



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 | v2 (current) |
| This version publication date | 01 September 2022 |
| First version publication date | 14 August 2022 |
| Version creation reason | <ul style="list-style-type: none">Correction of full data set Update to question "Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?", it should be Yes. |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | SYR-322_309 |
|-----------------------|-------------|

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? | Yes |

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 | Israel: 1 |
| Country: Number of subjects enrolled | Mexico: 73 |
| Country: Number of subjects enrolled | United States: 72 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Russian Federation: 3 |
| 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 |
|----------------------------|-------------------------------|

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 |
|------------------|------------------|

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 |
|----------|--------------|

| | |
|--|------------------|
| 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 | Alogliptin 25 mg v Placebo |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

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

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.

| | |
|-----------------------|------------------|
| 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.

| Serious adverse events | Placebo | Alogliptin 25 mg | |
|---|----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 2 / 75 (2.67%) | |
| 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 | 1 / 76 (1.32%) | 0 / 75 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip injury | | | |

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 75 (1.33%) | |
| 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 | 1 / 76 (1.32%) | 0 / 75 (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 | 0 / 76 (0.00%) | 1 / 75 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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