



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 $\geq 5.0\%$ at Week 28

| | |
|-----------------|--|
| End point title | Percentage of patients achieving weight loss $\geq 5.0\%$ at Week 28 |
|-----------------|--|

End point description:

To compare the percentage of patients achieving weight loss $\geq 5.0\%$ 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 $\geq 5\%$ |
|----------------------------|---|

Statistical analysis description:

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

| | |
|---|---|
| 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 $\geq 5\%$ |
|----------------------------|---|

Statistical analysis description:

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

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