



Clinical trial results:

A Randomized, Phase 3, Double-blind Trial Comparing the Effect of the Addition of Tirzepatide versus Placebo in Patients with Type 2 Diabetes Inadequately Controlled on Insulin Glargine with or without Metformin Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2019-000860-99 |
| Trial protocol | SK CZ DE PL ES |
| Global end of trial date | 13 January 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 28 December 2021 |
| First version publication date | 28 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | I8F-MC-GPGI |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04039503 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 16998 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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 | 13 January 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare the safety and efficacy of the study drug tirzepatide to placebo in participants with type 2 diabetes that are already on insulin glargine, with or without metformin. Participants will administer tirzepatide or placebo along with their previous glucose lowering medications. The study will last approximately 47 weeks and may include about 23 visits.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 30 August 2019 |
| 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 | Czechia: 94 |
| Country: Number of subjects enrolled | Germany: 129 |
| Country: Number of subjects enrolled | Japan: 82 |
| Country: Number of subjects enrolled | Poland: 36 |
| Country: Number of subjects enrolled | Puerto Rico: 12 |
| Country: Number of subjects enrolled | Slovakia: 31 |
| Country: Number of subjects enrolled | Spain: 57 |
| Country: Number of subjects enrolled | United States: 34 |
| Worldwide total number of subjects | 475 |
| EEA total number of subjects | 347 |

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) | 283 |
| From 65 to 84 years | 192 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

No Text Available

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 5 mg Tirzepatide |

Arm description:

5 milligrams (mg) tirzepatide administered subcutaneously (SC) once a week.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tirzepatide |
| Investigational medicinal product code | |
| Other name | LY3298176 |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered SC as add-on to the pre-trial background medication.

| | |
|------------------|-------------------|
| Arm title | 10 mg Tirzepatide |
|------------------|-------------------|

Arm description:

10 mg tirzepatide administered SC once a week.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tirzepatide |
| Investigational medicinal product code | |
| Other name | LY3298176 |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered SC as add-on to the pre-trial background medication.

| | |
|------------------|-------------------|
| Arm title | 15 mg Tirzepatide |
|------------------|-------------------|

Arm description:

15 mg tirzepatide administered SC once a week.

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tirzepatide |
| Investigational medicinal product code | |
| Other name | LY3298176 |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered SC as add-on to the pre-trial background medication.

| | |
|--|------------------|
| Arm title | Placebo |
| Arm description: | |
| Placebo administered SC once a week. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered SC as add-on to the pre-trial background medication.

| Number of subjects in period 1 | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide |
|---------------------------------------|------------------|-------------------|-------------------|
| Started | 116 | 119 | 120 |
| Completed | 109 | 115 | 110 |
| Not completed | 7 | 4 | 10 |
| Consent withdrawn by subject | 4 | 3 | 5 |
| Adverse event, non-fatal | 3 | - | 2 |
| Lost to follow-up | - | - | 1 |
| Protocol deviation | - | 1 | 2 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 120 |
| Completed | 117 |
| Not completed | 3 |
| Consent withdrawn by subject | 2 |
| Adverse event, non-fatal | - |
| Lost to follow-up | - |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|---|-------------------|
| Reporting group title | 5 mg Tirzepatide |
| Reporting group description: 5 milligrams (mg) tirzepatide administered subcutaneously (SC) once a week. | |
| Reporting group title | 10 mg Tirzepatide |
| Reporting group description: 10 mg tirzepatide administered SC once a week. | |
| Reporting group title | 15 mg Tirzepatide |
| Reporting group description: 15 mg tirzepatide administered SC once a week. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo administered SC once a week. | |

| Reporting group values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide |
|---|------------------|-------------------|-------------------|
| Number of subjects | 116 | 119 | 120 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 61.50 | 60.40 | 60.50 |
| standard deviation | ± 9.81 | ± 10.24 | ± 9.92 |
| Gender categorical Units: Subjects | | | |
| Female | 55 | 47 | 55 |
| Male | 61 | 72 | 65 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 4 | 8 | 5 |
| Not Hispanic or Latino | 94 | 95 | 93 |
| Unknown or Not Reported | 18 | 16 | 22 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 20 | 21 | 22 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |

| | | | |
|--|--------|--------|--------|
| Black or African American | 1 | 2 | 3 |
| White | 95 | 94 | 94 |
| More than one race | 0 | 1 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Czechia | 24 | 24 | 23 |
| Germany | 32 | 32 | 33 |
| Japan | 19 | 21 | 20 |
| Poland | 8 | 9 | 10 |
| Puerto Rico | 2 | 6 | 1 |
| Slovakia | 8 | 7 | 8 |
| Spain | 13 | 15 | 15 |
| United States | 10 | 5 | 10 |
| Hemoglobin A1c | | | |
| HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time. | | | |
| Units: Percentage of HbA1c | | | |
| arithmetic mean | 8.30 | 8.36 | 8.23 |
| standard deviation | ± 0.88 | ± 0.83 | ± 0.86 |

| Reporting group values | Placebo | Total | |
|--|---------|-------|--|
| Number of subjects | 120 | 475 | |
| 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.00 | | |
| standard deviation | ± 9.63 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 54 | 211 | |
| Male | 66 | 264 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 5 | 22 | |
| Not Hispanic or Latino | 98 | 380 | |
| Unknown or Not Reported | 17 | 73 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 2 | |

| | | | |
|--|--------|-----|--|
| Asian | 22 | 85 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 6 | |
| White | 97 | 380 | |
| More than one race | 1 | 2 | |
| Unknown or Not Reported | 0 | 0 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Czechia | 23 | 94 | |
| Germany | 32 | 129 | |
| Japan | 22 | 82 | |
| Poland | 9 | 36 | |
| Puerto Rico | 3 | 12 | |
| Slovakia | 8 | 31 | |
| Spain | 14 | 57 | |
| United States | 9 | 34 | |
| Hemoglobin A1c | | | |
| HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time. | | | |
| Units: Percentage of HbA1c | | | |
| arithmetic mean | 8.37 | | |
| standard deviation | ± 0.84 | - | |

End points

End points reporting groups

| | |
|------------------------------|---|
| Reporting group title | 5 mg Tirzepatide |
| Reporting group description: | 5 milligrams (mg) tirzepatide administered subcutaneously (SC) once a week. |
| Reporting group title | 10 mg Tirzepatide |
| Reporting group description: | 10 mg tirzepatide administered SC once a week. |
| Reporting group title | 15 mg Tirzepatide |
| Reporting group description: | 15 mg tirzepatide administered SC once a week. |
| Reporting group title | Placebo |
| Reporting group description: | Placebo administered SC once a week. |

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) (10 mg and 15 mg)

| | |
|-----------------|---|
| End point title | Change from Baseline in Hemoglobin A1c (HbA1c) (10 mg and 15 mg) ^[1] |
|-----------------|---|

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with Baseline + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares).

Analysis Population Description (APD): All randomized participants from who received at least 1 dose study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 40

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis planned for this outcome.

| End point values | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo | |
|-------------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 113 | 117 | 118 | |
| Units: Percentage of HbA1c | | | | |
| least squares mean (standard error) | -2.59 (± 0.081) | -2.59 (± 0.083) | -0.93 (± 0.079) | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Hemoglobin A1c (HbA1c) |
| Comparison groups | 10 mg Tirzepatide v Placebo |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 231 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.88 |
| upper limit | -1.43 |

| | |
|---|-----------------------------|
| Statistical analysis title | Hemoglobin A1c (HbA1c) |
| Comparison groups | 15 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.88 |
| upper limit | -1.43 |

Secondary: Change from Baseline in HbA1c (5 mg)

| | |
|-----------------|---|
| End point title | Change from Baseline in HbA1c (5 mg) ^[2] |
|-----------------|---|

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with Baseline + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares).

APD: All randomized participants who received at least one dose of 5 mg tirzepatide, placebo and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 40

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis planned for this outcome.

| End point values | 5 mg Tirzepatide | Placebo | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 118 | | |
| Units: Percentage of HbA1c | | | | |
| least squares mean (standard error) | -2.23 (\pm 0.081) | -0.93 (\pm 0.079) | | |

Statistical analyses

| Statistical analysis title | Hemoglobin A1c (HbA1c) |
|---|----------------------------|
| Comparison groups | 5 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.52 |
| upper limit | -1.07 |

Secondary: Change from Baseline in Body Weight

| | |
|---|-------------------------------------|
| End point title | Change from Baseline in Body Weight |
| End point description: | |
| Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with Baseline + Baseline HbA1c Group (\leq 8.0%, $>$ 8.0%) + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment + Time + Treatment*Time (Type III sum of squares). | |
| APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-------------------------------------|--------------------|--------------------|---------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 115 | 113 | 117 | 118 |
| Units: Kilograms (kg) | | | | |
| least squares mean (standard error) | -6.2 (\pm 0.58) | -8.2 (\pm 0.58) | -10.9 (\pm 0.59) | 1.7 (\pm 0.57) |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Change from Baseline in Body Weight |
| Comparison groups | 5 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.4 |
| upper limit | -6.3 |

| | |
|---|-------------------------------------|
| Statistical analysis title | Change from Baseline in Body Weight |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 231 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.5 |
| upper limit | -8.3 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Change from Baseline in Body Weight |
| Comparison groups | 15 mg Tirzepatide v Placebo |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -12.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.2 |
| upper limit | -11 |

Secondary: Percentage of Participants Achieving an HbA1c Target Value of <7%

| | |
|-----------------|---|
| End point title | Percentage of Participants Achieving an HbA1c Target Value of <7% |
|-----------------|---|

End point description:

Hemoglobin A1c (HbA1c) is the glycosylated fraction of hemoglobin A. HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time.

APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-----------------------------------|---------------------|----------------------|----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 115 | 113 | 117 | 118 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 93.04 | 97.35 | 94.02 | 33.90 |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | HbA1c Target Value of <7% |
| Comparison groups | Placebo v 5 mg Tirzepatide |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 37.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15.23 |
| upper limit | 93.7 |

| | |
|---|-----------------------------|
| Statistical analysis title | HbA1c Target Value of <7% |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 231 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 100.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 30.02 |
| upper limit | 333.62 |

| | |
|---|-----------------------------|
| Statistical analysis title | HbA1c Target Value of <7% |
| Comparison groups | 15 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 43.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.92 |
| upper limit | 110.83 |

Secondary: Change from Baseline in Fasting Serum Glucose

| | |
|-----------------|---|
| End point title | Change from Baseline in Fasting Serum Glucose |
|-----------------|---|

End point description:

Change from Baseline in Fasting Serum Glucose. LS Mean was determined by MMRM model with Baseline + Pooled Country + Baseline Metformin Use (Yes, No) + Baseline HbA1c Group ($\leq 8.0\%$, $>8.0\%$) + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|--|---------------------|----------------------|----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 115 | 116 | 118 | 118 |
| Units: milligram per Deciliter (mg/dL) | | | | |
| least squares mean (standard error) | -61.4 (± 2.55) | -67.9 (± 2.55) | -67.7 (± 2.64) | -38.9 (± 2.49) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from Baseline in Fasting Serum Glucose |
| Comparison groups | 5 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.5 |
| upper limit | -15.4 |

| | |
|---|---|
| Statistical analysis title | Change from Baseline in Fasting Serum Glucose |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36 |
| upper limit | -22 |

| | |
|---|---|
| Statistical analysis title | Change from Baseline in Fasting Serum Glucose |
| Comparison groups | 15 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 236 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -28.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.9 |
| upper limit | -21.6 |

Secondary: Mean Change from Baseline in Daily Average 7-Point Self-Monitored Blood Glucose (SMBG) Values

| | |
|---|---|
| End point title | Mean Change from Baseline in Daily Average 7-Point Self-Monitored Blood Glucose (SMBG) Values |
| End point description: | |
| <p>The self-monitored plasma glucose (SMBG) data were collected at the following 7 time points: Morning Premeal - Fasting, Morning 2-hour Postmeal, Midday Premeal, Midday 2-hour Postmeal, Evening Premeal, Evening 2-hour Postmeal and Bedtime. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with Baseline + Baseline HbA1c Group ($\leq 8.0\%$, $>8.0\%$) + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment (Type III sum of squares).</p> <p>APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 100 | 99 | 94 | 97 |
| Units: mg/dL | | | | |
| least squares mean (standard error) | -67.1 (± 2.05) | -71.7 (± 2.04) | -73.7 (± 2.10) | -39.4 (± 2.07) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved Weight Loss $\geq 5\%$

| | |
|---|--|
| End point title | Percentage of Participants who Achieved Weight Loss $\geq 5\%$ |
| End point description: | |
| Percentage of Participants who Achieved Weight Loss $\geq 5\%$. | |
| APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-----------------------------------|------------------|-------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 115 | 113 | 117 | 118 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 53.91 | 64.60 | 84.62 | 5.93 |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Weight Loss $\geq 5\%$ |
| Comparison groups | 5 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 17.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.55 |
| upper limit | 38.93 |

| | |
|---|-----------------------------|
| Statistical analysis title | Weight Loss $\geq 5\%$ |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 231 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 27.24 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.87 |
| upper limit | 62.55 |

| | |
|---|-----------------------------|
| Statistical analysis title | Weight Loss ≥5% |
| Comparison groups | 15 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 79.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 32.76 |
| upper limit | 193.44 |

Secondary: Percentage Change from Baseline in Daily Mean InsulinGlargine Dose

| | |
|-----------------|--|
| End point title | Percentage Change from Baseline in Daily Mean InsulinGlargine Dose |
|-----------------|--|

End point description:

LS mean was calculated using MMRM model with log (Baseline) + Baseline Metformin Use (Yes, No) + Pooled Country + Baseline HbA1c Group (<= 8.0%, >8.0%) + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 40

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-------------------------------------|---------------------|----------------------|----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 105 | 103 | 96 | 111 |
| Units: International Units (IU) | | | | |
| least squares mean (standard error) | 13.0 (± 7.34) | 8.1 (± 7.03) | -11.4 (± 5.85) | 75.0 (± 11.11) |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Daily Mean InsulinGlargine Dose |
| Comparison groups | 5 mg Tirzepatide v 10 mg Tirzepatide |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Estimate Difference |
| Point estimate | -35.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46 |
| upper limit | -22.8 |

| | |
|---|---------------------------------|
| Statistical analysis title | Daily Mean InsulinGlargine Dose |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Estimate Difference |
| Point estimate | -38.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -48.3 |
| upper limit | -26.1 |

| | |
|---|---------------------------------|
| Statistical analysis title | Daily Mean InsulinGlargine Dose |
| Comparison groups | 15 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Estimate Difference |
| Point estimate | -49.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -57.7 |
| upper limit | -39.4 |

Secondary: Rate of Hypoglycemia with Blood Glucose <54 milligram/deciliter (mg/dL) [<3.0 millimole/liter (mmol/L)] or Severe Hypoglycemia

| | |
|-----------------|---|
| End point title | Rate of Hypoglycemia with Blood Glucose <54 |
|-----------------|---|

End point description:

The hypoglycemia events were defined by participant reported events with blood glucose <54 mg/dL (<3.0 mmol/L) or severe hypoglycemia. Severe hypoglycemia is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. The rate of postbaseline hypoglycemia was estimated by negative binomial model: number of episodes = Pooled Country + Baseline Metformin Use (Yes, No) + Baseline HbA1c Group ($\leq 8.0\%$, $>8.0\%$) + Treatment, with log (exposure in days/365.25) as an offset variable.

APD: All randomly assigned participants who took at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline through Safety Follow-Up (Up to Week 44)

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 116 | 119 | 120 | 120 |
| Units: Episodes/participant/365.25 days | | | | |
| arithmetic mean (standard error) | 0.49 (± 0.141) | 0.66 (± 0.169) | 0.38 (± 0.099) | 0.51 (± 0.149) |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Steady State Area Under the Concentration Time Curve (AUC) of Tirzepatide

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK): Steady State Area Under the Concentration Time Curve (AUC) of Tirzepatide ^[3] |
|-----------------|---|

End point description:

AUC is a combined measure obtained from Week 7, 15, 23 and 39 and a single averaged measure of AUC was reported.

APD: All randomized participants who received at least one dose and had evaluable PK data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 7, 15, 23 and 39 post dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis planned for this outcome.

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | |
|---|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 115 | 116 | 118 | |
| Units: nanogram*hour per milliliter (ng*h/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 79700 (\pm 24.5) | 164000 (\pm 26.7) | 246000 (\pm 26.4) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an HbA1c Target Value of <5.7%

| | |
|-----------------|---|
| End point title | Percentage of Participants Achieving an HbA1c Target Value of <5.7% |
|-----------------|---|

End point description:

Hemoglobin A1c (HbA1c) is the glycosylated fraction of hemoglobin A. HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time.

APD: All randomly assigned participants who took at least 1 dose of study drug and had a baseline and at least 1 post-baseline value, excluding patients discontinuing study drug due to inadvertent enrollment and data after initiating rescue antihyperglycemic medication or prematurely stopping study drug

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 40 | |

| End point values | 5 mg Tirzepatide | 10 mg Tirzepatide | 15 mg Tirzepatide | Placebo |
|-----------------------------------|------------------|-------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 115 | 113 | 117 | 118 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 26.09 | 47.79 | 62.39 | 2.54 |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | HbA1c Target Value of <5.7% |
| Comparison groups | 5 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 12.22 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.93 |
| upper limit | 38 |

| | |
|---|-----------------------------|
| Statistical analysis title | HbA1c Target Value of <5.7% |
| Comparison groups | 10 mg Tirzepatide v Placebo |
| Number of subjects included in analysis | 231 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 32.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.52 |
| upper limit | 99.49 |

| | |
|---|-----------------------------|
| Statistical analysis title | HbA1c Target Value of <5.7% |
| Comparison groups | Placebo v 15 mg Tirzepatide |
| Number of subjects included in analysis | 235 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 56.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.27 |
| upper limit | 173.26 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline, 17 Months

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. Gender specific events only occurring in male or female participants have had the number of participants At Risk adjusted accordingly.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | TZP 5mg |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | TZP 10mg |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | TZP 15mg |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | TZP 5mg | TZP 10mg | TZP 15mg |
|---|-----------------|-------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 116 (7.76%) | 13 / 119 (10.92%) | 9 / 120 (7.50%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| papillary renal cell carcinoma | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 neoplasm | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| transitional cell carcinoma alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| uterine cancer alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed ^[1] | 0 / 55 (0.00%) | 1 / 47 (2.13%) | 0 / 55 (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 | | | |
| aortic stenosis alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peripheral arterial occlusive disease alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| cardiac ablation alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| pancreatic lesion excision alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| asthenia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| impaired healing | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| chronic obstructive pulmonary disease | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 2 / 120 (1.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| respiratory failure | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| sleep apnoea syndrome | | | |
| alternative dictionary used: | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 |
| Psychiatric disorders | | | |
| anxiety | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| hip fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| intestinal anastomosis complication | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| spinal compression fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: | | | |

| | | | | |
|---|-----------------|-----------------|-----------------|--|
| MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 1 / 120 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| angina pectoris | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| atrial fibrillation | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| cardiac failure | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 1 / 119 (0.84%) | 0 / 120 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| coronary artery disease | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 2 / 120 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| myocardial infarction | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| tachycardia | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| hypoglycaemic unconsciousness | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| orthostatic intolerance | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| syncope | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| Ear and labyrinth disorders | | | |
| deafness unilateral | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| abdominal hernia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| faecaloma | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 disorder | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| bladder disorder | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| calculus urinary | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| spinal stenosis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| synovial cyst | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| covid-19 pneumonia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| cellulitis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| coronavirus infection | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 119 (0.00%) | 0 / 120 (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 |
| postoperative wound infection | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 0 / 120 (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 |
| pyelonephritis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 0 / 119 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 119 (0.84%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 120 (8.33%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| papillary renal cell carcinoma | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| renal neoplasm | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| transitional cell carcinoma | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| uterine cancer | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed ^[1] | 0 / 54 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| aortic stenosis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| peripheral arterial occlusive disease | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| cardiac ablation | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| pancreatic lesion excision | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| impaired healing | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| chronic obstructive pulmonary disease | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| respiratory failure | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| sleep apnoea syndrome | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| anxiety | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| hip fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| intestinal anastomosis complication | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| spinal compression fracture | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 23.1 | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| angina pectoris | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| atrial fibrillation | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| cardiac failure | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| coronary artery disease | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| myocardial infarction | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| tachycardia | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|--|-----------------|--|--|
| Nervous system disorders | | | |
| hypoglycaemic unconsciousness | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| orthostatic intolerance | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| syncope | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| deafness unilateral | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| abdominal hernia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| faecaloma | | | |

| | | | |
|--|-----------------|--|--|
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| pancreatic disorder | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| bladder disorder | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| calculus urinary | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| spinal stenosis | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| synovial cyst | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| covid-19 pneumonia | | | |

| | | | | |
|--|-----------------|--|--|--|
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| cellulitis | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| coronavirus infection | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| gastroenteritis | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| postoperative wound infection | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| pyelonephritis | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| urinary tract infection | | | | |
| alternative dictionary used: MedDRA 23.1 | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

| Non-serious adverse events | TZP 5mg | TZP 10mg | TZP 15mg |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 116 (44.83%) | 60 / 119 (50.42%) | 67 / 120 (55.83%) |
| Investigations | | | |
| lipase increased | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 4 / 116 (3.45%) | 2 / 119 (1.68%) | 10 / 120 (8.33%) |
| occurrences (all) | 4 | 2 | 12 |
| Vascular disorders | | | |
| hypertension | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 3 / 119 (2.52%) | 1 / 120 (0.83%) |
| occurrences (all) | 3 | 3 | 1 |
| Gastrointestinal disorders | | | |
| constipation | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | 8 / 119 (6.72%) | 8 / 120 (6.67%) |
| occurrences (all) | 7 | 8 | 9 |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 14 / 116 (12.07%) | 15 / 119 (12.61%) | 25 / 120 (20.83%) |
| occurrences (all) | 22 | 46 | 44 |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| dyspepsia alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 8 / 116 (6.90%) 9 | 10 / 119 (8.40%) 12 | 6 / 120 (5.00%) 6 |
| eructation alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 6 / 116 (5.17%) 11 | 4 / 119 (3.36%) 16 | 7 / 120 (5.83%) 11 |
| flatulence alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 3 / 116 (2.59%) 3 | 6 / 119 (5.04%) 21 | 7 / 120 (5.83%) 12 |
| nausea alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 15 / 116 (12.93%) 26 | 21 / 119 (17.65%) 43 | 22 / 120 (18.33%) 44 |
| vomiting alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 8 / 116 (6.90%) 12 | 9 / 119 (7.56%) 18 | 15 / 120 (12.50%) 26 |
| Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 6 / 116 (5.17%) 7 | 4 / 119 (3.36%) 4 | 3 / 120 (2.50%) 3 |
| back pain alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 6 / 116 (5.17%) 8 | 6 / 119 (5.04%) 7 | 4 / 120 (3.33%) 6 |
| Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 18 / 116 (15.52%) 23 | 8 / 119 (6.72%) 11 | 15 / 120 (12.50%) 19 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------------|-------------------------|-------------------------|
| decreased appetite alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 8 / 116 (6.90%) 8 | 15 / 119 (12.61%) 17 | 17 / 120 (14.17%) 21 |
| hyperglycaemia alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 2 / 116 (1.72%) 2 | 0 / 119 (0.00%) 0 | 1 / 120 (0.83%) 1 |

| | | | |
|---|---|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 58 / 120 (48.33%) | | |
| Investigations lipase increased alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 2 / 120 (1.67%) 2 | | |
| Vascular disorders hypertension alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) | 7 / 120 (5.83%) 7 | | |
| Gastrointestinal disorders constipation alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) diarrhoea alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) dyspepsia alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all) eructation | 2 / 120 (1.67%) 2 12 / 120 (10.00%) 12 2 / 120 (1.67%) 2 | | |

| | | | |
|--|------------------------------------|--|--|
| <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 120 (0.83%)</p> <p>1</p> | | |
| <p>flatulence</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 120 (0.00%)</p> <p>0</p> | | |
| <p>nausea</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 120 (2.50%)</p> <p>3</p> | | |
| <p>vomiting</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 120 (2.50%)</p> <p>3</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 120 (1.67%)</p> <p>2</p> | | |
| <p>back pain</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>7 / 120 (5.83%)</p> <p>7</p> | | |
| <p>Infections and infestations</p> <p>nasopharyngitis</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>23 / 120 (19.17%)</p> <p>27</p> | | |
| <p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used: MedDRA 23.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 120 (1.67%)</p> <p>2</p> | | |
| <p>hyperglycaemia</p> | | | |

| | | | |
|---|-------------------|--|--|
| alternative dictionary used: MedDRA 23.1 | | | |
| subjects affected / exposed | 16 / 120 (13.33%) | | |
| occurrences (all) | 18 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 26 June 2020 | Protocol (b): Added language about the mobile (inhome) healthcare visits. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported