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 (DEPICT 1)

Summary

EudraCT number	2013-004674-97
Trial protocol	SE DK GB FI IT DE AT ES HU BE
Global end of trial date	25 August 2017

Results information

Result version number	v1 (current)
This version publication date	08 September 2018
First version publication date	08 September 2018

Trial information

Trial identification

Sponsor protocol code	MB102-229

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02268214
WHO universal trial number (UTN)	-
Other trial identifiers	AZ: D1695C00006

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 431 83
Public contact	Anna Maria Langkilde, AstraZeneca AB, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Anna Maria Langkilde, AstraZeneca AB, 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	10 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2017
Global end of trial reached?	Yes
Global end of trial date	25 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the change from baseline in HbA1c after 24 weeks of doubleblinded treatment.

Protection of trial subjects:

Independent data monitoring committee

Background therapy:

Insulin

Evidence for comparator: -

Actual start date of recruitment	11 November 2014
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	Australia: 55
Country: Number of subjects enrolled	Austria: 57
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Canada: 61
Country: Number of subjects enrolled	Germany: 169
Country: Number of subjects enrolled	Denmark: 29
Country: Number of subjects enrolled	Spain: 73
Country: Number of subjects enrolled	Finland: 43
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Israel: 97
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Mexico: 180
Country: Number of subjects enrolled	Romania: 142
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	United States: 440
Worldwide total number of subjects	1604
EEA total number of subjects	771

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)	1512
From 65 to 84 years	92
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 11 November 2014. The last subject completed the 24-week short-term treatment period 04 January 2017. This study was conducted at 138 sites in 17 countries.

Pre-assignment

Screening details:

833 participants were randomized to a treatment group. Of the 771 participants not randomized to a treatment group: 585 No longer met study criteria, 125 withdrew consent, 26 were lost to follow-up, and 35 did not continue for other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin 5 mg + Insulin

Arm description: -

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	Dapagliflozin 10 mg + Insulin

Arm description: -

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	Placebo + Insulin

Arm description: -

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]	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin
Started	277	296	260
Completed	235	255	218
Not completed	42	41	42
Subject request to discontinue treatment	10	8	6
Adverse event, non-fatal	11	14	9
Pregnancy	2	2	1
Not entering long-term period	2	3	5
Other reasons	7	3	3
Lost to follow-up	3	3	4
Poor/non-compliance	2	1	2
Subject no longer meets study criteria	-	2	-
Lack of efficacy	1	-	2
Withdrawal by subject	4	5	10

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: We only summarized data for the patients randomized in the study. Baseline period had all of patients randomized in the study.

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin 5 mg + Insulin
Reporting group description: -	
Reporting group title	Dapagliflozin 10 mg + Insulin
Reporting group description: -	
Reporting group title	Placebo + Insulin
Reporting group description: -	

Reporting group values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin
Number of subjects	277	296	260
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)	262	279	246
From 65-84 years	15	17	14
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	42.1	43.4	42.7
standard deviation	± 13.94	± 13.89	± 13.57
Gender Categorical Units: Subjects			
Female	158	144	128
Male	119	152	132
Age categorization Units: Subjects			
<65 years	262	279	246
>=65 to <75 years	15	16	14
>= 75 years	0	1	0
Age categorization by tertiles Units: Subjects			
< 35 years	97	84	78
>=35 to < 50 years	88	107	91
>= 50 years	92	105	91
Race Units: Subjects			
White	264	282	249
Black or African-American	5	7	3
Asian	2	0	1
Other	6	7	7

Ethnicity			
Ethnicity is reported only for US subjects			
Units: Subjects			
Hispanic/Latino	6	5	8
Non-Hispanic/Latino	63	75	53
Not reported	208	216	199
Body mass index categorization Units: Subjects			
<=23 Kg/m^2	40	40	32
>23 to <=25 Kg/m^2	37	38	38
>25 to <=27 Kg/m^2	42	57	38
>27 to <=30 Kg/m^2	68	53	63
>30 Kg/m^2	90	108	89
Body weight Units: Kg			
arithmetic mean	81.25	83.54	84.36
standard deviation	± 18.053	± 17.747	± 18.332
Body mass index Units: Kg/m^2			
arithmetic mean	28.43	28.49	28.62
standard deviation	± 5.711	± 5.226	± 5.251

Reporting group values	Total		
Number of subjects	833		
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)	787		
From 65-84 years	46		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	430		
Male	403		
Age categorization Units: Subjects			
<65 years	787		
>=65 to <75 years	45		
>= 75 years	1		
Age categorization by tertiles Units: Subjects			

< 35 years	259		
>=35 to < 50 years	286		
>= 50 years	288		
Race Units: Subjects			
White	795		
Black or African-American	15		
Asian	3		
Other	20		
Ethnicity			
Ethnicity is reported only for US subjects			
Units: Subjects			
Hispanic/Latino	19		
Non-Hispanic/Latino	191		
Not reported	623		
Body mass index categorization Units: Subjects			
<=23 Kg/m^2	112		
>23 to <=25 Kg/m^2	113		
>25 to <=27 Kg/m^2	137		
>27 to <=30 Kg/m^2	184		
>30 Kg/m^2	287		
Body weight Units: Kg arithmetic mean standard deviation	- -		
Body mass index Units: Kg/m^2 arithmetic mean standard deviation	- -		

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

Subject analysis set description:

Randomized subjects that received at least 1 dose of double-blind study medication. The first 55 randomized subjects will be excluded from the full analysis dataset due to the presence of a randomization system error.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety 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	Safety Analysis Set	
Number of subjects	778	833	
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)	734	787	
From 65-84 years	44	46	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	42.5	42.7	
standard deviation	± 13.91	± 13.80	
Gender Categorical			
Units: Subjects			
Female	405	430	
Male	373	403	
Age categorization			
Units: Subjects			
<65 years	734	787	
>=65 to <75 years	43	45	
>= 75 years	1	1	
Age categorization by tertiles			
Units: Subjects			
< 35 years	250	259	
>=35 to < 50 years	262	286	
>= 50 years	266	288	
Race			
Units: Subjects			
White	744	795	
Black or African-American	15	15	
Asian	1	3	
Other	18	20	
Ethnicity			
Ethnicity is reported only for US subjects			
Units: Subjects			
Hispanic/Latino	16	19	
Non-Hispanic/Latino	162	191	
Not reported	600	623	
Body mass index categorization			
Units: Subjects			
<=23 Kg/m^2	111	112	
>23 to <=25 Kg/m^2	109	113	
>25 to <=27 Kg/m^2	124	137	
>27 to <=30 Kg/m^2	174	184	
>30 Kg/m^2	260	287	
Body weight			
Units: Kg			
arithmetic mean	82.47	83.04	
standard deviation	± 18.078	± 18.058	
Body mass index			
Units: Kg/m^2			
arithmetic mean	28.38	28.51	

standard deviation	± 5.406	± 5.394	

End points

End points reporting groups

Reporting group title	Dapagliflozin 5 mg + Insulin
Reporting group description: -	
Reporting group title	Dapagliflozin 10 mg + Insulin
Reporting group description: -	
Reporting group title	Placebo + Insulin
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomized subjects that received at least 1 dose of double-blind study medication. The first 55 randomized subjects will be excluded from the full analysis dataset due to the presence of a randomization system error.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety 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 Hemoglobin A1C (HbA1c) at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean change from baseline in Hemoglobin A1C (HbA1c) at Week 24 (Repeated Measures Model [RMM])
End point description:	
HbA1c was measured as percent of hemoglobin by a central laboratory. Baseline was defined as the last assessment on or prior to the date of the first dose of the double-blind study medication. HbA1c measurements were obtained during the qualification and lead-in periods and on Day 1 and Weeks 4, 8, 12, 18, and 24 in the double-blind period.	
End point type	Primary
End point timeframe:	
From Baseline to Week 24	

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	254[1]	254[2]	257	
Units: Percent				
least squares mean (standard error)	-0.45 (± 0.0537)	-0.47 (± 0.0538)	-0.03 (± 0.0540)	

Notes:

[1] - 18 patients were excluded due to a randomization system error.

[2] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean

(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.28
Variability estimate	Standard error of the mean
Dispersion value	0.0697

Notes:

[3] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[4] - [A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Primary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.31
Variability estimate	Standard error of the mean
Dispersion value	0.0696

Notes:

[5] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[6] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Adjusted mean percent change from baseline in Total Daily Insulin Dose (IU) at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean percent change from baseline in Total Daily Insulin Dose (IU) at Week 24 (Repeated Measures Model [RMM])

End point description:

Secondary endpoint was tested using a Dunnett and Tamhane procedure according to the pre-specified order. Daily insulin dosing (basal and bolus) were recorded at baseline, Weeks 2, 12 and 24. Baseline

was defined as mean of last 7 days assessment on or prior to the date of the first dose of the double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline to 24 Weeks

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	258[7]	254[8]	258	
Units: IU				
least squares mean (standard error)	-7.74 (± 1.4881)	-12.16 (± 1.4326)	1.16 (± 1.6593)	

Notes:

[7] - 18 patients were excluded due to a randomization system error.

[8] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	First Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.05 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-13.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.75
upper limit	-9.43
Variability estimate	Standard error of the mean
Dispersion value	1.8643

Notes:

[9] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[10] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	First Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin

Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.05 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.56
upper limit	-4.88
Variability estimate	Standard error of the mean
Dispersion value	1.9555

Notes:

[11] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[12] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Adjusted mean percent change from baseline in Total Body Weight at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean percent change from baseline in Total Body Weight at Week 24 (Repeated Measures Model [RMM])

End point description:

End point type	Secondary

End point timeframe:

Baseline to 24 weeks

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[13]	258[14]	259	
Units: Kg				
least squares mean (standard error)	-3.00 (± 0.2330)	-3.67 (± 0.2299)	0.05 (± 0.2407)	

Notes:

[13] - 18 patients were excluded due to a randomization system error.

[14] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Second Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.05 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.68
upper limit	-2.41
Variability estimate	Standard error of the mean
Dispersion value	0.3251

Notes:

[15] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[16] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Second Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.05 [18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.34
upper limit	-3.08
Variability estimate	Standard error of the mean
Dispersion value	0.3213

Notes:

[17] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[18] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Adjusted mean change from baseline in 24-Hour CGM Mean at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean change from baseline in 24-Hour CGM Mean at Week 24 (Repeated Measures Model [RMM])

End point description:

Secondary endpoint was tested using a Dunnett and Tamhane procedure according to the pre-specified order. Continuous Glucose Monitoring (CGM) measured the subject's interstitial glucose level using electrodes that measure an electric signal produced by glucose oxidase reaction. 24-hour interstitial glucose levels (at a 5 min interval) were obtained during the lead-in period and at Weeks 12 and 24 of the double-blind period. Baseline was defined as mean of the last 7 days assessment on or prior to the

date of the first dose of the double-blind study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238[19]	239[20]	234	
Units: mg/dL				
least squares mean (standard error)	-10.28 (± 1.8862)	-12.97 (± 1.9231)	5.06 (± 1.9320)	

Notes:

[19] - 18 patients were excluded due to a randomization system error.

[20] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Third Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.05 [22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.22
upper limit	-10.46
Variability estimate	Standard error of the mean
Dispersion value	2.4859

Notes:

[21] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[22] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Third Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin

Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.05 [24]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-18.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.95
upper limit	-13.11
Variability estimate	Standard error of the mean
Dispersion value	2.505

Notes:

[23] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[24] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Adjusted mean change from baseline in 24-Hour Mean Amplified Glucose Excursion (MAGE) at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean change from baseline in 24-Hour Mean Amplified Glucose Excursion (MAGE) at Week 24 (Repeated Measures Model [RMM])

End point description:

Secondary endpoint was tested using a Dunnett and Tamhane procedure according to the pre-specified order. Continuous Glucose Monitoring (CGM) measured the subject's interstitial glucose level using electrodes that measure an electric signal produced by glucose oxidase reaction. 24-hour interstitial glucose levels (at a 5 min interval) were obtained during the lead-in period and at Weeks 12 and 24 of the double-blind period. Baseline was defined as mean of the last 7 days assessment on or prior to the date of the first dose of the double-blind study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238[25]	239[26]	234	
Units: mg/dL				
least squares mean (standard error)	-14.92 (± 1.9915)	-16.55 (± 2.0419)	2.38 (± 2.0477)	

Notes:

[25] - 18 patients were excluded due to a randomization system error.

[26] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Fourth Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean

(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.05 [28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-18.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.13
upper limit	-13.73
Variability estimate	Standard error of the mean
Dispersion value	2.6482

Notes:

[27] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[28] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Fourth Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.05 [30]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.46
upper limit	-12.14
Variability estimate	Standard error of the mean
Dispersion value	2.6273

Notes:

[29] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[30] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Adjusted mean change from baseline in 24-hour CGM values > 70 mg/dL and <= 180 mg/dL (%) at Week 24 (Repeated Measures Model [RMM])

End point title	Adjusted mean change from baseline in 24-hour CGM values > 70 mg/dL and <= 180 mg/dL (%) at Week 24 (Repeated Measures Model [RMM])

End point description:

Secondary endpoint was tested using a Dunnett and Tamhane procedure according to the pre-specified order. Continuous Glucose Monitoring (CGM) measured the subject's interstitial glucose level using

electrodes that measure an electric signal produced by glucose oxidase reaction. 24-hour interstitial glucose levels (at a 5 min interval) were obtained during the lead-in period and at Weeks 12 and 24 of the double-blind period. Baseline was defined as mean of the last 7 days assessment on or prior to the date of the first dose of the double-blind study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238[31]	239[32]	234	
Units: mg/dL				
least squares mean (standard error)	6.98 (± 0.8824)	8.52 (± 0.9000)	-2.13 (± 0.9032)	

Notes:

[31] - 18 patients were excluded due to a randomization system error.

[32] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Fifth Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.05 [34]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	9.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.83
upper limit	11.39
Variability estimate	Standard error of the mean
Dispersion value	1.1611

Notes:

[33] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[34] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Fifth Secondary Endpoint Analysis

Statistical analysis description:

H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin

Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.05 [36]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.35
upper limit	12.94
Variability estimate	Standard error of the mean
Dispersion value	1.1689

Notes:

[35] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[36] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Secondary: Percentage of Subjects with Hemoglobin A1c [HbA1C]) reduction from baseline to Week 24 (Last Observation Carried Forward [LOCF]) >= 0.5% and without severe hypoglycemia events

End point title	Percentage of Subjects with Hemoglobin A1c [HbA1C]) reduction from baseline to Week 24 (Last Observation Carried Forward [LOCF]) >= 0.5% and without severe hypoglycemia events

End point description:

Secondary endpoint was tested using a Dunnett and Tamhane procedure according to the pre-specified order. Percent adjusted for baseline HbA1c and randomization strata. HbA1c was measured as a percent of hemoglobin. Severe hypoglycemia is classified according to recommendations by workgroup on hypoglycemia, American Diabetes Association (2005).

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	256[37]	254[38]	257	
Units: Subjects				
Subjects, reduction in A1c >=0.5% & no severe hypo	127	129	65	

Notes:

[37] - 18 patients were excluded due to a randomization system error.

[38] - 37 patients were excluded due to a randomization system error.

Statistical analyses

Statistical analysis title	Sixth Secondary Endpoint Analysis

Statistical analysis description:

H0: odds ratio (treat/placebo) = 1 versus the alternative HA: odds ratio (treat/placebo) =/= 1

Comparison groups	Dapagliflozin 5 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.05 [40]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	4.56
Variability estimate	Standard error of the mean
Dispersion value	0.198

Notes:

[39] - Dapagliflozin 5 mg + Insulin Vs. Placebo + Insulin

[40] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Statistical analysis title	Sixth Secondary Endpoint Analysis

Statistical analysis description:

H0: odds ratio (treat/placebo) = 1 versus the alternative HA: odds ratio (treat/placebo) =/= 1

Comparison groups	Dapagliflozin 10 mg + Insulin v Placebo + Insulin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.05 [42]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.23
upper limit	4.85
Variability estimate	Standard error of the mean
Dispersion value	0.1979

Notes:

[41] - Dapagliflozin 10 mg + Insulin Vs. Placebo + Insulin

[42] - A Dunnett and Tamhane procedure was used to control Type I error across the primary & secondary objectives. Statistical significance for both Dapa doses at 5% if 2-sided p-values from both comparisons <5%. Or the comparison with p-values <2.62%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Onset on or after the first date of double-blind treatment and on or prior to the last day of treatment 24-week short-term period, 28-week extension period and the 30-day folllow-up period.

Adverse event reporting additional description:

Participants were questioned at each study visit about the occurrence of any health problems and any examination conducted at a study visit was assessed in comparison to the status at study entry.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Dapagliflozin 5 mg + Insulin

Reporting group description:

Dapagliflozin 5 mg + Insulin

Reporting group title	Dapagliflozin 10 mg + Insulin

Reporting group description:

Dapagliflozin 10 mg + Insulin

Reporting group title	Placebo + Insulin

Reporting group description:

Placebo + Insulin

Serious adverse events	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 277 (13.36%)	40 / 296 (13.51%)	30 / 260 (11.54%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Bone cancer			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Breast cancer			

subjects affected / exposed	1 / 277 (0.36%)	1 / 296 (0.34%)	0 / 260 (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
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Keratoacanthoma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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			
Embolism			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Thrombosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 277 (0.36%)	2 / 296 (0.68%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Pyrexia			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
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			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Gynaecomastia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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 mass			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
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			
Adjustment disorder			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Liver function test increased			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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			
Ankle fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 277 (0.36%)	1 / 296 (0.34%)	0 / 260 (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
Hand fracture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Intentional overdose			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Limb injury			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Overdose			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Procedural pain			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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			
Angina pectoris			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Sinus tachycardia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cubital tunnel syndrome			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Multiple sclerosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Cataract			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Ophthalmoplegia			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	2 / 277 (0.72%)	0 / 296 (0.00%)	0 / 260 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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

Abdominal pain upper			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Cyclic vomiting syndrome			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Diabetic gastroparesis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Gastritis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Oesophagitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Pancreatitis chronic			

subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haematoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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			
Diabetic foot			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Renal and urinary disorders			
Obstructive uropathy			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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 colic			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
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			
Foot deformity			

subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Osteoarthritis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			

subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Influenza			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Localised infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Nasal abscess			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal abscess			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (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
Pneumonia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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
Tooth infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 296 (0.00%)	0 / 260 (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 / 277 (0.36%)	1 / 296 (0.34%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 296 (0.34%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 277 (0.00%)	0 / 296 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	10 / 277 (3.61%)	7 / 296 (2.36%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	3 / 11	5 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	2 / 277 (0.72%)	4 / 296 (1.35%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	2 / 2	1 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ketoacidosis			
subjects affected / exposed	2 / 277 (0.72%)	4 / 296 (1.35%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	1 / 2	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	2 / 277 (0.72%)	2 / 296 (0.68%)	0 / 260 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	1 / 277 (0.36%)	1 / 296 (0.34%)	0 / 260 (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

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

Non-serious adverse events	Dapagliflozin 5 mg + Insulin	Dapagliflozin 10 mg + Insulin	Placebo + Insulin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 277 (44.40%)	118 / 296 (39.86%)	99 / 260 (38.08%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 277 (5.05%)	20 / 296 (6.76%)	13 / 260 (5.00%)
occurrences (all)	17	27	13
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 277 (3.97%)	21 / 296 (7.09%)	9 / 260 (3.46%)
occurrences (all)	13	25	10
Nausea			
subjects affected / exposed	14 / 277 (5.05%)	15 / 296 (5.07%)	7 / 260 (2.69%)
occurrences (all)	18	20	7
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	15 / 277 (5.42%)	10 / 296 (3.38%)	8 / 260 (3.08%)
occurrences (all)	16	13	10
Influenza			
subjects affected / exposed	15 / 277 (5.42%)	15 / 296 (5.07%)	17 / 260 (6.54%)
occurrences (all)	18	17	23
Upper respiratory tract infection			
subjects affected / exposed	19 / 277 (6.86%)	28 / 296 (9.46%)	15 / 260 (5.77%)
occurrences (all)	26	36	28
Urinary tract infection			
subjects affected / exposed	27 / 277 (9.75%)	10 / 296 (3.38%)	19 / 260 (7.31%)
occurrences (all)	37	12	20
Viral upper respiratory tract infection			
subjects affected / exposed	51 / 277 (18.41%)	46 / 296 (15.54%)	48 / 260 (18.46%)
occurrences (all)	67	65	66

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2015	The primary purpose was to modify the Inclusion and Exclusion Criteria, based on feedback from the European Medicines Agency. EMA endorsed removing the requirement that HbA1c may not drop more than 0.5% during the lead-in phase.
16 May 2016	The primary purpose of this amendment was to increase the randomization target by 55 to maintain the power for the primary endpoint as the first 55 randomized subjects will be excluded from the primary efficacy analysis due to an IVRS randomization system error.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported