EU Clinical Trials Register

Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to
Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects
with Type 1 Diabetes Mellitus - Study Two

Summary

EudraCT number	2014-004599-49
Trial protocol	SE GB DE NL PL BE
Global end of trial date	18 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 April 2019
First version publication date	03 April 2019

Trial information

Trial identification

Sponsor protocol code	MB102-230

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Pepparedsleden 1, MoIndal, Sweden, 431 83
Public contact	Anna Maria Langkilde, AstraZeneca AB, +46 31 7761000, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Anna Maria Langkilde, AstraZeneca, +46 31 7761000, ClinicalTrialTransparency@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	17 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 September 2017
Global end of trial reached?	Yes
Global end of trial date	18 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the change from baseline in HbA1c after 24 weeks of double-blinded treatment with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin.

Protection of trial subjects:

Independent Data Monitoring Committee

Background therapy:

Insulin

Evidence for comparator: -

Actual start date of recruitment	08 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 141
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 73
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Germany: 96
Country: Number of subjects enrolled	Japan: 225
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 188
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	Sweden: 56
Country: Number of subjects enrolled	Switzerland: 20
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	United States: 494
Worldwide total number of subjects	1465
EEA total number of subjects	392

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)	1376
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The results on this form are from the 24 week short-term double-blind treatment period. This study was conducted at 148 centers in 13 countries from 8 July 2015 to 2 Sep 2017.

Pre-assignment

Screening details:

815 participants were randomized. Of the 195 participants not randomized: 97 No longer met study criteria, 44 withdrew consent, 13 were lost to follow-up, and 41 did not continue for other reasons. Two participants did not receive any study drug and were excluded from analyses. Thus, the total number of subjects is 813.

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

Blinding implementation details:

Double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	DAPA 5 MG + INS

Arm description:

Dapagliflozin 5 mg plus insulin

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

Dosage and administration details:

5 mg oral administration

Arm title	DAPA 10 MG + INS

Arm description:

Dapagliflozin 10 mg plus insulin

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

Dosage and administration details:

10 mg oral administration

Arm title	PLA + INS

Arm description:

Placebo plus insulin

Arm type	Placebo

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

Dosage and administration details:

Oral administration

Number of subjects in period 1[1]	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS
Started	271	270	272
Completed	244	245	239
Not completed	27	25	33
Consent withdrawn by subject	5	5	14
Discontinued due to DKA/hypoglycemia	2	5	4
Adverse event, non-fatal	17	11	11
Pregnancy	-	-	2
Lost to follow-up	2	3	1
Protocol deviation	1	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of enrolled subjects will generally be higher than the number of subjects in the baseline period since not all enrolled subjects actually make it into the study

Baseline characteristics

Reporting groups

Reporting group title	DAPA 5 MG + INS
Reporting group description: Dapagliflozin 5 mg plus insulin	
Reporting group title	DAPA 10 MG + INS
Reporting group description: Dapagliflozin 10 mg plus insulin	
Reporting group title	PLA + INS
Reporting group description: Placebo plus insulin	

Reporting group values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS
Number of subjects	271	270	272
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)	258	258	261
From 65-84 years	13	12	11
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	42.7	42.4	43.0
standard deviation	± 13.35	± 12.80	± 13.73
Sex: Female, Male Units: Subjects			
Female	153	149	153
Male	118	121	119
Race/Ethnicity, Customized Units: Subjects			
White|	210	219	208
Black or African-American|	4	7	1
Asian|	57	44	59
Other|	0	0	4
Ethnicity Units: Subjects			
Hispanic/Latino	3	17	11
Non-Hispanic/Latino	78	63	65
Not reported	190	190	196
Age Categorization by Tertiles Units: Subjects			

<65 years	258	258	261
>=65 - <75 years	12	12	11
>=75 years	1	0	0
Age Categorization 2 by Tertiles Units: Subjects			
<35 years	81	79	84
>=35 - <50 years	94	110	95
>=50 years	96	81	93
Body Mass Index Units: Subjects			
<=23 Kg/m2	58	47	52
>23 Kg/m2 - <=25 Kg/m2	42	43	44
>25 Kg/m2 - <=27 Kg/m2	47	44	45
>27 Kg/m2 - <=30 Kg/m2	59	69	50
>30 Kg/m2	65	67	81
Body Weight Units: kg			
arithmetic mean	78.74	80.06	78.88
standard deviation	± 17.384	± 18.302	± 18.867
Body Mass Index Units: Kg/m2			
arithmetic mean	27.27	27.80	27.62
standard deviation	± 5.128	± 5.525	± 5.414

Reporting group values	Total		
Number of subjects	813		
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)	777		
From 65-84 years	36		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	455		
Male	358		
Race/Ethnicity, Customized Units: Subjects			
White|	637		
Black or African-American|	12		
Asian|	160		

Other|	4		
Ethnicity			
Units: Subjects			
Hispanic/Latino	31		
Non-Hispanic/Latino	206		
Not reported	576		
Age Categorization by Tertiles			
Units: Subjects			
<65 years	777		
>=65 - <75 years	35		
>=75 years	1		
Age Categorization 2 by Tertiles			
Units: Subjects			
<35 years	244		
>=35 - <50 years	299		
>=50 years	270		
Body Mass Index			
Units: Subjects			
<=23 Kg/m2	157		
>23 Kg/m2 - <=25 Kg/m2	129		
>25 Kg/m2 - <=27 Kg/m2	136		
>27 Kg/m2 - <=30 Kg/m2	178		
>30 Kg/m2	213		
Body Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: Kg/m2			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who took at least one dose of double-blind study medication during the short-term double-blind period.

Reporting group values	Full Analysis Set		
Number of subjects	813		
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)	777		
From 65-84 years	36		
85 years and over	0		

Age Continuous			
Units: Years			
arithmetic mean	42.7		
standard deviation	± 13.29		

Sex: Female, Male			
Units: Subjects			
Female	455		
Male	358		

Race/Ethnicity, Customized			
Units: Subjects			
White|	637		
Black or African-American|	12		
Asian|	160		
Other|	4		

Ethnicity			
Units: Subjects			
Hispanic/Latino	31		
Non-Hispanic/Latino	206		
Not reported	576		

Age Categorization by Tertiles			
Units: Subjects			
<65 years	777		
>=65 - <75 years	35		
>=75 years	1		

Age Categorization 2 by Tertiles			
Units: Subjects			
<35 years	244		
>=35 - <50 years	299		
>=50 years	270		

Body Mass Index			
Units: Subjects			
<=23 Kg/m2	157		
>23 Kg/m2 - <=25 Kg/m2	129		
>25 Kg/m2 - <=27 Kg/m2	136		
>27 Kg/m2 - <=30 Kg/m2	178		
>30 Kg/m2	213		

Body Weight			
Units: kg			
arithmetic mean	79.22		
standard deviation	± 18.183		

Body Mass Index			
Units: Kg/m2			
arithmetic mean	27.56		
standard deviation	± 5.357		

End points

End points reporting groups

Reporting group title	DAPA 5 MG + INS
Reporting group description:	
Dapagliflozin 5 mg plus insulin	
Reporting group title	DAPA 10 MG + INS
Reporting group description:	
Dapagliflozin 10 mg plus insulin	
Reporting group title	PLA + INS
Reporting group description:	
Placebo plus insulin	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who took at least one dose of double-blind study medication during the short-term double-blind period.	

Primary: Adjusted mean change from baseline in HbA1c at Week 24

End point title	Adjusted mean change from baseline in HbA1c at Week 24
End point description:	
To compare the change from baseline in HbA1c between dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment	
End point type	Primary
End point timeframe:	
Baseline and 24 weeks	

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	266	267	267	
Units: HbA1c (%)				
least squares mean (confidence interval 95%)	-0.34 (-0.43 to -0.25)	-0.39 (-0.48 to -0.30)	0.03 (-0.06 to 0.12)	

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	PLA + INS v DAPA 5 MG + INS

Number of subjects included in analysis	533
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.0579

Statistical analysis title	Primary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.0578

Secondary: Adjusted mean percentage change from baseline in total daily insulin dose at Week 24

End point title	Adjusted mean percentage change from baseline in total daily insulin dose at Week 24
End point description:	
To compare the percent change from baseline in total daily insulin dose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment	
End point type	Secondary
End point timeframe:	
Baseline and 24 weeks	

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	270	267	266	
Units: Percentage change				
least squares mean (confidence interval 95%)	-8.73 (-11.09 to -6.31)	-9.05 (-11.43 to -6.60)	2.29 (-0.41 to 5.06)	

Statistical analyses

Statistical analysis title	First Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean percentage change from baseline	
Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-10.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.73
upper limit	-7.72
Variability estimate	Standard error of the mean
Dispersion value	1.5291

Statistical analysis title	First Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean percentage change from baseline	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	533
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-11.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.04
upper limit	-8.02
Variability estimate	Standard error of the mean
Dispersion value	1.5331

Secondary: Adjusted mean percentage change from baseline in body weight at Week 24

End point title	Adjusted mean percentage change from baseline in body weight at Week 24
End point description:	
To compare the percentage change from baseline in body weight with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment	
End point type	Secondary
End point timeframe:	
Baseline and 24 weeks	

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	269	272	
Units: Percentage change				
least squares mean (confidence interval 95%)	-3.22 (-3.76 to -2.69)	-3.76 (-4.29 to -3.22)	-0.02 (-0.57 to 0.54)	

Statistical analyses

Statistical analysis title	Second Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean percentage change from baseline	
Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.96
upper limit	-2.45

Variability estimate	Standard error of the mean
Dispersion value	0.3829

Statistical analysis title	Second Secondary Endpoint Analysis

Statistical analysis description:

Difference vs. placebo in adjusted mean percentage change from baseline

Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	541
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	-2.99
Variability estimate	Standard error of the mean
Dispersion value	0.3812

Secondary: Adjusted mean change from baseline in 24-hour continuous glucose monitoring (CGM) mean value at Week 24

End point title	Adjusted mean change from baseline in 24-hour continuous glucose monitoring (CGM) mean value at Week 24

End point description:

To compare the change from baseline in mean value of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	255	257	
Units: mg/dL				
least squares mean (confidence interval 95%)	-6.46 (-10.04 to -2.87)	-10.54 (-14.14 to -6.94)	9.20 (5.57 to 12.83)	

Statistical analyses

Statistical analysis title	Third Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-19.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.34
upper limit	-15.14
Variability estimate	Standard error of the mean
Dispersion value	2.3419

Statistical analysis title	Third Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.26
upper limit	-11.05
Variability estimate	Standard error of the mean
Dispersion value	2.3468

Secondary: Adjusted mean change from baseline in 24-hour CGM mean amplitude of glycemic excursion (MAGE) value at Week 24

End point title	Adjusted mean change from baseline in 24-hour CGM mean amplitude of glycemic excursion (MAGE) value at Week 24
End point description:	

To compare the change from baseline in mean amplitude of glucose excursions (MAGE) of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

End point type	Secondary
End point timeframe: Baseline and 24 weeks	

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	255	257	
Units: mg/dL				
least squares mean (confidence interval 95%)	-10.17 (-13.90 to -6.45)	-9.68 (-13.44 to -5.93)	-0.33 (-4.12 to 3.46)	

Statistical analyses

Statistical analysis title	Fourth Secondary Endpoint Analysis
Statistical analysis description: Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-9.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.66
upper limit	-5.03
Variability estimate	Standard error of the mean
Dispersion value	2.4519

Statistical analysis title	Fourth Secondary Endpoint Analysis
Statistical analysis description: Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-9.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.16
upper limit	-4.55
Variability estimate	Standard error of the mean
Dispersion value	2.4487

Secondary: Change from baseline in the percent of 24-hour glucose readings obtained from CGM that falls within the target range of > 70 mg/dL and <= 180 mg/dL (%) at Week 24

End point title	Change from baseline in the percent of 24-hour readings obtained from CGM that falls within the target range of > 70 mg/dL and <= 180 mg/dL (%) at Week 24

End point description:

To compare the change from baseline in the percent of 24-hour glucose readings obtained from CGM that falls within the target range of >70 mg/dL and <=180 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	252	255	257	
Units: % of readings				
least squares mean (confidence interval 95%)	5.92 (4.32 to 7.52)	7.60 (5.98 to 9.21)	-3.10 (-4.73 to -1.47)	

Statistical analyses

Statistical analysis title	Fifth Secondary Endpoint Analysis

Statistical analysis description:

Difference vs. placebo in adjusted mean change from baseline

Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	9.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.97
upper limit	11.06
Variability estimate	Standard error of the mean
Dispersion value	1.0415

Statistical analysis title	Fifth Secondary Endpoint Analysis
Statistical analysis description:	
Difference vs. placebo in adjusted mean change from baseline	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.66
upper limit	12.74
Variability estimate	Standard error of the mean
Dispersion value	1.0396

Secondary: Percentage of subjects with HbA1c reduction from baseline to week 24 last observation carried forward (LOCF) >= 0.5% and without severe hypoglycemia events at Week 24

End point title	Percentage of subjects with HbA1c reduction from baseline to week 24 last observation carried forward (LOCF) >= 0.5% and without severe hypoglycemia events at Week 24
End point description:	
To compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit >=0.5% without severe hypoglycemia events	
End point type	Secondary
End point timeframe:	
Baseline and 24 weeks	

End point values	DAPA 5 MG + INS	DAPA 10 MG + INS	PLA + INS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	266	267	269	
Units: Participants				
Number of Responders	105	111	54	

Statistical analyses

Statistical analysis title	Sixth Secondary Endpoint Analysis
Statistical analysis description:	
Odds Ratio vs. Placebo	
Comparison groups	DAPA 5 MG + INS v PLA + INS
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.81
upper limit	4.06
Variability estimate	Standard error of the mean
Dispersion value	0.2058

Statistical analysis title	Sixth Secondary Endpoint Analysis
Statistical analysis description:	
Odds Ratio vs. Placebo	
Comparison groups	DAPA 10 MG + INS v PLA + INS
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.05
upper limit	4.6
Variability estimate	Standard error of the mean
Dispersion value	0.2054

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs), including serious adverse events (SAEs), were collected from the time informed consent was signed throughout the short-term plus long-term treatment period (through week 52).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	DAPA 5 MG + INS
Reporting group description:	
Dapagliflozin 5 mg plus insulin	
Reporting group title	PLA + INS
Reporting group description:	
Placebo plus insulin	
Reporting group title	DAPA 10 MG + INS
Reporting group description:	
Dapagliflozin 10 mg plus insulin	

Serious adverse events	DAPA 5 MG + INS	PLA + INS	DAPA 10 MG + INS
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 271 (11.81%)	16 / 272 (5.88%)	19 / 270 (7.04%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid neoplasm			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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

Histiocytic necrotising lymphadenitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
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 respiratory failure			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subarachnoid haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Road traffic accident			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture	Additional description: Humerus fracture		
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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
Intentional overdose			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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
Upper limb fracture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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 disorders			
Cardiac arrest			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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			

Cerebral haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic hyperglycaemic coma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of Encephalic Mass	Additional description: Loss Of Encephalic Mass (Severe Brain Injury)		

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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

Cerebral vasoconstriction

Additional description: Cerebral vasoconstriction

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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

Migraine

Additional description: Migraine with aura

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders

Enteritis

subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anal polyp

subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Small intestinal obstruction

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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

Gastrooesophageal reflux disease

Additional description: Gastrooesophageal reflux disease

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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

Upper gastrointestinal haemorrhage

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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

Cholecystitis acute			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder outlet obstruction			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
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			
Periarthritis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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			
Cellulitis			

subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Pneumonia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Urinary tract infection			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 271 (0.00%)	0 / 272 (0.00%)	1 / 270 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Peritonsillar abscess			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Wound infection			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (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
Infection			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	13 / 271 (4.80%)	1 / 272 (0.37%)	7 / 270 (2.59%)
occurrences causally related to treatment / all	8 / 13	1 / 1	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycemia			
subjects affected / exposed	3 / 271 (1.11%)	2 / 272 (0.74%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	2 / 271 (0.74%)	1 / 272 (0.37%)	0 / 270 (0.00%)
occurrences causally related to treatment / all	0 / 2	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	DAPA 5 MG + INS	PLA + INS	DAPA 10 MG + INS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 271 (79.34%)	202 / 272 (74.26%)	204 / 270 (75.56%)
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 271 (6.27%)	13 / 272 (4.78%)	18 / 270 (6.67%)
occurrences (all)	18	16	20
General disorders and administration site conditions			
Thirst			
subjects affected / exposed	6 / 271 (2.21%)	2 / 272 (0.74%)	14 / 270 (5.19%)
occurrences (all)	7	2	14
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	14 / 271 (5.17%)	8 / 272 (2.94%)	16 / 270 (5.93%)
occurrences (all)	20	11	24
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	22 / 271 (8.12%)	7 / 272 (2.57%)	14 / 270 (5.19%)
occurrences (all)	23	7	15
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	26 / 271 (9.59%)	15 / 272 (5.51%)	17 / 270 (6.30%)
occurrences (all)	34	19	20
Nasopharyngitis			
subjects affected / exposed	57 / 271 (21.03%)	69 / 272 (25.37%)	63 / 270 (23.33%)
occurrences (all)	79	97	91

Gastroenteritis			
subjects affected / exposed	14 / 271 (5.17%)	12 / 272 (4.41%)	12 / 270 (4.44%)
occurrences (all)	16	14	16
Urinary tract infection			
subjects affected / exposed	13 / 271 (4.80%)	15 / 272 (5.51%)	11 / 270 (4.07%)
occurrences (all)	16	18	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2015	The primary purpose of the amendment was to modify the Inclusion and Exclusion Criteria based on feedback from the European Medicines Agency (EMA). Specifically, the EMA has endorsed removing the requirement that HbA1c may not drop more than 0.5% during the lead-in phase.
18 May 2016	The primary purpose of this amendment is to provide study visit scheduling flexibility by allowing optional phone visits to be done at week -4, week 2 and for the Continuous Glucose Monitoring visits (weeks 10/11 and weeks 22/23) during the 24 week double blinded short term treatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported