Clinical trial results:
A Phase 2b Randomised, Double-Blind, Placebo-Controlled, Multi-Centre, Dose-Ranging Study of AZD5718 in Participants with Proteinuric Chronic Kidney Disease

Summary

EudraCT number	2020-002263-54
Trial protocol	DE HU PL
Global end of trial date	06 September 2022

Results information

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

Trial information

Trial identification

Sponsor protocol code	D7551C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04492722
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Global Clinical Head, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Head, AstraZeneca Clinical Study Information Center, +1 8772409479, 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	30 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the dose-response efficacy, safety, and pharmacokinetics (PK) of AZD5718 in participants with proteinuric chronic kidney disease.

Protection of trial subjects:

This study will be conducted in accordance with the protocol and with the following: consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH GCP Guidelines, applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Japan: 135
Country: Number of subjects enrolled	Brazil: 142
Country: Number of subjects enrolled	United States: 110
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	Malaysia: 47
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	613
EEA total number of subjects	64

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)	289
From 65 to 84 years	319
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in this study from 01 October 2020 to 06 September 2022. The study was terminated early on 01 July 2022 due to lack of efficacy.

Pre-assignment

Screening details:

The screening period was for 4 weeks. Participants who met all the inclusion and none of the exclusion criteria were enrolled to the study. All study assessments were performed as per the schedule of assessment.

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	AZD5718 Dose 1 + Dapagliflozin 10 mg

Arm description:

Participants received once daily oral dose of AZD5718 Dose 1 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 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:

Participants received AZD5718 along with an add-on therapy of 10 mg of dapagliflozin for 8 weeks after having AZD5718 for 12 weeks alone

Investigational medicinal product name	AZD5718
Investigational medicinal product code	AZD5718
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received once daily oral dose of AZD5718 for 20 weeks as per the arm they were randomised to

Arm title	AZD5718 Dose 2 + Dapagliflozin 10 mg

Arm description:

Participants received once daily oral dose of AZD5718 Dose 2 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 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:

Participants received AZD5718 along with an add-on therapy of 10 mg of dapagliflozin for 8 weeks after having AZD5718 for 12 weeks alone

Investigational medicinal product name	AZD5718
Investigational medicinal product code	AZD5718
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received once daily oral dose of AZD5718 for 20 weeks as per the arm they were randomised to

Arm title	AZD5718 Dose 3 + Dapagliflozin 10 mg

Arm description:

Participants received once daily oral dose of AZD5718 Dose 3 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 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:

Participants received AZD5718 along with an add-on therapy of 10 mg of dapagliflozin for 8 weeks after having AZD5718 for 12 weeks alone

Investigational medicinal product name	AZD5718
Investigational medicinal product code	AZD5718
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received once daily oral dose of AZD5718 for 20 weeks as per the arm they were randomised to

Arm title	Placebo + Dapagliflozin 10 mg

Arm description:

Participants received once daily oral dose of placebo matched to AZD5718 for 12 weeks, thereafter add-on therapy of 10 mg dapagliflozin for 8 weeks.

Arm type	Placebo and an add-on therapy
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a matching placebo to AZD5718 along with an add-on therapy of 10 mg of dapagliflozin for 8 weeks after having matching placebo to AZD5718 for 12 weeks alone

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

Dosage and administration details:

Participants received once daily oral dose of matching placebo to AZD5718 for 20 weeks

Number of subjects in period 1	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg
Started	154	153	153
Completed	72	82	82
Not completed	82	71	71
Due to Covid-19 pandemic	7	3	7
Consent withdrawn by subject	6	6	-
Physician decision	-	3	1
Adverse event, non-fatal	7	2	3
Death	-	-	-
Failure to meet randomisation criteria	2	3	4
Early termination from the study	54	51	50
Development of Study Specific Withdrawal Criteria	3	1	2
Lost to follow-up	-	1	-
Missing	3	-	-
Participants who did not receive treatment	-	1	4

Number of subjects in period 1	Placebo + Dapagliflozin 10 mg
Started	153
Completed	82
Not completed	71
Due to Covid-19 pandemic	6
Consent withdrawn by subject	3
Physician decision	1
Adverse event, non-fatal	-
Death	1
Failure to meet randomisation criteria	2
Early termination from the study	50
Development of Study Specific Withdrawal Criteria	2
Lost to follow-up	1
Missing	5
Participants who did not receive treatment	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All Randomised Subjects	

Reporting group values	Overall Study	Total	
Number of subjects	613	613	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	289	289	
From 65-84 years	319	319	
85 years and over	5	5	
Age Continuous Units: years			
arithmetic mean	64.5		
standard deviation	± 10.37	-	
Gender Categorical Units: Subjects			
Female	208	208	
Male	405	405	

End points

End points reporting groups

Reporting group title	AZD5718 Dose 1 + Dapagliflozin 10 mg
Reporting group description:	
Participants received once daily oral dose of AZD5718 Dose 1 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	AZD5718 Dose 2 + Dapagliflozin 10 mg
Reporting group description:	
Participants received once daily oral dose of AZD5718 Dose 2 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	AZD5718 Dose 3 + Dapagliflozin 10 mg
Reporting group description:	
Participants received once daily oral dose of AZD5718 Dose 3 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	Placebo + Dapagliflozin 10 mg
Reporting group description:	
Participants received once daily oral dose of placebo matched to AZD5718 for 12 weeks, thereafter add-on therapy of 10 mg dapagliflozin for 8 weeks.	

Primary: Percentage change from baseline in reduction of urine albumin to creatinine ratio (ACR) to Week 20

End point title	Percentage change from baseline in reduction of urine albumin to creatinine ratio (ACR) to Week 20[1]
End point description:	
The dose response effect of AZD5718 on urine ACR at 20 weeks was evaluated. Values less than 1 indicate improvement from baseline. Per-protocol analysis set consisted of all participants who received the additional treatment with dapagliflozin post-Week 12 and who did not violate the terms of the protocol in a way that could affect the primary efficacy endpoint significantly.	
End point type	Primary
End point timeframe:	
From Week 1 to Week 20	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Percentage change from baseline values added for ease of common public to understand.

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	67	75	76
Units: Percentage change from baseline				
number (confidence interval 95%)				
Week 20	-5.49 (-21.37 to 13.60)	-3.58 (-19.74 to 15.82)	-8.07 (-23.24 to 10.10)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in reduction of urine ACR to Week 12

End point title	Percentage change from baseline in reduction of urine ACR to Week 12

End point description:

The dose response effect of AZD5718 on urine ACR at 12 weeks was evaluated. Values less than 1 indicate improvement from baseline. Per-protocol analysis set consisted of all participants who received the additional treatment with dapagliflozin post-Week 12.

End point type	Secondary

End point timeframe:

From Week 1 to Week 12

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	97	101	104
Units: Precentage change from baseline				
arithmetic mean (confidence interval 95%)				
Week 12	-14.91 (-26.57 to -1.41)	-6.71 (-19.46 to 8.07)	-13.28 (-25.04 to 0.33)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events and serious adverse events

End point title	Number of participants with adverse events and serious adverse events

End point description:

The safety and tolerability profile of AZD5718 treatment was assessed. All participants who were randomised and received any study treatment. Participants were evaluated according to the actual treatment they received. If a participant had received a different treatment dose than randomised throughout the study, they would have been analysed according to the treated dose, not the randomisation dose.

ST- study treatment

End point type	Secondary

End point timeframe:

From Screening (Week -4 to 0) to Week 24

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	154	152	149	153
Units: Participants				
Any AE	89	89	108	96
Any AE with outcome = death	0	0	0	1
Any SAE (including events with outcome = death)	13	10	13	10
Any AE leading to discontinuation of ST	12	3	3	7
Any AE leading to dose interruption	7	6	5	10
Any AE leading to withdrawal from study	7	0	3	1
Any AE possibly related to ST by PI	14	12	8	14

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of AZD5718

End point title	Plasma concentrations of AZD5718

End point description:

The PK (plasma concentrations) of AZD5718 after repeated oral dosing for 20 weeks was supposed to be evaluated. However, due to the study termination and reduced scope of the analysis, the PK analysis was not been performed. Hence the number of participants analyzed was mentioned as "0".

End point type	Secondary

End point timeframe:

From Week 2 to Week 20

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Participants				

Notes:

[2] - Due to the study termination, participants analyzed was "0"

[3] - Due to the study termination, participants analyzed was "0"

[4] - Due to the study termination, participants analyzed was "0"

[5] - Due to the study termination, participants analyzed was "0"

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 24-hours mean systolic blood pressure to Week 12

End point title	Change from baseline in 24-hours mean systolic blood pressure to Week 12

End point description:

The effect of AZD5718 on ambulatory blood pressure was assessed. All participants in the Full Analysis Population who had valid Ambulatory Blood Pressure data for change from baseline analyses.

End point type	Secondary

End point timeframe:

From baseline (Week 1, Day 1) to Week 12

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	78	70	85
Units: millimeter mercury (mm Hg)				
arithmetic mean (standard deviation)	-2.06 (± 10.782)	1.56 (± 11.407)	-1.83 (± 9.986)	3.76 (± 11.779)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in estimated glomerular filtration rate (eGFR) to Week 12

End point title	Change from baseline in estimated glomerular filtration rate (eGFR) to Week 12

End point description:

The effect of AZD5718 on renal function was evaluated. Per-protocol analysis set consisted of all participants who received the additional treatment with dapagliflozin post-Week 12.

End point type	Secondary

End point timeframe:

From Week 1 to Week 12

End point values	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg	Placebo + Dapagliflozin 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	101	105	106
Units: milliltire/minute/1.73m^2				
arithmetic mean (standard deviation)				
Week 2 (n= 100, 100, 105, 106)	-0.470 (± 6.3936)	-0.140 (± 5.2801)	-0.429 (± 5.7175)	0.547 (± 5.7124)
Week 4 (n= 98,100,104, 103)	-0.735 (± 6.5764)	0.140 (± 5.2628)	-0.817 (± 6.1986)	0.058 (± 6.3583)
Week 8 (n=100,101,104,103)	-0.760 (± 6.0304)	-0.535 (± 5.8865)	-1.144 (± 6.5142)	-0.068 (± 5.3729)

Week 12 (n=98,94,99,101)	-0.612 (± 6.2138)	-1.149 (± 6.1783)	-0.394 (± 6.4678)	-0.257 (± 6.4508)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Screening (Week -4 to 0) to Week 24	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	AZD5718 Dose 1 + Dapagliflozin 10 mg
Reporting group description: Participants received once daily oral dose of AZD5718 Dose 1 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	AZD5718 Dose 2 + Dapagliflozin 10 mg
Reporting group description: Participants received once daily oral dose of AZD5718 Dose 2 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	AZD5718 Dose 3 + Dapagliflozin 10 mg
Reporting group description: Participants received once daily oral dose of AZD5718 Dose 3 for 12 weeks, and thereafter an add-on therapy of 10 mg dapagliflozin for 8 weeks.	
Reporting group title	Placebo + Dapagliflozin 10 mg
Reporting group description: Participants received once daily oral dose of placebo matched to AZD5718 for 12 weeks, thereafter add-on therapy of 10 mg dapagliflozin for 8 weeks.	

Serious adverse events	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 154 (7.79%)	8 / 152 (5.26%)	11 / 149 (7.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Acute leukaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Vascular disorders			

Venous haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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
Asthenia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Chest pain			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			

subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body ingestion			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Radius fracture			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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			
Acute myocardial infarction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Coronary artery disease			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Cardiac failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Angina unstable			

subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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			
Ischaemic stroke			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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
Diverticulum			
subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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
Cholecystitis acute			

subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Cholangitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Diabetic nephropathy			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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
Endocrine disorders			
Pituitary apoplexy			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 154 (0.00%)	1 / 152 (0.66%)	0 / 149 (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			
Urinary tract infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	2 / 149 (1.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Septic shock			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Liver abscess			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	2 / 149 (1.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	0 / 149 (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
Pelvic abscess			
subjects affected / exposed	1 / 154 (0.65%)	0 / 152 (0.00%)	0 / 149 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 154 (0.00%)	0 / 152 (0.00%)	1 / 149 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + Dapagliflozin 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 153 (3.92%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute leukaemia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous haemorrhage			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Asthenia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Limb traumatic amputation			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foreign body ingestion			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure chronic			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Ischaemic stroke			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic nephropathy			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Pituitary apoplexy			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver abscess			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	AZD5718 Dose 1 + Dapagliflozin 10 mg	AZD5718 Dose 2 + Dapagliflozin 10 mg	AZD5718 Dose 3 + Dapagliflozin 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 154 (10.39%)	8 / 152 (5.26%)	9 / 149 (6.04%)
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	8 / 154 (5.19%)	3 / 152 (1.97%)	5 / 149 (3.36%)
occurrences (all)	9	3	9
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 154 (5.19%)	8 / 152 (5.26%)	1 / 149 (0.67%)
occurrences (all)	8	8	2
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	6 / 154 (3.90%)	7 / 152 (4.61%)	9 / 149 (6.04%)
occurrences (all)	6	7	9

Non-serious adverse events	Placebo + Dapagliflozin 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 153 (5.23%)		
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	10		
Infections and infestations			
Urinary tract infection			

subjects affected / exposed occurrences (all)	6 / 153 (3.92%) 6		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	 6 / 153 (3.92%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2020	Amendment 1: Inclusion Criterion #5 Clarification that females must be of non-childbearing potential and that a pregnancy test is required for all female participants. Inclusion Criterion #6 Text added to clarify the contraceptive requirements for male participants in regions where male condoms with spermicide are not available Inclusion Criterion #6 (h) Clarification that alcohol and drug screening is completed locally using laboratory kits provided by the central laboratory, and that screening must be completed for all participants
25 January 2021	Amendment 2: Inclusion criterion 5 was updated to provide more details on the eligibility of female study participants with regard to their childbearing potential. Inclusion criterion 6 was updated to accommodate Japanese Pharmaceuticals and Medical Devices Agency (PMDA) regulations. Exclusion criterion 15 was added to exclude participants who had a known hypersensitivity to dapagliflozin or any of the excipients of the product. Exclusion criterion 23 was added to the study as follows: Participants working night shifts, and who cannot avoid strenuous manual labour during the study.

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.

Following study termination and reduced scope of the analysis, the PK analysis has not been performed.

Notes: