Clinical trial results:
A 28-week, Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Study with a 24-week Extension Phase Followed by a 52-week Extension Phase to Evaluate the Efficacy and Safety of Simultaneous Administration of Exenatide Once Weekly 2 mg and Dapagliflozin Once Daily 10 mg Compared to Exenatide Once Weekly 2 mg Alone and Dapagliflozin Once Daily 10 mg Alone in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin

Summary

EudraCT number	2014-003503-29
Trial protocol	SK HU
Global end of trial date	28 December 2017

Results information

Result version number	v1 (current)
This version publication date	22 December 2018
First version publication date	22 December 2018

Trial information

Trial identification

Sponsor protocol code	D5553C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02229396
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, MD 20878
Public contact	Global Clinical Leader, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Leader, AstraZeneca, 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	28 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the change from baseline in hemoglobin A1c (HbA1c) at 28 weeks between exenatide once weekly (EQW) 2 milligrams (mg) and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Dapagliflozin was administered orally and EQW as subcutaneous (SC) injection.

Protection of trial subjects:

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

Background therapy:

Patients continued to administer the same type and dose of metformin therapy they were using at study entry (at least 1500 mg/day).

Evidence for comparator: -

Actual start date of recruitment	04 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 394
Country: Number of subjects enrolled	Hungary: 78
Country: Number of subjects enrolled	Slovakia: 71
Country: Number of subjects enrolled	Romania: 70
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	South Africa: 58
Worldwide total number of subjects	695
EEA total number of subjects	243

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)	608
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study conducted between 04 September 2014 and 28 December 2017. 118 centers in 6 countries randomized patients in the study. A Primary Analysis was performed following completion of the 28-week Treatment Period with a data cut-off date of 26 April 2016. All Primary and Secondary End Points were reported at the time of the Primary Analysis.

Pre-assignment

Screening details:

The study had a Screening Visit, a 1-week placebo Lead-in Period, a Randomization Visit, and 9 further visits at 1- to 4-week intervals during a 28-week Treatment Period. Patients then entered a 24-week Extension Period 1 and subsequent 52-week Extension Period 2. A follow-up visit occurred 10 weeks after last dose of study medication.

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	Investigator, Monitor, Carer, Data analyst, Subject, Assessor

Blinding implementation details:

Patients received single-blind dapagliflozin and exenatide placebo during the Lead-in Period. From the Randomization Visit and throughout the 28-week Treatment Period, the study was double-blind. The Sponsor and its applicable representatives were unblinded in the Extension Periods (ie, from Week 28 onwards). Sites and patients remained blinded during the Extension Periods.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapagliflozin + Placebo

Arm description:

Dapagliflozin 10 mg tablet administered orally once daily + matching placebo for exenatide administered as SC injection once weekly. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	
Other name	Farxiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg tablets administered once daily.

Investigational medicinal product name	Placebo-matched exenatide once weekly
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo powder for injection administered once weekly.

Arm title	Exenatide + Dapagliflozin

Arm description:

Exenatide once weekly (EQW) 2 mg administered as SC injection + dapagliflozin 10 mg tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Arm type	Experimental
Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW, Bydureon
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2.0 mg powder for injection administered once weekly.

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

Dosage and administration details:

10 mg tablets administered once daily.

Arm title	Exenatide + Placebo

Arm description:

Exenatide once weekly (EQW) 2 mg administered as SC injection + matching placebo for dapagliflozin tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Arm type	Active comparator
Investigational medicinal product name	Placebo-matched dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets administered once daily.

Investigational medicinal product name	Exenatide once weekly
Investigational medicinal product code	
Other name	EQW, Bydureon
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2.0 mg powder for injection administered once weekly.

Number of subjects in period 1	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo
Started	233	231	231
Randomization Code Allocated	233	231	231
Safety Analysis Set	233	231	230
Intent-to-Treat (ITT) Analysis Set	230	228	227
Completed 28-Week Study Period	208	202	193
Completed 52-Week Study Period	194	193	177
Completed	155	154	136
Not completed	78	77	95
Adverse event, serious fatal	2	3	1

Consent withdrawn by subject	42	28	41
Adverse event, non-fatal	6	12	12
Withdrew; No Record on Termination Page	2	-	1
Unspecified	10	18	15
Lost to follow-up	14	14	21
Patient Incorrectly Randomized	-	-	1
Protocol deviation	2	1	-
Study-Specific Withdrawal Criteria	-	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Dapagliflozin + Placebo
Reporting group description:	
Dapagliflozin 10 mg tablet administered orally once daily + matching placebo for exenatide administered as SC injection once weekly. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	
Reporting group title	Exenatide + Dapagliflozin
Reporting group description:	
Exenatide once weekly (EQW) 2 mg administered as SC injection + dapagliflozin 10 mg tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	
Reporting group title	Exenatide + Placebo
Reporting group description:	
Exenatide once weekly (EQW) 2 mg administered as SC injection + matching placebo for dapagliflozin tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	

Reporting group values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo
Number of subjects	233	231	231
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)	206	200	202
From 65-84 years	27	31	29
85 years and over	0	0	0
Gender, Male/Female Units: Subjects			
Female	121	128	114
Male	112	103	117
Race, Customized Units: Subjects			
American Indian Or Alaska Native|	0	0	2
Asian|	1	3	1
Black Or African American|	33	36	27
Other|	7	1	3
White|	192	191	198

Reporting group values	Total		
Number of subjects	695		
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)	608		
From 65-84 years	87		
85 years and over	0		
Gender, Male/Female Units: Subjects			
Female	363		
Male	332		
Race, Customized Units: Subjects			
American Indian Or Alaska Native|	2		
Asian|	5		
Black Or African American|	96		
Other|	11		
White|	581		

End points

End points reporting groups

Reporting group title	Dapagliflozin + Placebo
Reporting group description:	
Dapagliflozin 10 mg tablet administered orally once daily + matching placebo for exenatide administered as SC injection once weekly. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	
Reporting group title	Exenatide + Dapagliflozin
Reporting group description:	
Exenatide once weekly (EQW) 2 mg administered as SC injection + dapagliflozin 10 mg tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	
Reporting group title	Exenatide + Placebo
Reporting group description:	
Exenatide once weekly (EQW) 2 mg administered as SC injection + matching placebo for dapagliflozin tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.	

Primary: Change in HbA1c from baseline to Week 28

End point title	Change in HbA1c from baseline to Week 28
End point description:	
To compare the change from baseline to Week 28 in HbA1c between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.	
End point type	Primary
End point timeframe:	
Baseline to Week 28	

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: % HbA1c				
least squares mean (confidence interval 95%)	-1.39 (-1.57 to -1.21)	-1.98 (-2.16 to -1.79)	-1.60 (-1.79 to -1.41)	

Statistical analyses

Statistical analysis title	Change in HbA1c - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo

Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.129

Statistical analysis title	Change in HbA1c - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.127

Secondary: Change in body weight from baseline to Week 28

End point title	Change in body weight from baseline to Week 28
End point description:	
To compare the change from baseline to Week 28 in body weight between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.	
End point type	Secondary
End point timeframe:	
Baseline to Week 28	

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: kilogram				
least squares mean (confidence interval 95%)	-2.22 (-2.78 to -1.66)	-3.55 (-4.12 to -2.99)	-1.56 (-2.13 to -0.98)	

Statistical analyses

Statistical analysis title	Change in body weight - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	-1.2
Variability estimate	Standard error of the mean
Dispersion value	0.406

Statistical analysis title	Change in body weight - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.55
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Change in fasting plasma glucose from baseline to Week 28

End point title	Change in fasting plasma glucose from baseline to Week 28

End point description:

To compare the change from baseline to Week 28 in fasting plasma glucose (FPG) between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: milligrams/deciliter (mg/dL)				
least squares mean (confidence interval 95%)	-49.19 (-54.91 to -43.47)	-65.83 (-71.60 to -60.06)	-45.75 (-51.67 to -39.83)	

Statistical analyses

Statistical analysis title	Change in FPG - baseline to Week 28

Statistical analysis description:

Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.

Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.95
upper limit	-12.2
Variability estimate	Standard error of the mean
Dispersion value	4.007

Statistical analysis title	Change in FPG - baseline to Week 28

Statistical analysis description:

Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.

Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-16.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.39
upper limit	-8.89
Variability estimate	Standard error of the mean
Dispersion value	3.947

Secondary: Change from baseline to Week 28 in 2-hour postprandial glucose after a standard Meal Tolerance Test

End point title	Change from baseline to Week 28 in 2-hour postprandial glucose after a standard Meal Tolerance Test

End point description:

To compare the change from baseline to Week 28 in 2-hour postprandial glucose (PPG) after a standard Meal Tolerance Test (MTT) between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: mg/dL				
least squares mean (confidence interval 95%)	-61.05 (-69.10 to -53.00)	-87.83 (-95.83 to -79.84)	-60.09 (-68.48 to -51.71)	

Statistical analyses

Statistical analysis title	Change in 2 hr PPG - baseline to Week 28

Statistical analysis description:

Treatment, region, and baseline HbA1c stratum (<9.0% or ≥9.0%), as fixed factors; baseline value as covariate.

Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-27.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.89
upper limit	-17.59
Variability estimate	Standard error of the mean
Dispersion value	5.168

Statistical analysis title	Change in 2 hr PPG - baseline to Week 28

Statistical analysis description:

Treatment, region, and baseline HbA1c stratum (<9.0% or ≥9.0%), as fixed factors; baseline value as covariate.

Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-26.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.78
upper limit	-16.78

Variability estimate	Standard error of the mean
Dispersion value	5.09

Secondary: Percentage of patients achieving weight loss ≥5.0% at Week 28

End point title	Percentage of patients achieving weight loss ≥5.0% at Week 28

End point description:

To compare the percentage of patients achieving weight loss ≥5.0% at 28 weeks between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: % of patients				
number (confidence interval 95%)	20.0 (14.8 to 25.2)	33.3 (27.2 to 39.5)	13.7 (9.2 to 18.1)	

Statistical analyses

Statistical analysis title	Percentage of patients achieving weight loss >=5%

Statistical analysis description:

Treatment comparison at Week 28 is based on a Cochran-Mantel-Haenszel test, stratified by baseline HbA1c (<9.0% or ≥9.0%).

Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Difference in percentages = 19.7

Statistical analysis title	Percentage of patients achieving weight loss >=5%

Statistical analysis description:

A Cochran-Mantel-Haenszel analysis was performed at Week 28, stratified by baseline HbA1c (<9.0% or ≥9.0%).

Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Difference in percentages = 13.3

Secondary: Change in fasting plasma glucose from baseline to Week 2

End point title	Change in fasting plasma glucose from baseline to Week 2

End point description:

To compare the change from baseline to Week 2 in FPG between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 2

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: mg/dL				
least squares mean (confidence interval 95%)	-26.31 (-31.42 to -21.20)	-41.34 (-46.48 to -36.20)	-21.08 (-26.29 to -15.86)	

Statistical analyses

Statistical analysis title	Change in FPG - baseline to Week 2

Statistical analysis description:

Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.

Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.12
upper limit	-13.4
Variability estimate	Standard error of the mean
Dispersion value	3.494

Statistical analysis title	Change in FPG - baseline to Week 2

Statistical analysis description:

Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.

Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.85
upper limit	-8.2
Variability estimate	Standard error of the mean
Dispersion value	3.477

Notes:

[3] - This is a nominal p-value.

Secondary: Percentage of patients achieving HbA1c <7% at Week 28

End point title	Percentage of patients achieving HbA1c <7% at Week 28

End point description:

To compare the percentage of patients achieving HbA1c <7% at 28 weeks between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: % of patients				
number (confidence interval 95%)	19.1 (14.1 to 24.2)	44.7 (38.3 to 51.2)	26.9 (21.1 to 32.6)	

Statistical analyses

Statistical analysis title	Percentage of patients achieving HbA1c <7%

Statistical analysis description:

A Cochran-Mantel-Haenszel analysis was performed at Week 28, stratified by baseline HbA1c (<9.0% or ≥9.0%).

Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Difference in percentages = 17.9

Statistical analysis title	Percentage of patients achieving HbA1c <7%

Statistical analysis description:

A Cochran-Mantel-Haenszel analysis was performed at Week 28, stratified by baseline HbA1c (<9.0% or ≥9.0%).

Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Difference in percentages = 25.6

Secondary: Change in systolic blood pressure from baseline to Week 28

End point title	Change in systolic blood pressure from baseline to Week 28

End point description:

To compare the change from baseline to Week 28 in systolic blood pressure between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone. Analysis performed on the ITT analysis set which included all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Dapagliflozin + Placebo	Exenatide + Dapagliflozin	Exenatide + Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	228	227	
Units: millimeters of mercury (mmHg)				
least squares mean (confidence interval 95%)	-1.8 (-3.4 to -0.3)	-4.3 (-5.8 to -2.7)	-1.2 (-2.8 to 0.4)	

Statistical analyses

Statistical analysis title	Change in SBP - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Exenatide + Dapagliflozin v Exenatide + Placebo
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	1.08

Statistical analysis title	Change in SBP - baseline to Week 28
Statistical analysis description:	
Treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors; baseline value as covariate.	
Comparison groups	Dapagliflozin + Placebo v Exenatide + Dapagliflozin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	1.06

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 1) up to Week 104 (28-week Treatment Period + 24-week Extension Period 1 + 52-week Extension Period 2).

Adverse event reporting additional description:

Treatment-emergent adverse event (AE) data is reported for the Safety Analysis set defined as all randomized patients receiving at least 1 dose of study medication. One patient who was randomized did not receive study medication (the patient was randomized in error); this patient was not counted as completing or discontinuing treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Dapagliflozin + Placebo

Reporting group description:

Dapagliflozin 10 mg tablet administered orally once daily + matching placebo for exenatide administered as SC injection once weekly. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Reporting group title	Exenatide + Placebo

Reporting group description:

Exenatide once weekly (EQW) 2 mg administered as SC injection + matching placebo for dapagliflozin tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Reporting group title	Exenatide + Dapagliflozin

Reporting group description:

Exenatide once weekly (EQW) 2 mg administered as SC injection + dapagliflozin 10 mg tablet administered orally once daily. Patients continued to administer the same type and dose of metformin therapy they were using at study entry.

Serious adverse events	Dapagliflozin + Placebo	Exenatide + Placebo	Exenatide + Dapagliflozin
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 233 (7.73%)	18 / 230 (7.83%)	17 / 231 (7.36%)
number of deaths (all causes)	2	1	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Lipoma			

subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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			
Hypertension			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Hypotension			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 233 (0.43%)	1 / 230 (0.43%)	0 / 231 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 233 (0.43%)	1 / 230 (0.43%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Interstitial lung disease			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 233 (0.00%)	2 / 230 (0.87%)	0 / 231 (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
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Splenic rupture			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Multiple injuries			

subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Spinal compression fracture			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Toxicity to various agents			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 233 (0.86%)	1 / 230 (0.43%)	0 / 231 (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
Angina pectoris			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	1 / 233 (0.43%)	2 / 230 (0.87%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			

subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Myocardial infarction			
subjects affected / exposed	0 / 233 (0.00%)	2 / 230 (0.87%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Palpitations			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Tachycardia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 233 (0.43%)	1 / 230 (0.43%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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 disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
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 haemorrhage			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic necrosis			

subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	2 / 231 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Endocrine disorders			
Pituitary-dependent Cushing's syndrome			

subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
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			
Exostosis			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
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 / 233 (0.00%)	0 / 230 (0.00%)	1 / 231 (0.43%)
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	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Diverticulitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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
Meningitis viral			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	0 / 231 (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

Osteomyelitis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Pneumonia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 230 (0.43%)	1 / 231 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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
Hypoglycaemia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 230 (0.00%)	0 / 231 (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

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

Non-serious adverse events	Dapagliflozin + Placebo	Exenatide + Placebo	Exenatide + Dapagliflozin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 233 (31.33%)	78 / 230 (33.91%)	87 / 231 (37.66%)
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 233 (5.15%)	12 / 230 (5.22%)	16 / 231 (6.93%)
occurrences (all)	12	12	18
General disorders and administration site conditions			
Injection site nodule			
subjects affected / exposed	13 / 233 (5.58%)	14 / 230 (6.09%)	20 / 231 (8.66%)
occurrences (all)	22	24	40
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 233 (4.72%)	17 / 230 (7.39%)	13 / 231 (5.63%)
occurrences (all)	14	25	17

Nausea			
subjects affected / exposed	10 / 233 (4.29%)	26 / 230 (11.30%)	13 / 231 (5.63%)
occurrences (all)	12	29	14
Vomiting			
subjects affected / exposed	7 / 233 (3.00%)	12 / 230 (5.22%)	8 / 231 (3.46%)
occurrences (all)	7	15	10
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 233 (5.15%)	8 / 230 (3.48%)	15 / 231 (6.49%)
occurrences (all)	15	10	17
Upper respiratory tract infection			
subjects affected / exposed	22 / 233 (9.44%)	17 / 230 (7.39%)	15 / 231 (6.49%)
occurrences (all)	25	29	22
Urinary tract infection			
subjects affected / exposed	16 / 233 (6.87%)	15 / 230 (6.52%)	19 / 231 (8.23%)
occurrences (all)	23	24	31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2014	-Exclusion/inclusion criteria amended for clarification of patients that could be included in the study (those on antihypertensive agents, thyroid replacement therapy and antidepressant agents were eligible if on a stable treatment regimen for 2 months prior to Visit 1). -Exclusion criterion amended to reduce threshold for exclusion based on calcitonin levels to align with new project-wide criteria. -Exclusion criterion amended to correct errors in exclusionary laboratory values for serum creatinine. -Methods for ensuring blinding amended to clarify blinding during the Extension Periods and blinding procedures for central laboratory results updated to help prevent indirect unblinding of study treatment. -Restrictions updated to clarify substances and activities from which patients were to abstain for 24 hours prior to visits. -Procedures for discontinuation amended to allow patients that temporarily stop drug treatment due to an AE or other significant event to continue participating in the trial. -Study Plan and Timing of Procedures updated. -Treatment period and study assessment text amended to clarify procedures for performing the 6-point self-monitored blood glucose profile for patients receiving rescue therapy. -Removed requirement that patients take doses of study medication during clinic visits. -Study assessment text regarding the MTT updated to include additional instruction on timing and to clarify the sequence of steps of the MTT. -Urinalysis text updated to specify that urine glucose results were blinded to reduce the possibility of study treatment unblinding. -Text added to clarify procedures for monitoring and assessing potential liver injuries. -Text updated to clarify Hy's Law information to conform with updated Sponsor standards. -Updated description of hypoglycaemia assessment and reporting to clarify that classification would be done programmatically rather than by Investigators.
20 February 2015	-Exclusion criterion modified to be less restrictive with respect to prior study participation. -Study Plan and Timing of Procedures were updated. -Review of potential cardiovascular (CV) event triggers was added to all visits where AEs and concomitant medication were reviewed. -Text was added to indicate that metformin should be taken with the next meal, and does not need to be taken at the study site, and that urine should be collected right before time 0 of the MTT. -Extension Period Visit text was amended so that instead of plasma fasting glucose, HbA1c levels were used to determine the need for rescue during the extension period. -New section regarding paternal exposure was added to align with current AstraZeneca protocol template language. -New section regarding CV adjudication was added to enable assessment of CV risk across the exenatide clinical program.
02 September 2015	-A 52-week extension (Extension Period 2) was added to the study. -Sample collection during the End of Treatment Period Visit or Early Termination or Rescue during Treatment Period was amended to state that blood samples were to be collected after administration of dapagliflozin and that a between visit telephone contact was to take place between Visit 12 to 13 for safety information. -Sample collection and storage of biological samples for future research was amended for clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported