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 (± 0.081)	-0.93 (± 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 (<= 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 (± 0.58)	-8.2 (± 0.58)	-10.9 (± 0.59)	1.7 (± 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 (<= 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:

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 (<= 8.0%, >8.0%) + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment (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	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 ≥5%

End point title	Percentage of Participants who Achieved Weight Loss ≥5%

End point description:

Percentage of Participants who Achieved Weight Loss ≥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 ≥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 ≥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

	milligram/deciliter (mg/dL) [<3.0 millimole/liter (mmol/L)] or Severe Hypoglycemia

End point description:

The hypoglycemia events were defined by participant reported events with blood glucose <54mg/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 (<= 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 (± 24.5)	164000 (± 26.7)	246000 (± 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	8 / 116 (6.90%)	10 / 119 (8.40%)	6 / 120 (5.00%)
occurrences (all)	9	12	6
eructation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 116 (5.17%)	4 / 119 (3.36%)	7 / 120 (5.83%)
occurrences (all)	11	16	11
flatulence			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 116 (2.59%)	6 / 119 (5.04%)	7 / 120 (5.83%)
occurrences (all)	3	21	12
nausea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	15 / 116 (12.93%)	21 / 119 (17.65%)	22 / 120 (18.33%)
occurrences (all)	26	43	44
vomiting			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 116 (6.90%)	9 / 119 (7.56%)	15 / 120 (12.50%)
occurrences (all)	12	18	26
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 116 (5.17%)	4 / 119 (3.36%)	3 / 120 (2.50%)
occurrences (all)	7	4	3
back pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 116 (5.17%)	6 / 119 (5.04%)	4 / 120 (3.33%)
occurrences (all)	8	7	6
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	18 / 116 (15.52%)	8 / 119 (6.72%)	15 / 120 (12.50%)
occurrences (all)	23	11	19
Metabolism and nutrition disorders			

decreased appetite			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 116 (6.90%)	15 / 119 (12.61%)	17 / 120 (14.17%)
occurrences (all)	8	17	21
hyperglycaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 116 (1.72%)	0 / 119 (0.00%)	1 / 120 (0.83%)
occurrences (all)	2	0	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	2 / 120 (1.67%)		
occurrences (all)	2		
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	7		
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	12		
dyspepsia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
eructation			

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

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