	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Potassium (K+)

End point title	Change from Baseline in Serum Potassium (K+)

End point description:

Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on serum K+ was assessed.
Here, -999.999 and 999.999 indicates that the lower and upper limits of the 95% CI were not calculated due to insufficient number of participants enrolled in this arm.

Safety analysis set included all subjects who were randomized and received any study intervention.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	21	25	4
Units: millimoles per liter (mmol/L)				
least squares mean (confidence interval 95%)	0.056 (-0.106 to 0.219)	0.003 (-0.184 to 0.190)	0.109 (-0.061 to 0.279)	0.55 (-999.999 to 999.999)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	3		
Units: millimoles per liter (mmol/L)				
least squares mean (confidence interval 95%)	0.040 (-0.129 to 0.209)	0.03 (-999.999 to 999.999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Value of Serum Potassium Over Time

End point title	Absolute Value of Serum Potassium Over Time

End point description:

Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on serum K+ was assessed.

Safety analysis set included all subjects who were randomized and received any study intervention. Here, "n" specifies the number of subjects who were evaluated for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	25	29	5
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n=30, 25, 29, 5, 33, 5)	4.60 (± 0.38)	4.44 (± 0.61)	4.46 (± 0.44)	4.50 (± 0.38)
Week 12 (n=27, 21, 25, 4, 25, 3)	4.62 (± 0.50)	4.53 (± 0.43)	4.63 (± 0.43)	5.00 (± 0.61)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	5		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n=30, 25, 29, 5, 33, 5)	4.60 (± 0.66)	4.50 (± 0.28)		
Week 12 (n=27, 21, 25, 4, 25, 3)	4.64 (± 0.40)	4.33 (± 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point title	Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point description:

Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on eGFR was assessed.
Here, -999.999 and 999.999 indicates that the lower and upper limits of the 95% CI were not calculated due to insufficient number of participants enrolled in this arm.
Safety analysis set included all subjects who were randomized and received any study intervention.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	21	24	4
Units: mL/min/1.73 m^2				
least squares mean (confidence interval 95%)	-1.432 (-4.305 to 1.441)	-1.160 (-4.351 to 2.030)	-5.307 (-8.295 to -2.320)	-0.923 (-999.999 to 999.999)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: mL/min/1.73 m^2				
least squares mean (confidence interval 95%)	-3.498 (-6.528 to -0.469)	6.880 (-999.999 to		

	999.999)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Value of eGFR Over Time

End point title	Absolute Value of eGFR Over Time

End point description:

Effect of all doses of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on eGFR was assessed.

Safety analysis set included all subjects who were randomized and received any study intervention. Here, "n" specifies the number of subjects who were evaluated for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	33	5
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Baseline (n=32, 31, 33, 5, 32, 5)	41.341 (± 12.902)	38.586 (± 10.155)	43.663 (± 16.168)	36.874 (± 12.626)
Week 12 (n=26, 21, 24, 4, 23, 3)	41.219 (± 15.112)	39.429 (± 8.998)	39.063 (± 13.819)	34.075 (± 21.071)

End point values	Dapagliflozin 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	5		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Baseline (n=32, 31, 33, 5, 32, 5)	41.895 (± 12.791)	40.288 (± 15.176)		
Week 12 (n=26, 21, 24, 4, 23, 3)	37.973 (± 11.571)	48.920 (± 21.111)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 1) until Day 113

Adverse event reporting additional description:

Safety set included all subjects who were randomized and received any study intervention. All AEs that were reported with an onset date and time, or worsening, on or after date and time of first dose of IP up to and including 5 days after last dose of IP were included in the safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	AZD9977 15 mg + Dapagliflozin 10 mg

Reporting group description:

Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

Reporting group title	AZD9977 50 mg + Dapagliflozin 10 mg

Reporting group description:

Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

Reporting group title	AZD9977 150 mg

Reporting group description:

Subjects received AZD9977 150 mg orally once daily for 12 weeks.

Reporting group title	Dapagliflozin 10 mg

Reporting group description:

Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.

Reporting group title	AZD9977 150 mg + Dapagliflozin 10 mg

Reporting group description:

Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

Serious adverse events	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	3 / 31 (9.68%)	0 / 6 (0.00%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	2	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Serious adverse events	Dapagliflozin 10 mg	Placebo	AZD9977 150 mg + Dapagliflozin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)	2 / 5 (40.00%)	2 / 34 (5.88%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 50 mg + Dapagliflozin 10 mg	AZD9977 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	4 / 31 (12.90%)	5 / 6 (83.33%)

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival recession			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Spinal osteoarthritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection bacterial			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

Non-serious adverse events	Dapagliflozin 10 mg	Placebo	AZD9977 150 mg + Dapagliflozin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 33 (21.21%)	2 / 5 (40.00%)	13 / 34 (38.24%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 33 (6.06%)	0 / 5 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Vascular disorders			

Hypertensive crisis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Colitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Gingival recession			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 5 (20.00%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Urinary tract infection bacterial			
subjects affected / exposed	0 / 33 (0.00%)	0 / 5 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	3 / 33 (9.09%)	0 / 5 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 5 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 5 (0.00%)	2 / 34 (5.88%)
occurrences (all)	3	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2020	Protocol version 1.0 was updated to include modifications to the number of sites and countries and updates to laboratory parameters for clarity.
26 January 2021	Protocol version 2.0 was updated to clarify randomisation of subgroups; clarify the lower limit of eGFR; addition of text "to use of bioimpedance devices that was contraindicated for patients with pacemakers or other electronic implanted devices"; clarify regarding hypertension treatment; describe addition of new device for site-based ECG monitoring; to include findings from recent clinical trials with dapagliflozin and to further describe the risk and benefit in patients with chronic kidney disease; to clarify eligibility criteria and medication restrictions, time frames for procedures performed, availability of results and handling of health-related issues, overdose definition; addition of new section Clinical Study Medical Device/ Device Constituent Report Form included; and to describe statistical considerations of the study.
15 July 2021	Protocol version 4.0 was updated to implement patient-centric measures and improve recruitment.
20 December 2021	Protocol version 5.0 was updated to adjust the design to heart failure treatment guidelines (ESC Guidelines 2021), by dropping the placebo and AZD9977 monotherapy arms to ensure all patients receive SGLT2i (dapagliflozin) during the study, as well as to reduce the burden of study assessments on study patients.
02 February 2022	Protocol Version 6.0 was updated to correct the typo in Table 1, clarification of study procedures, provide the correct literature reference and to align with revised study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 November 2021	Recruitment was paused while implementing the amended Protocol (Protocol amendment number 5)	01 March 2022

Notes:

Limitations and caveats

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

Enrolment stopped early because of slow recruitment. Therefore, pre-specified sample size of 500 and planned statistical power were not achieved. Nine subjects were excluded from analysis due to site misconduct and GCP non-compliance.

Notes: