



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared With Placebo in Pediatric Subjects With Type 2 Diabetes Mellitus

Summary

EudraCT number	2015-000208-25
Trial protocol	IT PL Outside EU/EEA
Global end of trial date	13 February 2022

Results information

Result version number	v1
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	SYR-322_309
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02856113
WHO universal trial number (UTN)	U1111-1174-1923

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000496-PIP01-08
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	Interim
Date of interim/final analysis	06 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2021
Global end of trial reached?	Yes
Global end of trial date	13 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of alogliptin 25 mg once daily compared to placebo when administered as monotherapy, or when added onto a background of metformin alone, insulin alone, or a combination of metformin and insulin, as measured by the glycosylated hemoglobin (HbA1c) change from Baseline at Week 26 in pediatric participants with type 2 diabetes mellitus (T2DM).

Protection of trial subjects:

Study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Mexico: 73
Country: Number of subjects enrolled	United States: 72
Worldwide total number of subjects	151
EEA total number of subjects	1

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)	18
Adolescents (12-17 years)	133

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 152 participants took part in the study at 67 investigative sites in Mexico, United States, Brazil, Israel, Italy and Russia from 14 October 2016 to 14 February 2022.

Pre-assignment

Screening details:

Participants with type 2 diabetes mellitus were enrolled to receive placebo or alogliptin 25 mg in a 1:1 ratio in this study.

Pre-assignment period milestones

Number of subjects started	77 ^[1]
Number of subjects completed	76

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not Treated: 1
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There was 1 participant who was randomized but not treated.

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Alogliptin matching-placebo tablets, orally, once daily (QD) for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.

Arm type	Placebo
Investigational medicinal product name	Alogliptin matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alogliptin matching placebo tablets

Arm title	Alogliptin 25 mg
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Arm description:

Alogliptin 25 mg tablets, orally, QD for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.

Arm type	Experimental
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Investigational medicinal product name	Alogliptin 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alogliptin matching placebo tablets

Number of subjects in period 1	Placebo	Alogliptin 25 mg
Started	76	75
Safety Population	76	75
Completed	66	60
Not completed	10	15
Pretreatment Event/Adverse Event	1	-
Voluntary Withdrawal	3	5
Significant Protocol Deviation	1	-
Pregnancy	-	1
Principal Investigator Discretion	2	1
Did not Complete Study but Contacted at Week 52	-	3
Lost to follow-up	3	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Alogliptin matching-placebo tablets, orally, once daily (QD) for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.	
Reporting group title	Alogliptin 25 mg
Reporting group description: Alogliptin 25 mg tablets, orally, QD for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.	

Reporting group values	Placebo	Alogliptin 25 mg	Total
Number of subjects	76	75	151
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	14.3 ± 2.21	14.2 ± 1.92	-
Gender categorical Units: Subjects			
Female	51	53	104
Male	25	22	47
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	9	15
Not Hispanic or Latino	31	26	57
Unknown or Not Reported	39	40	79
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	14	11	25
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	16	16	32
White	44	44	88
More than one race	1	4	5
Unknown or Not Reported	0	0	0
Height Units: centimetres (cm) arithmetic mean standard deviation	164.7 ± 9.54	163.1 ± 8.79	-
Weight Units: kilograms (kg) arithmetic mean standard deviation	92.23 ± 26.826	90.72 ± 28.815	-

Body Mass Index (BMI)			
BMI was calculated as weight (kg) divided by square of height (m ²).			
Units: kg/m ²			
arithmetic mean	33.632	33.669	
standard deviation	± 7.8581	± 8.6592	-
Baseline of Glycosylated Hemoglobin (HbA1c)			
HbA1c is defined as the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound.			
Units: percentage of HbA1c			
arithmetic mean	8.11	8.16	
full range (min-max)	5.7 to 11.3	6.3 to 11.5	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Alogliptin matching-placebo tablets, orally, once daily (QD) for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.	
Reporting group title	Alogliptin 25 mg
Reporting group description: Alogliptin 25 mg tablets, orally, QD for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.	

Primary: Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Week 26

End point title	Change From Baseline in Glycosylated Hemoglobin (HbA1c) at Week 26
End point description: Change in the value of HbA1c (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) was collected at Week 26 relative to Baseline. Mixed model for repeated measures (MMRM) was used for the analysis.	
End point type	Primary
End point timeframe: Baseline and Week 26	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	54		
Units: percentage of HbA1c				
least squares mean (standard deviation)	-0.011 (\pm 0.2809)	0.091 (\pm 0.2879)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Alogliptin 25 mg
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.782 ^[1]
Method	MMRM
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.102

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.627
upper limit	0.831
Variability estimate	Standard error of the mean
Dispersion value	0.3677

Notes:

[1] - P-values was assessed at 0.05 significance level using MMRM.

Secondary: Change From Baseline in HbA1c at Weeks 12, 18, 39 and 52

End point title	Change From Baseline in HbA1c at Weeks 12, 18, 39 and 52
End point description:	
Change in the value of HbA1c (the concentration of glucose bound to hemoglobin as a percent of the absolute maximum that can be bound) was collected at Weeks 12, 18, 39 and 52 relative to Baseline. MMRM was used for the analysis.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 12, 18, 39 and 52	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: percentage of HbA1c				
least squares mean (standard deviation)				
Change From Baseline to Week 12	-0.319 (± 0.2173)	-0.365 (± 0.2223)		
Change From Baseline to Week 18	-0.206 (± 0.2458)	-0.202 (± 0.2529)		
Change From Baseline to Week 39	0.502 (± 0.2802)	0.091 (± 0.2866)		
Change From Baseline to Week 52	0.764 (± 0.3118)	0.281 (± 0.3199)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change From Baseline at Week 12	
Comparison groups	Placebo v Alogliptin 25 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.863 ^[2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.046

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.567
upper limit	0.476
Variability estimate	Standard error of the mean
Dispersion value	0.2635

Notes:

[2] - P-values was assessed at 0.05 significance level using MMRM.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change From Baseline at Week 18	
Comparison groups	Placebo v Alogliptin 25 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 ^[3]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.614
upper limit	0.622
Variability estimate	Standard error of the mean
Dispersion value	0.3123

Notes:

[3] - P-values was assessed at 0.05 significance level using MMRM.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change From Baseline at Week 39	
Comparison groups	Placebo v Alogliptin 25 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264 ^[4]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.139
upper limit	0.316
Variability estimate	Standard error of the mean
Dispersion value	0.3664

Notes:

[4] - P-values was assessed at 0.05 significance level using MMRM.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Change From Baseline at Week 52	
Comparison groups	Placebo v Alogliptin 25 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 ^[5]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.483
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.314
upper limit	0.348
Variability estimate	Standard error of the mean
Dispersion value	0.4165

Notes:

[5] - P-values was assessed at 0.05 significance level using MMRM.

Secondary: Percentage of Participants with Clinically Significant Physical Examination Findings

End point title	Percentage of Participants with Clinically Significant Physical Examination Findings
End point description:	
Physical examination included examination of the following body systems: (1) respiratory system; (2) cardiovascular system; (3) nervous system (4) dermatologic system; and (5) gastrointestinal system. A summarized data for the above body systems was reported for participants with clinically significant findings.	
End point type	Secondary
End point timeframe:	
From Day 1 to end of treatment period (up to 52 weeks)	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: percentage of participants				
number (not applicable)				
Week 4(n=1,0)	0	0		
Week 12(n=71,71)	0	0		
Week 18(n=2,1)	0	0		
Week 26(n=69,68)	0	0		
Week 32(n=3,0)	0	0		
Week 39(n=66,67)	0	0		

Week 45(n=2,0)	0	0		
Week 52(n=57,50)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Abnormal Vital Signs Values

End point title	Percentage of Participants With Abnormal Vital Signs Values
End point description: Vital signs included body temperature (oral or tympanic measurement), respiratory rate, blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] resting more than 5 minutes, and pulse (beats per minute). Data for participants with abnormal vital signs was reported.	
End point type	Secondary
End point timeframe: From Day 1 to end of treatment period (up to 52 weeks)	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (not applicable)				
SBP (millimeters of mercury [mmHg]): >150	1.3	2.8		
DBP (mmHg): >95	4.0	4.2		
Pulse Rate (beats per minute [bpm]): <50	0	1.4		
Pulse Rate (bpm): >120	0	1.4		
Temperature (Celsius [C]): <35.6	0	3.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Abnormal 12-lead Electrocardiogram (ECG) Findings

End point title	Percentage of Participants with Abnormal 12-lead Electrocardiogram (ECG) Findings
End point description:	
End point type	Secondary
End point timeframe: Week 26 and 52	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: participants				
number (not applicable)				
Week 26: Abnormal, Not Clinically Significant	7	6		
Week 26: Abnormal, Clinically Significant	2	0		
Week 52: Abnormal, Not Clinically Significant	7	6		
Week 52: Abnormal, Clinically Significant	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment-emergent Adverse Events (TEAE)

End point title	Percentage of Participants with Treatment-emergent Adverse Events (TEAE)
End point description: An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment.	
End point type	Secondary
End point timeframe: From the study start up to end of the study (up to 54 weeks)	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (not applicable)	76.3	80.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Total, Urinary and Respiratory Tract Infections and Hypersensitivity Reactions

End point title	Percentage of Participants with Total, Urinary and Respiratory Tract Infections and Hypersensitivity Reactions
End point description:	
End point type	Secondary
End point timeframe:	
From Day 1 to end of treatment period (up to 52 weeks)	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (not applicable)				
Bladder Infection	0.0	11.1		
COVID-19 Infection	9.1	0.0		
Low Urinary Tract Infection	0.0	11.1		
Respiratory Tract Infection	9.1	11.1		
Sinus Infection	9.1	11.1		
Upper Respiratory Infection	18.2	44.4		
Upper Respiratory Tract Infection	9.1	0.0		
Urinary Tract Infection	9.1	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hypoglycemia

End point title	Percentage of Participants with Hypoglycemia
End point description:	
Mild to moderate hypoglycemia (abnormal low blood sugar) was defined as blood glucose less than (<) 60 milligram per deciliter (mg/dL) (3.33 millimole per liter [mmol/L]) in the presence of symptoms, or blood glucose <50 mg/dL (2.78 mmol/L) with or without symptoms. Severe hypoglycemia was defined as any episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, associated with a documented blood glucose <60 mg/dL (3.33 mmol/L) (unless the clinical situation makes obtaining a blood glucose difficult [example, it involves coma or seizure]).	
End point type	Secondary
End point timeframe:	
From Day 1 to end of treatment period (up to 52 weeks)	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (not applicable)	7.9	5.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Abnormal Safety Laboratory Findings

End point title	Percentage of Participants with Abnormal Safety Laboratory Findings
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End point description:

The percentage of participants with any abnormal standard safety laboratory values (hematology, serum chemistry, and urinalysis) were collected throughout study. Abnormal values for hematology included hematocrit (percentage of hematocrit [%]), hemoglobin (grams per liter [g/L]), erythrocyte mean corpuscular volume (MCV)(femtoliter [fL]), erythrocytes ($10^{12}/L$), and leukocytes ($10^9/L$). Abnormal values for serum chemistry included for alanine aminotransferase (units per liter [U/L]), aspartate aminotransferase (U/L), cholesterol (millimoles per liter [mmol/L]), gamma glutamyl transferase (U/L), glucose (mmol/L): < 2.8 mmol/L, potassium (mmol/L), sodium (mmol/L), and triglycerides (mmol/L). ULN is upper limit of normal and LLN is lower limit of normal.

End point type	Secondary
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End point timeframe:

From Day 1 to end of treatment period (up to 52 weeks)

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	73		
Units: percentage of participants				
number (not applicable)				
Alanine Aminotransferase (U/L): $\geq 3 \times \text{ULN}$ (n=75,72)	10.7	5.6		
Aspartate Aminotransferase (U/L): $\geq 3 \times \text{ULN}$ (n=75,0)	2.7	999		
Cholesterol (mmol/L): >7.72 mmol/L (n=75,72)	1.3	1.4		
Gamma Glutamyl Transferase (U/L): $\geq 3 \times \text{ULN}$ (n=75,72)	2.7	6.9		
Glucose (mmol/L): <2.8 mmol/L (n=75,73)	13.3	20.5		
Glucose (mmol/L): >19.4 mmol/L (n=75,73)	10.7	13.7		
Potassium (mmol/L): <3.0 mmol/L (n=0,72)	999	1.4		
Phosphate (mmol/L): >2.00 mmol/L (n=0,72)	999	1.4		
Sodium (mmol/L): <130 mmol/L (n=75,0)	1.3	999		

Triglycerides (mmol/L): >2.5xULN(n=75,72)	6.7	1.4		
Hematocrit (%): >1.2 x ULN(n=74,72)	9.5	8.3		
Hemoglobin (g/L): < 0.8 x LLN(n=0,72)	999	1.4		
Hemoglobin (g/L): >1.2 x ULN(n=74,72)	4.1	2.8		
Erythrocyte MCV (fL): <70 fL(n=74,72)	2.7	2.8		
Erythrocyte MCV(fL): >100 fL(n=0,72)	999	2.8		
Erythrocytes (10 ¹² /L): >1.2 x ULN(n=74,72)	1.4	1.4		
Leukocytes (10 ⁹ /L): >1.5 x ULN(n=74,72)	2.7	2.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Biomarkers of Bone Turnover at Weeks 26 and 52

End point title	Change from Baseline in Biomarkers of Bone Turnover at Weeks 26 and 52
End point description:	Biomarkers of bone turnover are bone-specific alkaline phosphatase to assess changes in bone formation and C-terminal telopeptide (CTX) to assess changes in bone resorption.
End point type	Secondary
End point timeframe:	Baseline, Weeks 26 and 52

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	68		
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
Baseline(n=76,75)	62.09 (± 37.084)	62.62 (± 43.180)		
Change From Baseline at Week 26(n=60,59)	-6.20 (± 18.021)	-7.47 (± 20.139)		
Change From Baseline at Week 52(n=49,44)	-14.36 (± 18.000)	-15.43 (± 22.497)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CD26 (CD4+T cells) Surface Antigen Levels at Weeks 26 and 52

End point title	Change from Baseline in CD26 (CD4+T cells) Surface Antigen Levels at Weeks 26 and 52
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 26 and 52	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: percentage of CD4+ T cells				
arithmetic mean (standard deviation)				
Baseline(n=57,58)	78.2 (± 8.60)	77.7 (± 7.23)		
Change From Baseline at Week 26(n=45,42)	1.2 (± 6.00)	1.6 (± 7.20)		
Change From Baseline at Week 52(n=35,32)	1.0 (± 5.39)	0.8 (± 4.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD26 (CD8+T cells) Surface Antigen Levels at Weeks 26 and 52

End point title	Change From Baseline in CD26 (CD8+T cells) Surface Antigen Levels at Weeks 26 and 52
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 26 and 52	

End point values	Placebo	Alogliptin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: percentage of CD8+ T cells				
arithmetic mean (standard deviation)				
Baseline	59.7 (± 13.51)	59.6 (± 15.30)		
Change From Baseline at Week 26(n=46,41)	-0.2 (± 9.15)	1.7 (± 8.76)		
Change From Baseline at Week 52(n=37,32)	1.0 (± 7.63)	-0.3 (± 10.51)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the study start up to end of the study (up to 54 weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment. Safety Set included all participants who took at least 1 dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Alogliptin 25 mg
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Reporting group description:

Alogliptin 25 mg tablets, orally, QD for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.

Reporting group title	Placebo
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Reporting group description:

Alogliptin matching-placebo tablets, orally, QD for 52 weeks and background antidiabetic therapy (metformin and/or insulin), if applicable, maintained at the same dose throughout the first 26 weeks of the treatment period.

Serious adverse events	Alogliptin 25 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 75 (2.67%)	3 / 76 (3.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip injury			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alogliptin 25 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 75 (41.33%)	39 / 76 (51.32%)	
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 75 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 75 (18.67%)	8 / 76 (10.53%)	
occurrences (all)	19	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 75 (9.33%)	7 / 76 (9.21%)	
occurrences (all)	8	11	
Nausea			
subjects affected / exposed	0 / 75 (0.00%)	5 / 76 (6.58%)	
occurrences (all)	0	6	
Vomiting			
subjects affected / exposed	4 / 75 (5.33%)	6 / 76 (7.89%)	
occurrences (all)	5	9	

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	5 / 75 (6.67%)	0 / 76 (0.00%)	
occurrences (all)	9	0	
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 75 (9.33%)	0 / 76 (0.00%)	
occurrences (all)	10	0	
Sinusitis			
subjects affected / exposed	0 / 75 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	4	
Upper respiratory tract infection			
subjects affected / exposed	4 / 75 (5.33%)	0 / 76 (0.00%)	
occurrences (all)	5	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	9 / 75 (12.00%)	9 / 76 (11.84%)	
occurrences (all)	12	10	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 75 (0.00%)	5 / 76 (6.58%)	
occurrences (all)	0	5	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 75 (0.00%)	5 / 76 (6.58%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2016	<p>-Study entry criteria were modified, including broadening HbA1c criteria and hepatic enzyme criteria, in order to better reflect the study population and allow participants with non-alcoholic fatty liver disease (NAFLD) into the study. -The number of schedules was reduced in order to simplify the study design. -A Pre-Randomization Stabilization Period was added for those participants who were not yet stabilized on their current antidiabetic therapy or who have not yet met certain entry criteria. -The guidance for hepatic safety monitoring and withdrawal criteria was revised to reflect the potential inclusion of participants with NAFLD. -The assessment of retinopathy by fundus photography was removed as this microvascular complication is very unlikely to have manifested at this early stage in the natural history of T2DM in this population to warrant evaluation. -Home glucose management and hyperglycemic rescue language were clarified to allow investigators to individualize glucose management based on the needs of the participants and according to local guidance. -The schedule of assessments was adjusted to decrease the number of clinic visits, allow for telephone visits, and minimize fasting requirements in order to reduce the burden on participants.</p>
08 November 2016	<p>-Added respiratory tract infections and hypersensitivity reactions to the "incidence of infections" in the safety endpoints. -Removed dual-energy x-ray absorptiometry scans. -Added changes from Baseline in microalbuminuria, insulin like growth factor (IGF)-1, and IGF-BP3 as exploratory endpoints. -Modified the length of time for the maintenance of stable anti-hyperglycemic therapy from 1 month to 2 months. -Added recommendations regarding managing insulin therapy. -Clarified that inclusion criteria regarding C-peptide, autoantibodies, age, and BMI apply at randomization and C-peptide, autoantibodies, and BMI criteria apply to participants who have had the diagnosis of T2DM for <1 year and/or who were taking insulin. -Changed eGFR calculations to be based on the Schwartz formula rather than Cockcroft-Gault. -Modified wording of exclusion criteria regarding sexual activity. -Added a randomization criterion for participants on insulin to require and HbA1c level of $\geq 7.0\%$. -Updated laboratory testing terminology from islet cell antigen (ICA) 512 antibody to Islet Antigen (IA)-2 antibody. -Added clarification regarding the use of oral or parenteral steroids, wording of the renal safety withdrawal criteria, details regarding assessment of pubertal development, clarification regarding BMI measurements and recommendation for annual ophthalmologic examinations. -Adjusted the volume of blood collected for clinical laboratory samples. -Removed insulin and proinsulin measurements and clarified that C-peptide will only be measured once prior to randomization. -Clarified that glutamic acid decarboxylase (GAD) and IA-2 antibody testing may be performed by the central laboratory. -Added clarification regarding postprandial glucose testing, hematology and serum chemistry testing at the Week -1 Visit. -Clarified that fasting plasma glucose (FPG) testing can be done at the Screening and Week -1 Visits. -Added eGFR measurements at Baseline and at Weeks 26 and 52.</p>
11 August 2020	<p>-Reduced the sample size from 100 participants per arm to 75 participants per arm. -Removed the specific dropout/hyperglycemic rescue rate of 30%. -Updated text to reflect availability of liraglutide for children and adolescents aged 10 to 17 years. -Added instructions for managing study procedures, data collection, and investigational product during unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster). -Discontinued collection of pharmacogenomic sample. -Added sensitivity analysis for the primary endpoint only that excludes participants affected by COVID-19.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported