



Clinical trial results:

A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control

Summary

| | |
|--------------------------|--|
| EudraCT number | 2011-002528-42 |
| Trial protocol | LV LT DE ES IT BG AT DK SE HU PL SK Outside EU/EEA GR FR |
| Global end of trial date | 09 October 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 24 April 2020 |
| First version publication date | 24 April 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 0431-083 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01485614 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck Protocol Number: MK-0431-083 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000470-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 | Final |
| Date of interim/final analysis | 09 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 October 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to assess the effect of treatment with sitagliptin compared with placebo on glycated hemoglobin (A1C), and the safety and tolerability of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control. The primary hypothesis for this study was that sitagliptin reduces A1C more than placebo after 20 weeks of treatment. Amendment 5 of the protocol removed 2 arms from the study (Metformin arm and the Placebo followed by Sitagliptin arm). Participants already in these 2 arms continued in the study. EUPASS4468 is a follow-up, observational assessment of safety of participants who participated in the MK-0431-083 study for up to 5 years.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure defined for this study was in place for the protection of trial participants: glycemic rescue therapy, as appropriate, and as per the study glycemic rescue criteria, consisted of sitagliptin or metformin as an initial glycemic rescue (glycemic Rescue Step 1) and insulin as an additional glycemic rescue (glycemic Rescue Step 2), if needed.

Background therapy:

Participants who were on insulin at screening continued receiving insulin during the study.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 10 February 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Brazil: 1 |
| Country: Number of subjects enrolled | Bulgaria: 6 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Colombia: 3 |
| Country: Number of subjects enrolled | Costa Rica: 1 |
| Country: Number of subjects enrolled | Dominican Republic: 12 |
| Country: Number of subjects enrolled | Guatemala: 14 |
| Country: Number of subjects enrolled | Honduras: 3 |
| Country: Number of subjects enrolled | Hungary: 6 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Israel: 19 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Latvia: 1 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Malaysia: 13 |
| Country: Number of subjects enrolled | Mauritius: 8 |
| Country: Number of subjects enrolled | Mexico: 23 |
| Country: Number of subjects enrolled | Philippines: 8 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Romania: 2 |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Saudi Arabia: 7 |
| Country: Number of subjects enrolled | Serbia: 2 |
| Country: Number of subjects enrolled | Thailand: 3 |
| Country: Number of subjects enrolled | United Arab Emirates: 2 |
| Country: Number of subjects enrolled | United States: 28 |
| Worldwide total number of subjects | 200 |
| EEA total number of subjects | 21 |

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) | 25 |
| Adolescents (12-17 years) | 175 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study recruited participants in clinics/clinical offices in 26 countries.

Pre-assignment

Screening details:

The Pre-Assignment Period included a one-week single-blind placebo run-in prior to randomization during which participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Randomization |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sitagliptin |

Arm description:

In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received one tablet of sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|------------------|-------------------|
| Arm title | Placebo/Metformin |
|------------------|-------------------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|------------------|-----------|
| Arm title | Metformin |
|------------------|-----------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, but ongoing participants in this arm continued in the same arm.

| | |
|--|------------------|
| Arm type | Internal control |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm received two tablets of metformin prior to both the morning and evening meals (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------------------|
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|------------------|---------------------|
| Arm title | Placebo/Sitagliptin |
|------------------|---------------------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, but ongoing participants in this arm continued in the same arm.

| | |
|--|----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|------------------------------|
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| Number of subjects in period 1 | Sitagliptin | Placebo/Metformin | Metformin |
|---------------------------------------|-------------|-------------------|-----------|
| Started | 96 | 90 | 9 |
| Completed | 95 | 90 | 9 |
| Not completed | 1 | 0 | 0 |
| Randomized but not treated | 1 | - | - |

| Number of subjects in period 1 | Placebo/Sitagliptin |
|---------------------------------------|---------------------|
| Started | 5 |
| Completed | 5 |
| Not completed | 0 |
| Randomized but not treated | - |

Period 2

| | |
|------------------------------|---------------------------------------|
| Period 2 title | Weeks 0-20 |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sitagliptin |

Arm description:

In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received one tablet of sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria received metformin as glycemic Rescue Step 1 (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| | |
|------------------|-------------------|
| Arm title | Placebo/Metformin |
|------------------|-------------------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20.

| | |
|--|------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm meeting protocol-specific glycemic rescue criteria received metformin as glycemic Rescue Step 1 (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| | |
|------------------|-----------|
| Arm title | Metformin |
|------------------|-----------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20.

| | |
|--|------------------|
| Arm type | Internal control |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm received two tablets of metformin prior to both the morning and evening meals (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------------------|
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|--|-------------|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm meeting protocol-specific glycemic rescue criteria received one tablet of sitagliptin 100 mg as glycemic Rescue Step 1.

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Metformin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| | |
|------------------|---------------------|
| Arm title | Placebo/Sitagliptin |
|------------------|---------------------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20.

| | |
|--|------------------------------|
| Arm type | Internal control |
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|-------------|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria received one tablet of sitagliptin 100 mg as glycemic Rescue Step 1.

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Subjects reported in the baseline period (Weeks 0-20, Period 2) were in the all-subjects-as-treated population. The worldwide number of subjects enrolled in the trial was the same as the all-subjects-as-randomized population (Randomization, Period 1). Baseline characteristics were available for the all-subjects-as-treated population (Weeks 0-20, Period 2).

| Number of subjects in period 2^[2] | Sitagliptin | Placebo/Metformin | Metformin |
|---|-------------|-------------------|-----------|
| Started | 95 | 90 | 9 |
| Completed | 85 | 86 | 8 |
| Not completed | 10 | 4 | 1 |
| Consent withdrawn by subject | 3 | 2 | 1 |

| | | | |
|-------------------------------|---|---|---|
| Withdrawal by Parent/Guardian | 5 | 2 | - |
| Lost to follow-up | 2 | - | - |

| Number of subjects in period 2 ^[2] | Placebo/Sitagliptin |
|---|---------------------|
| Started | 5 |
| Completed | 5 |
| Not completed | 0 |
| Consent withdrawn by subject | - |
| Withdrawal by Parent/Guardian | - |
| Lost to follow-up | - |

Notes:

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

Justification: Subjects reported in the baseline period (Weeks 0-20, Period 2) were in the all-subjects-as-treated population. The worldwide number of subjects enrolled in the trial was the same as the all-subjects-as-randomized population (Randomization, Period 1).

Period 3

| | |
|------------------------------|---------------------------------------|
| Period 3 title | Weeks 20-54 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sitagliptin |

Arm description:

In this period, participants continued to receive 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received one tablet of sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|----------|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria received metformin as glycemic Rescue Step 1 (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|-----------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| | |
|------------------|-------------------|
| Arm title | Placebo/Metformin |
|------------------|-------------------|

Arm description:

In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54.

| | |
|--|------------|
| Arm type | Comparator |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received two tablets of metformin prior to both the morning and evening meals (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------------------|
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal.

| | |
|--|-------------|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm meeting protocol-specific glycemic rescue criteria received one tablet of sitagliptin 100 mg as glycemic Rescue Step 1.

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Placebo/Metformin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic

Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| | |
|---|------------------------------|
| Arm title | Metformin |
| Arm description: In this period, participants continued to receive 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, but ongoing participants in this arm continued in the same arm during Weeks 20-54. | |
| Arm type | Internal control |
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: In this period, participants in the Metformin treatment arm received two tablets of metformin prior to both the morning and evening meals. | |
| Investigational medicinal product name | Placebo matching Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: In this period, participants in the Metformin treatment arm received one tablet of placebo matching sitagliptin 100 mg prior to the morning meal. | |
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: In this period, participants in the Metformin treatment arm meeting protocol-specific glycemic rescue criteria received one tablet of sitagliptin 100 mg as glycemic Rescue Step 1. | |
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: In this period, participants in the Metformin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2. | |
| Arm title | Placebo/Sitagliptin |
| Arm description: In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, but ongoing participants in this arm continued in the same arm during Weeks 20-54. | |
| Arm type | Comparator |

| | |
|--|-------------|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | MK-0431 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received one tablet of sitagliptin 100 mg prior to the morning meal.

| | |
|--|----------------------------|
| Investigational medicinal product name | Placebo matching Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm received two tablets of placebo matching metformin 500 mg prior to both the morning and evening meals.

| | |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria received metformin as glycemic Rescue Step 1 (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg twice daily).

| | |
|--|------------------|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

In this period, participants in the Placebo/Sitagliptin treatment arm meeting protocol-specific glycemic rescue criteria after initiating glycemic Rescue Step 1 continued taking the medication from glycemic Rescue Step 1 and initiated insulin (glycemic Rescue Step 2). Participants on background insulin had their insulin dose increased for glycemic Rescue Step 2.

| Number of subjects in period 3 | Sitagliptin | Placebo/Metformin | Metformin |
|--------------------------------|-------------|-------------------|-----------|
| Started | 85 | 86 | 8 |
| Completed | 74 | 78 | 6 |
| Not completed | 11 | 8 | 2 |
| Consent withdrawn by subject | 5 | 3 | - |
| Withdrawal by Parent/Guardian | 2 | 2 | 1 |
| Lost to follow-up | 4 | 3 | 1 |

| Number of subjects in period 3 | Placebo/Sitagliptin |
|--------------------------------|---------------------|
| Started | 5 |
| Completed | 5 |
| Not completed | 0 |

| | |
|-------------------------------|---|
| Consent withdrawn by subject | - |
| Withdrawal by Parent/Guardian | - |
| Lost to follow-up | - |

Baseline characteristics

Reporting groups

| | |
|--|---------------------|
| Reporting group title | Sitagliptin |
| Reporting group description: | |
| In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. | |
| Reporting group title | Placebo/Metformin |
| Reporting group description: | |
| In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. | |
| Reporting group title | Metformin |
| Reporting group description: | |
| In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20. | |
| Reporting group title | Placebo/Sitagliptin |
| Reporting group description: | |
| In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20. | |

| Reporting group values | Sitagliptin | Placebo/Metformin | Metformin |
|--|-------------|-------------------|-----------|
| Number of subjects | 95 | 90 | 9 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 11 | 11 | 3 |
| Adolescents (12-17 years) | 84 | 79 | 6 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 14.3 | 13.7 | 13.3 |
| standard deviation | ± 2.0 | ± 1.9 | ± 3.0 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 54 | 58 | 6 |
| Male | 41 | 32 | 3 |

| | | | |
|---|------------|------------|------------|
| Race | | | |
| Units: Subjects | | | |
| American Indian Or Alaska Native | 6 | 9 | 0 |
| Asian | 13 | 14 | 1 |
| Black Or African American | 8 | 2 | 1 |
| Multiple | 20 | 18 | 1 |
| White | 48 | 47 | 6 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic Or Latino | 36 | 33 | 2 |
| Not Hispanic Or Latino | 53 | 54 | 5 |
| Unknown or Not Reported | 6 | 3 | 2 |
| Glycated Hemoglobin (A1C) | | | |
| A1C is a blood marker used to report average blood glucose levels over prolonged periods of time. A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population includes all randomized participants who received ≥ 1 dose of study medication and had a baseline measurement of A1C. | | | |
| Units: Percentage | | | |
| arithmetic mean | 7.43 | 7.56 | 7.43 |
| standard deviation | ± 1.02 | ± 1.08 | ± 1.07 |

| Reporting group values | Placebo/Sitagliptin | Total | |
|--|---------------------|-------|--|
| Number of subjects | 5 | 199 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 25 | |
| Adolescents (12-17 years) | 5 | 174 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Unknown | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 15.0 | | |
| standard deviation | ± 1.6 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 121 | |
| Male | 2 | 78 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian Or Alaska Native | 0 | 15 | |
| Asian | 2 | 30 | |
| Black Or African American | 0 | 11 | |
| Multiple | 0 | 39 | |
| White | 3 | 104 | |
| Ethnicity | | | |

| | | | |
|---|--------|-----|--|
| Units: Subjects | | | |
| Hispanic Or Latino | 2 | 73 | |
| Not Hispanic Or Latino | 3 | 115 | |
| Unknown or Not Reported | 0 | 11 | |
| Glycated Hemoglobin (A1C) | | | |
| A1C is a blood marker used to report average blood glucose levels over prolonged periods of time. A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population includes all randomized participants who received ≥1 dose of study medication and had a baseline measurement of A1C. | | | |
| Units: Percentage | | | |
| arithmetic mean | 8.02 | | |
| standard deviation | ± 0.75 | - | |

Subject analysis sets

| | |
|--|---------------------|
| Subject analysis set title | Sitagliptin |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint. | |
| Subject analysis set title | Placebo/Metformin |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint. | |
| Subject analysis set title | Metformin |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint. | |
| Subject analysis set title | Placebo/Sitagliptin |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint. | |
| Subject analysis set title | Placebo (pooled) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| This analysis set, used only for analyses of data during Weeks 0-20, contains the pooled population of placebo-treated participants from the groups "Placebo/Sitagliptin" and "Placebo/Metformin". | |

| Reporting group values | Sitagliptin | Placebo/Metformin | Metformin |
|--|-------------|-------------------|-----------|
| Number of subjects | 95 | 90 | 9 |
| 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 Unknown | | | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Gender Categorical Units: Subjects | | | |
| Female Male | | | |
| Race Units: Subjects | | | |
| American Indian Or Alaska Native Asian Black Or African American Multiple White | | | |
| Ethnicity Units: Subjects | | | |
| Hispanic Or Latino Not Hispanic Or Latino Unknown or Not Reported | | | |
| Glycated Hemoglobin (A1C) | | | |
| A1C is a blood marker used to report average blood glucose levels over prolonged periods of time. A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population includes all randomized participants who received ≥1 dose of study medication and had a baseline measurement of A1C. | | | |
| Units: Percentage arithmetic mean standard deviation | ± | ± | ± |

| Reporting group values | Placebo/Sitagliptin | Placebo (pooled) | |
|---|---------------------|------------------|--|
| Number of subjects | 5 | 95 | |
| 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) | | 11 | |
| Adolescents (12-17 years) | | 84 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Unknown | | 0 | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | 13.7 ± 1.9 | |

| | | | |
|---|-------|------------|--|
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | | 61 | |
| Male | | 34 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian Or Alaska Native | | 9 | |
| Asian | | 16 | |
| Black Or African American | | 2 | |
| Multiple | | 18 | |
| White | | 50 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic Or Latino | | 35 | |
| Not Hispanic Or Latino | | 57 | |
| Unknown or Not Reported | | 3 | |
| Glycated Hemoglobin (A1C) | | | |
| A1C is a blood marker used to report average blood glucose levels over prolonged periods of time. A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population includes all randomized participants who received ≥ 1 dose of study medication and had a baseline measurement of A1C. | | | |
| Units: Percentage | | | |
| arithmetic mean | | 7.58 | |
| standard deviation | \pm | ± 1.06 | |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | Sitagliptin |
| Reporting group description: In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals. | |
| Reporting group title | Placebo/Metformin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals. | |
| Reporting group title | Metformin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, but ongoing participants in this arm continued in the same arm. | |
| Reporting group title | Placebo/Sitagliptin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, but ongoing participants in this arm continued in the same arm. | |
| Reporting group title | Sitagliptin |
| Reporting group description: In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. | |
| Reporting group title | Placebo/Metformin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. | |
| Reporting group title | Metformin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20. | |
| Reporting group title | Placebo/Sitagliptin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, ongoing participants in this arm continued in the same arm during Weeks 0-20. | |
| Reporting group title | Sitagliptin |
| Reporting group description: In this period, participants continued to receive 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. | |
| Reporting group title | Placebo/Metformin |
| Reporting group description: In this period, participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. | |
| Reporting group title | Metformin |

Reporting group description:

In this period, participants continued to receive 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, but ongoing participants in this arm continued in the same arm during Weeks 20-54.

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo/Sitagliptin |
|-----------------------|---------------------|

Reporting group description:

In this period, participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin treatment arm, but ongoing participants in this arm continued in the same arm during Weeks 20-54.

| | |
|----------------------------|-------------|
| Subject analysis set title | Sitagliptin |
|----------------------------|-------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint.

| | |
|----------------------------|-------------------|
| Subject analysis set title | Placebo/Metformin |
|----------------------------|-------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint.

| | |
|----------------------------|-----------|
| Subject analysis set title | Metformin |
|----------------------------|-----------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint.

| | |
|----------------------------|---------------------|
| Subject analysis set title | Placebo/Sitagliptin |
|----------------------------|---------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The analysis set consisted of all randomized participants in this study arm who received at least 1 dose of study medication and had at least 1 observation for the analysis endpoint.

| | |
|----------------------------|------------------|
| Subject analysis set title | Placebo (pooled) |
|----------------------------|------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

This analysis set, used only for analyses of data during Weeks 0-20, contains the pooled population of placebo-treated participants from the groups "Placebo/Sitagliptin" and "Placebo/Metformin".

Primary: Change from Baseline in Hemoglobin A1C (A1C) at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in Hemoglobin A1C (A1C) at Week 20 ^[1] |
|-----------------|--|

End point description:

Glycated hemoglobin (A1C) is a blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Change from baseline was estimated as the Week 20 A1C minus the Week 0 A1C. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 78 | 70 | 8 | 3 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -0.13 (± 1.58) | -0.02 (± 1.45) | -1.03 (± 0.72) | 0.57 (± 1.62) |

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline In A1C at Week 20 (Including Treatment Difference)

| | |
|-----------------|--|
| End point title | Change from Baseline In A1C at Week 20 (Including Treatment Difference) ^[2] |
|-----------------|--|

End point description:

Glycated hemoglobin (A1C) is a blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Change from baseline was estimated as the Week 20 A1C minus the Week 0 A1C from a longitudinal data analysis model (LDA model). The analysis population included all randomized participants who received ≥1 dose of study medication and who had at least 1 measurement for the analysis endpoint.

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

End point timeframe:

Baseline and Week 20

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: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo (pooled) | | |
|--|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 95 | 95 | | |
| Units: Percentage | | | | |
| least squares mean (confidence interval 95%) | -0.01 (-0.35 to 0.34) | 0.18 (-0.17 to 0.53) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Difference in Change from Baseline |
|----------------------------|------------------------------------|

Statistical analysis description:

The Least Squares (LS) Mean for the arm "Sitagliptin" is compared against that of "Placebo (pooled)".

| | |
|-------------------|--------------------------------|
| Comparison groups | Sitagliptin v Placebo (pooled) |
|-------------------|--------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.448 |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares Means Difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.3 |

Primary: Number of Participants Who Experienced ≥ 1 Adverse Event During Weeks 0-56

| | |
|-----------------|--|
| End point title | Number of Participants Who Experienced ≥ 1 Adverse Event During Weeks 0-56 ^[3] |
|-----------------|--|

End point description:

The number of participants experiencing ≥ 1 adverse event during Weeks 0-56 was reported. An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The analysis population includes all randomized participants who received ≥ 1 dose of study medication.

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

End point timeframe:

Up to Week 56

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Participants | 73 | 67 | 7 | 4 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced ≥ 1 Adverse Event During Weeks 0-56 (Including Treatment Difference)

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Experienced ≥ 1 Adverse Event During Weeks 0-56 (Including Treatment Difference) |
|-----------------|--|

End point description:

The percentage of participants experiencing ≥ 1 adverse event during Weeks 0-56 was reported. An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The analysis population includes all randomized participants who received ≥ 1 dose of study medication.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Up to Week 56 | |

| End point values | Sitagliptin | Placebo/Metformin | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 76.8 | 74.4 | | |

Statistical analyses

| Statistical analysis title | Difference in Percentage |
|---|---------------------------------|
| Statistical analysis description: | |
| The percentage of participants who experienced ≥ 1 adverse event for the arm "Sitagliptin" is compared against that of "Placebo/Metformin". Analysis based on the Miettinen & Nurminen method. | |
| Comparison groups | Sitagliptin v Placebo/Metformin |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | 2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10 |
| upper limit | 14.9 |

Primary: Number of Participants Who Discontinued Study Drug Due to an Adverse Event During Weeks 0-54

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Drug Due to an Adverse Event During Weeks 0-54 ^[4] |
|-----------------|---|

End point description:

The number of participants who discontinued from study drug due to an adverse event during Weeks 0-54 was reported. An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The analysis population includes all randomized participants who received ≥ 1 dose of study medication.

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

End point timeframe:

Up to Week 54

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Participants | 5 | 1 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event During Weeks 0-54 (Including Treatment Difference)

| | |
|--|---|
| End point title | Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event During Weeks 0-54 (Including Treatment Difference) |
| End point description: The percentage of participants who discontinued from study drug due to an adverse event during Weeks 0-54 was reported. An adverse event is defined as any untoward medical occurrence in a person administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. The analysis population includes all randomized participants who received ≥ 1 dose of study medication. | |
| End point type | Primary |
| End point timeframe: Up to Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 95 | 90 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 5.3 | 1.1 | | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | Difference in percentage |
| Statistical analysis description: The percentage of participants who experienced ≥ 1 adverse event for the arm "Sitagliptin" is compared against that of "Placebo/Metformin". Analysis based on the Miettinen & Nurminen method. | |
| Comparison groups | Sitagliptin v Placebo/Metformin |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in percentage |
| Point estimate | 4.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 10.8 |

Secondary: Change from Baseline in A1C at Week 54

| | |
|--|--|
| End point title | Change from Baseline in A1C at Week 54 |
| End point description: | |
| A1C is a blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. This change from baseline reflects the Week 54 A1C minus the Week 0 A1C. The analysis population included all randomized participants who took at least one dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 41 | 48 | 4 | 1 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -0.19 (± 1.37) | -0.90 (± 1.41) | -0.70 (± 0.94) | -0.50 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With A1C at Goal (<7.0%) at Week 20

| | |
|---|--|
| End point title | Percentage of Participants With A1C at Goal (<7.0%) at Week 20 |
| End point description: | |
| The percentage of participants with A1C at goal (<7.0%) at Week 20 was presented. All numbers shown in each individual treatment group are based on the observed values (Missing = Not at Goal). The analysis population included all randomized participants who received ≥1 dose of study medication. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 49.5 | 37.8 | 77.8 | 20.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With A1C at Goal (<7.0%) at Week 20 (Including Treatment Difference)

| | |
|-----------------|--|
| End point title | Percentage of Participants With A1C at Goal (<7.0%) at Week 20 (Including Treatment Difference) ^[5] |
|-----------------|--|

End point description:

The percentage of participants with A1C at goal (<7.0%) at Week 20 was presented. The analysis table includes the observed values for each treatment group (Missing = Not at Goal) and the estimated treatment difference (Missing = Multiple Imputation). The analysis population included all randomized participants who received ≥ 1 dose of study medication.

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

End point timeframe:

Week 20

Notes:

[5] - 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: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo (pooled) | | |
|-----------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 95 | 95 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 49.5 | 36.8 | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Difference in Percentage |
|----------------------------|--------------------------|

Statistical analysis description:

The percentage of participants with an A1C at the A1C goal (7.0%) in the arm "Sitagliptin" was compared against the arm "Placebo (pooled)". For estimating the treatment difference, when the A1C result for a participant at Week 20 was not available, a multiple imputation method based on the LDA model was used to impute whether the participant had met the goal.

| | |
|-------------------|--------------------------------|
| Comparison groups | Sitagliptin v Placebo (pooled) |
|-------------------|--------------------------------|

| | |
|---|--------------------------|
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.374 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in percentage |
| Point estimate | 6.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.1 |
| upper limit | 21.2 |

Secondary: Percentage of Participants With A1C at Goal (<6.5%) at Week 20

| | |
|---|--|
| End point title | Percentage of Participants With A1C at Goal (<6.5%) at Week 20 |
| End point description: The percentage of participants with A1C at goal (<6.5%) at Week 20 was presented. All numbers shown in each individual treatment group are based on the observed values (Missing = Not at Goal). The analysis population included all randomized participants who received ≥1 dose of study medication. | |
| End point type | Secondary |
| End point timeframe: Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 30.5 | 23.3 | 66.7 | 20.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With A1C at Goal (<6.5) at Week 20 (Including Treatment Difference)

| | |
|---|---|
| End point title | Percentage of Participants With A1C at Goal (<6.5) at Week 20 (Including Treatment Difference) ^[6] |
| End point description: The percentage of participants with A1C at goal (<6.5%) at Week 20 was presented. The analysis table includes the observed values for each treatment group (Missing = Not at Goal) and the estimated treatment difference (Missing = Multiple Imputation). The analysis population included all randomized participants who received ≥1 dose of study medication. | |
| End point type | Secondary |

End point timeframe:

Week 20

Notes:

[6] - 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: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo (pooled) | | |
|-----------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 95 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 30.5 | 23.2 | | |

Statistical analyses

| Statistical analysis title | Difference in Percentage |
|----------------------------|--------------------------|
|----------------------------|--------------------------|

Statistical analysis description:

The percentage of participants with an A1C at the A1C goal (6.5%) in the arm "Sitagliptin" was compared against the arm "Placebo (pooled)". For estimating the treatment difference, when the A1C result for a participant at Week 20 was not available, a multiple imputation method based on the LDA model was used to impute whether the participant had met the goal. model.

| | |
|---|--------------------------------|
| Comparison groups | Sitagliptin v Placebo (pooled) |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.639 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in percentage |
| Point estimate | 3.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.6 |
| upper limit | 18.3 |

Secondary: Percentage of Participants With A1C at Goal (<7.0%) at Week 54

| | |
|-----------------|--|
| End point title | Percentage of Participants With A1C at Goal (<7.0%) at Week 54 |
|-----------------|--|

End point description:

The percentage of participants with A1C at goal (<7.0%) at Week 54 was presented. All numbers shown in each individual treatment group are based on the observed values (Missing = Not at Goal). The analysis population included all randomized participants who received ≥ 1 dose of study medication.

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

End point timeframe:

Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 28.4 | 40.0 | 33.3 | 20.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With A1C at Goal (<6.5%) at Week 54

| | |
|---|--|
| End point title | Percentage of Participants With A1C at Goal (<6.5%) at Week 54 |
| End point description: The percentage of participants with A1C at goal (<6.5%) at Week 54 was presented. All numbers shown in each individual treatment group are based on the observed values (Missing = Not at Goal). The analysis population included all randomized participants who received ≥ 1 dose of study medication. | |
| End point type | Secondary |
| End point timeframe: Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 20.0 | 35.6 | 22.2 | 20.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 20

| | |
|--|---|
| End point title | Change from Baseline in Fasting Plasma Glucose (FPG) at Week 20 |
| End point description: Blood glucose was measured on a fasting basis. Change in plasma glucose levels was FPG at Week 20 minus FPG at baseline. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |

End point timeframe:
Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|---------------------|---------------------|-----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 81 | 74 | 8 | 3 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | 9.98 (\pm 61.86) | 7.59 (\pm 41.11) | -19.88 (\pm 49.78) | 57.67 (\pm 51.05) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FPG at Week 20 (Including Treatment Difference)

| | |
|-----------------|--|
| End point title | Change from Baseline in FPG at Week 20 (Including Treatment Difference) ^[7] |
|-----------------|--|

End point description:

Blood glucose was measured on a fasting basis. Change in plasma glucose levels was FPG at Week 20 minus FPG at baseline and was estimated from a longitudinal data analysis model. The analysis population includes all randomized participants who received ≥ 1 dose of study medication, and who had at least 1 measurement for the analysis endpoint.

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

End point timeframe:

Baseline and Week 20

Notes:

[7] - 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: Summary data only was obtained for this primary end point, no between group statistical analysis was planned or performed.

| End point values | Sitagliptin | Placebo (pooled) | | |
|--|--------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 95 | 95 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | 7.2 (-4.2 to 18.7) | 5.7 (-6.0 to 17.4) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Difference in Change from Baseline |
|----------------------------|------------------------------------|

Statistical analysis description:

The Least Squares (LS) Mean for the arm "Sitagliptin" was compared against that of "Placebo (pooled)".

| | |
|-------------------|--------------------------------|
| Comparison groups | Sitagliptin v Placebo (pooled) |
|-------------------|--------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.849 |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares Means Difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.4 |
| upper limit | 17.5 |

Secondary: Change from Baseline in FPG at Week 54

| | |
|--|--|
| End point title | Change from Baseline in FPG at Week 54 |
| End point description: Blood glucose was measured on a fasting basis. Change in plasma glucose levels was FPG at Week 54 minus FPG at baseline. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|-----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 51 | 6 | 1 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -3.03 (\pm 48.55) | -4.52 (\pm 50.68) | -29.92 (\pm 53.19) | 3.00 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 2-Hour Post-meal Glucose (PMG) at Week 20

| | |
|---|---|
| End point title | Change from Baseline in 2-Hour Post-meal Glucose (PMG) at Week 20 |
| End point description: PMG endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 2-hour PMG minus the Week 0 2-hour PMG. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |

End point timeframe:
Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 4 | 2 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -2.9 (± 42.6) | 2.1 (± 72.1) | -6.8 (± 21.1) | 63.5 (± 171.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 2-hour PMG at Week 54

| | |
|---|---|
| End point title | Change from Baseline in 2-hour PMG at Week 54 |
| End point description: PMG endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 2-hour PMG minus the Week 0 2-hour PMG. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 3 | 1 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -1.7 (± 21.3) | -16.8 (± 48.9) | -39.7 (± 32.3) | -28.0 (± 0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 2-hour Incremental PMG at Week 20

| | |
|---|---|
| End point title | Change from Baseline in 2-hour Incremental PMG at Week 20 |
| End point description: 2-Hour incremental PMG = Glucose at 120 minutes – glucose at 0 minutes. PMG endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 2-hour incremental PMG minus the Week 0 2-hour incremental PMG. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to | |

participate in the MTT, and had data for the analysis endpoint both at baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 4 | 2 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | 1.5 (± 55.3) | 0.7 (± 35.9) | 0.8 (± 15.6) | 12.5 (± 98.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 2-Hour Incremental PMG at Week 54

| | |
|---|---|
| End point title | Change from Baseline in 2-Hour Incremental PMG at Week 54 |
| End point description: | |
| 2-Hour incremental PMG = Glucose at 120 minutes – glucose at 0 minutes. PMG endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 2-hour incremental PMG minus the Week 0 2-hour incremental PMG. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 3 | 1 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | -0.6 (± 64.6) | -26.6 (± 39.0) | -31.3 (± 34.8) | -32.0 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin at Week 20 for Participants Not on Background Insulin

| | |
|--|---|
| End point title | Change from Baseline in Insulin at Week 20 for Participants Not on Background Insulin |
| End point description: This change from baseline reflects the Week 20 insulin minus the Week 0 insulin. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 67 | 58 | 7 | 3 |
| Units: mIU/L | | | | |
| arithmetic mean (standard deviation) | 1.59 (\pm 47.24) | -3.91 (\pm 22.31) | -7.25 (\pm 60.58) | -1.23 (\pm 20.55) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin at Week 54 For Participants Not on Background Insulin

| | |
|--|---|
| End point title | Change from Baseline in Insulin at Week 54 For Participants Not on Background Insulin |
| End point description: This change from baseline reflects the Week 54 insulin minus the Week 0 insulin. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|-----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 45 | 5 | 1 |
| Units: mIU/L | | | | |
| arithmetic mean (standard deviation) | -9.65 (\pm 40.82) | -6.64 (\pm 32.01) | -20.50 (\pm 65.08) | -9.95 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin at Week 20 For Participants Not on Background Insulin

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin at Week 20 For Participants Not on Background Insulin |
|-----------------|--|

End point description:

This change from baseline reflects the Week 20 proinsulin minus the Week 0 proinsulin. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|---------------------|-----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 68 | 57 | 7 | 3 |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | 0.91 (\pm 81.88) | -10.88 (\pm 55.12) | 12.57 (\pm 36.98) | -1.33 (\pm 9.07) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin at Week 54 For Participants Not on Background Insulin

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin at Week 54 For Participants Not on Background Insulin |
|-----------------|--|

End point description:

This change from baseline reflects the Week 54 proinsulin minus the Week 0 proinsulin. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------------|-----------------------|-----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 38 | 42 | 5 | 1 |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | -10.62 (\pm 67.54) | -16.13 (\pm 81.52) | -23.30 (\pm 42.36) | -0.50 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin/Insulin Ratio at Week 20 for Participants Not on Background Insulin

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin/Insulin Ratio at Week 20 for Participants Not on Background Insulin |
|-----------------|--|

End point description:

Change from baseline was the Week 20 proinsulin/insulin ratio minus the Week 0 proinsulin/insulin ratio. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|--------------------|--------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 65 | 55 | 6 | 3 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 0.02 (\pm 0.22) | 0.02 (\pm 0.16) | -0.03 (\pm 0.10) | -0.19 (\pm 0.45) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin/Insulin Ratio at Week 54 For Participants Not on Background Insulin

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin/Insulin Ratio at Week 54 For Participants Not on Background Insulin |
|-----------------|--|

End point description:

The change from baseline was Week 54 proinsulin/insulin ratio minus the Week 0 proinsulin/insulin ratio. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 41 | 5 | 1 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 0.02 (± 0.23) | -0.03 (± 0.19) | -0.01 (± 0.06) | 0.02 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Homeostatic Model Assessment of β -cell Function (HOMA- β) at Week 20 For Participants Not on Background Insulin

| | |
|---|---|
| End point title | Change from Baseline in Homeostatic Model Assessment of β -cell Function (HOMA- β) at Week 20 For Participants Not on Background Insulin |
| End point description: HOMA- β = $20 \times \text{fasting insulin (in mcIU/mL)} \div \{[\text{FPG (in mg/dL)/18}] - 3.5\}$. The change from baseline was Week 20 HOMA- β minus the Week 0 HOMA- β . The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|------------------|-------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 67 | 58 | 7 | 3 |
| Units: Percentage of Beta Cell Function | | | | |
| arithmetic mean (standard deviation) | 15.72 (± 162.47) | -53.23 (± 296.23) | -1757.50 (± 4765.46) | -64.78 (± 126.65) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HOMA- β at Week 54 For Participants Not on Background Insulin

| | |
|---|---|
| End point title | Change from Baseline in HOMA- β at Week 54 For Participants Not on Background Insulin |
| End point description: HOMA- β = $20 \times \text{fasting insulin (in mcIU/mL)} \div \{[\text{FPG (in mg/dL)/18}] - 3.5\}$. This change from baseline | |

was Week 54 HOMA- β minus the Week 0 HOMA- β . The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|------------------------|------------------------|---------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 45 | 5 | 1 |
| Units: Percentage of Beta Cell Function | | | | |
| arithmetic mean (standard deviation) | -41.15 (\pm 183.17) | -63.88 (\pm 339.74) | -1860.69 (\pm 4099.22) | -121.48 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) at Week 20 For Participants Not on Background Insulin

| | |
|-----------------|--|
| End point title | Change from Baseline in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) at Week 20 For Participants Not on Background Insulin |
|-----------------|--|

End point description:

HOMA-IR = fasting insulin (in mIU/mL) \times FPG (in mg/dL) / (22.5 \times 18). This change from baseline was Week 20 HOMA-IR minus the Week 0 HOMA-IR. The analysis population included all randomized participants not on background insulin who received ≥ 1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|---------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 67 | 58 | 7 | 3 |
| Units: mU*mmol/L ² | | | | |
| arithmetic mean (standard deviation) | -0.50 (\pm 31.62) | -0.86 (\pm 9.02) | -4.46 (\pm 34.65) | 2.58 (\pm 9.30) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HOMA-IR at Week 54 For Participants Not on Background Insulin

| | |
|-----------------|---|
| End point title | Change from Baseline in HOMA-IR at Week 54 For Participants Not on Background Insulin |
|-----------------|---|

End point description:

HOMA-IR = fasting insulin (in mIU/mL) × FPG (in mg/dL) / (22.5×18). This change from baseline was Week 54 HOMA-IR minus the Week 0 HOMA-IR. The analysis population included all randomized participants not on background insulin who received ≥1 dose of study medication and had data for the analysis endpoint both at baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 45 | 5 | 1 |
| Units: mU * mmol/L ² | | | | |
| arithmetic mean (standard deviation) | -6.13 (± 34.86) | -1.30 (± 15.31) | -15.18 (± 36.41) | -2.21 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Glucose 3-Hour Total Area Under the Curve (AUC) at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in Glucose 3-Hour Total Area Under the Curve (AUC) at Week 20 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 glucose 3-hour AUC minus the Week 0 glucose 3-hour AUC. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 4 | 2 |
| Units: mg*hr/dL | | | | |
| arithmetic mean (standard deviation) | -49.3 (± 103.6) | 2.0 (± 190.0) | 18.6 (± 50.9) | 191.0 (± 434.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin 3-hour AUC at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin 3-hour AUC at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 insulin 3-hour AUC minus the Week 0 insulin 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|----------------------|---------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 2 | 2 |
| Units: $\mu\text{IU}\cdot\text{hr}/\text{mL}$ | | | | |
| arithmetic mean (standard deviation) | -14.5 (\pm 128.0) | -32.8 (\pm 99.9) | 141.7 (\pm 206.1) | -145.6 (\pm 180.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-peptide 3-Hour AUC at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in C-peptide 3-Hour AUC at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 C-peptide 3-hour AUC minus the Week 0 C-peptide 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 2 | 2 |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | -1.8 (± 4.9) | -0.1 (± 3.3) | 5.9 (± 7.6) | -6.4 (± 7.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin 3-Hour AUC at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin 3-Hour AUC at Week 20 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 proinsulin 3-hour AUC minus the Week 0 proinsulin 3-hour AUC. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC. Proinsulin was collected only at a single time point and therefore AUC could not be derived.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | 0 ^[10] | 0 ^[11] |
| Units: pmol*hr/L | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[8] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[9] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[10] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[11] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin 3-Hour AUC/Insulin 3-Hour AUC Ratio at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Proinsulin 3-Hour AUC/Insulin 3-Hour AUC Ratio at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 proinsulin total AUC/insulin total AUC ratio minus the Week 0 proinsulin total AUC/insulin total AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC. Proinsulin was collected at only a single time point and therefore AUC could not be derived.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|-------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | 0 ^[14] | 0 ^[15] |
| Units: Ratio | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[12] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[13] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[14] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[15] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin 3-Hour AUC/ Glucose 3-Hour AUC Ratio at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin 3-Hour AUC/ Glucose 3-Hour AUC Ratio at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 20 insulin total AUC/glucose total AUC ratio minus the Week 0 insulin total AUC/glucose total AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 2 | 2 |
| Units: [μ IU*hr/mL]/[mg/dL] | | | | |
| arithmetic mean (standard deviation) | 0.0 (\pm 0.3) | -0.1 (\pm 0.3) | 0.2 (\pm 0.4) | -0.2 (\pm 0.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Glucose Excursion 3-Hour AUC at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Glucose Excursion 3-Hour AUC at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 glucose Excursion 3-hour AUC minus the Week 0 glucose Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|---------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 4 | 2 |
| Units: mg*hr/dL | | | | |
| arithmetic mean (standard deviation) | -43.5 (\pm 97.4) | 10.8 (\pm 58.6) | 39.8 (\pm 50.1) | 46.2 (\pm 201.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Excursion 3-Hour AUC at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin Excursion 3-Hour AUC at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 insulin Excursion 3-hour AUC minus the Week 0 insulin Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 2 | 2 |
| Units: $\mu\text{IU}\cdot\text{hr}/\text{mL}$ | | | | |
| arithmetic mean (standard deviation) | -12.4 (\pm 89.4) | -19.4 (\pm 93.6) | 87.5 (\pm 124.5) | -82.8 (\pm 93.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-peptide Excursion 3-Hour AUC at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in C-peptide Excursion 3-Hour AUC at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 C-peptide Excursion 3-hour AUC minus the Week 0 C-peptide Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--|-------------------|-------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 2 | 2 |
| Units: $\text{ng}\cdot\text{hr}/\text{mL}$ | | | | |
| arithmetic mean (standard deviation) | -1.1 (\pm 3.1) | -0.4 (\pm 4.4) | 4.1 (\pm 5.6) | -4.8 (\pm 5.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin Excursion 3-Hour AUC at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin Excursion 3-Hour AUC at Week 20 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 proinsulin Excursion 3-hour AUC minus the Week 0 proinsulin Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|-------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | 0 ^[18] | 0 ^[19] |
| Units: pmol*hr/L | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[16] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[17] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[18] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[19] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin Excursion 3-Hour AUC/Insulin Excursion 3-Hour AUC Ratio at Week 20

| | |
|-----------------|---|
| End point title | Change from Baseline in Proinsulin Excursion 3-Hour AUC/Insulin Excursion 3-Hour AUC Ratio at Week 20 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 proinsulin Excursion 3-hour AUC/insulin Excursion 3-hour AUC ratio minus the Week 0 proinsulin Excursion 3-hour AUC/insulin Excursion 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 20 (-10 min. before the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|-------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[20] | 0 ^[21] | 0 ^[22] | 0 ^[23] |
| Units: Ratio | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[20] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[21] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[22] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[23] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Excursion 3-Hour AUC/Glucose Excursion 3-Hour AUC Ratio at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in Insulin Excursion 3-Hour AUC/Glucose Excursion 3-Hour AUC Ratio at Week 20 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 20 insulin Excursion 3-hour AUC/glucose Excursion 3-hour AUC ratio minus the Week 0 insulin Excursion 3-hour AUC/glucose Excursion 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 20 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 10 | 2 | 2 |
| Units: [$\mu\text{IU}\cdot\text{hr}/\text{mL}$]/[mg/dL] | | | | |
| arithmetic mean (standard deviation) | 2.2 (\pm 9.6) | 7.2 (\pm 17.5) | -2.5 (\pm 3.2) | 1.4 (\pm 2.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Glucose 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Glucose 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 glucose 3-hour AUC minus the Week 0 glucose 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study

medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 3 | 1 |
| Units: mg*hr/dL | | | | |
| arithmetic mean (standard deviation) | -21.1 (± 47.7) | -36.0 (± 136.1) | -73.1 (± 95.8) | -63.3 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 insulin 3-hour AUC minus the Week 0 insulin 3-hour AUC. The analysis population included all randomized participants who received ≥1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 2 | 1 |
| Units: µIU*hr/mL | | | | |
| arithmetic mean (standard deviation) | -43.2 (± 259.8) | -253.9 (± 282.7) | -37.8 (± 9.4) | -184.4 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-peptide 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in C-peptide 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 C-peptide 3-hour AUC minus the Week 0 C-peptide 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 2 | 1 |
| Units: ng*hr/ml | | | | |
| arithmetic mean (standard deviation) | -0.1 (\pm 5.7) | -6.1 (\pm 8.2) | 1.7 (\pm 1.0) | -8.9 (\pm 0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin 3-Hour AUC at Week 54

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin 3-Hour AUC at Week 54 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 proinsulin 3-hour AUC minus the Week 0 proinsulin 3-hour AUC. The analysis population included all randomized who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 (12 June 2018) removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[24] | 0 ^[25] | 0 ^[26] | 0 ^[27] |
| Units: pmol*hr/L | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

- [24] - Protocol Amendment 16 (12 June 2018) removed endpoints involving proinsulin analyzed as AUC.
[25] - Protocol Amendment 16 (12 June 2018) removed endpoints involving proinsulin analyzed as AUC.
[26] - Protocol Amendment 16 (12 June 2018) removed endpoints involving proinsulin analyzed as AUC.
[27] - Protocol Amendment 16 (12 June 2018) removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin 3-Hour AUC/Insulin 3-Hour AUC Ratio at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Proinsulin 3-Hour AUC/Insulin 3-Hour AUC Ratio at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 proinsulin 3-hour AUC/insulin 3-hour AUC ratio minus the Week 0 proinsulin 3-hour AUC/insulin 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[28] | 0 ^[29] | 0 ^[30] | 0 ^[31] |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

- [28] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.
[29] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.
[30] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.
[31] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin 3-Hour AUC/Glucose 3-Hour AUC Ratio at Week 54

| | |
|-----------------|--|
| End point title | Change from Baseline in Insulin 3-Hour AUC/Glucose 3-Hour AUC Ratio at Week 54 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. This change from baseline was Week 54 insulin 3-hour AUC/glucose 3-hour AUC ratio minus the Week 0 insulin 3-hour AUC/glucose 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 2 | 1 |
| Units: [μ IU*hr/mL]/[mg/dL] | | | | |
| arithmetic mean (standard deviation) | -0.1 (\pm 0.5) | -0.6 (\pm 0.8) | -0.0 (\pm 0.2) | -0.3 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Glucose Excursion 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Glucose Excursion 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 glucose Excursion 3-hour AUC minus the Week 0 glucose Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 3 | 1 |
| Units: mg*hr/dL | | | | |
| arithmetic mean (standard deviation) | -30.7 (\pm 100.7) | -50.1 (\pm 79.5) | -49.0 (\pm 87.5) | -74.0 (\pm 0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Excursion 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Insulin Excursion 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 insulin Excursion 3-hour AUC minus the Week 0 insulin Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|-----------------------|-----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 2 | 1 |
| Units: $\mu\text{IU} \cdot \text{hr}/\text{mL}$ | | | | |
| arithmetic mean (standard deviation) | -103.8 (\pm 151.0) | -198.5 (\pm 263.0) | -40.2 (\pm 11.5) | -116.6 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-Peptide Excursion 3-Hour AUC at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in C-Peptide Excursion 3-Hour AUC at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 C-peptide Excursion 3-hour AUC minus the Week 0 C-peptide Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 2 | 1 |
| Units: $\text{ng} \cdot \text{hr}/\text{ml}$ | | | | |
| arithmetic mean (standard deviation) | -1.8 (\pm 3.0) | -5.2 (\pm 8.8) | 0.9 (\pm 0.5) | -5.9 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin Excursion 3-Hour AUC at Week 54

| | |
|-----------------|--|
| End point title | Change from Baseline in Proinsulin Excursion 3-Hour AUC at Week 54 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 proinsulin Excursion 3-hour AUC minus the Week 0 proinsulin Excursion 3-hour AUC. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[32] | 0 ^[33] | 0 ^[34] | 0 ^[35] |
| Units: pmol*hr/L | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[32] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[33] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[34] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[35] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proinsulin Excursion 3-Hour AUC/Insulin Excursion 3-Hour AUC Ratio at Week 54

| | |
|-----------------|---|
| End point title | Change from Baseline in Proinsulin Excursion 3-Hour AUC/Insulin Excursion 3-Hour AUC Ratio at Week 54 |
|-----------------|---|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 proinsulin Excursion 3-hour AUC/insulin Excursion 3-hour AUC ratio minus the Week 0 proinsulin Excursion 3-hour AUC/insulin Excursion 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements. Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[36] | 0 ^[37] | 0 ^[38] | 0 ^[39] |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[36] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[37] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[38] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

[39] - Protocol Amendment 16 removed endpoints involving proinsulin analyzed as AUC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Excursion 3-Hour AUC/Glucose Excursion 3-Hour AUC Ratio at Week 54

| | |
|-----------------|--|
| End point title | Change from Baseline in Insulin Excursion 3-Hour AUC/Glucose Excursion 3-Hour AUC Ratio at Week 54 |
|-----------------|--|

End point description:

AUC endpoints were derived via the trapezoidal rule using 9-point Meal Tolerance Test (MTT) measurements. Excursion AUC = Incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal did not contribute to the Excursion AUC. This change from baseline was Week 54 insulin Excursion 3-hour AUC/glucose Excursion 3-hour AUC ratio minus the Week 0 insulin Excursion 3-hour AUC/glucose Excursion 3-hour AUC ratio. The analysis population included all randomized participants who received ≥ 1 dose of study medication, consented to participate in the MTT, and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Baseline and Week 54 (-10 min. before ingesting the meal, 0 min. prior to the meal, 10, 20, 30, 60, 90, 120, 180 minutes after ingesting the meal)

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 6 | 2 | 1 |
| Units: [$\mu\text{IU}\cdot\text{hr}/\text{mL}$]/[mg/dL] | | | | |
| arithmetic mean (standard deviation) | 4.1 (\pm 13.1) | 3.7 (\pm 5.6) | -2.7 (\pm 4.3) | 1.4 (\pm 0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Initiating Glycemic Rescue Therapy by Week 20

| | |
|--|--|
| End point title | Percentage of Participants Initiating Glycemic Rescue Therapy by Week 20 |
| End point description: The percentage of participants who initiated glycemic rescue therapy prior to Week 20 was reported. The analysis population included all randomized participants who received ≥ 1 dose of study medication. | |
| End point type | Secondary |
| End point timeframe: Up to Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 5.3 | 11.1 | 0.0 | 40.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Initiating Glycemic Rescue Therapy by Week 54

| | |
|--|--|
| End point title | Percentage of Participants Initiating Glycemic Rescue Therapy by Week 54 |
| End point description: The percentage of participants who initiated glycemic rescue therapy prior to Week 54 was reported. The analysis population included all randomized participants who received ≥ 1 dose of study medication. | |
| End point type | Secondary |
| End point timeframe: Up to Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 95 | 90 | 9 | 5 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 35.8 | 28.9 | 11.1 | 80.0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Mass Index (BMI) at Week 20

| | |
|---|--|
| End point title | Change from Baseline in Body Mass Index (BMI) at Week 20 |
| End point description: This change from baseline was Week 20 BMI minus the Week 0 BMI. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 84 | 82 | 8 | 5 |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | 0.0 (\pm 2.2) | -0.7 (\pm 1.9) | -0.8 (\pm 1.4) | -1.7 (\pm 2.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in BMI at Week 54

| | |
|---|--|
| End point title | Change from Baseline in BMI at Week 54 |
| End point description: This change from baseline was Week 54 BMI minus the Week 0 BMI. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 72 | 73 | 6 | 5 |
| Units: kg/m ² | | | | |
| arithmetic mean (standard deviation) | -0.4 (\pm 2.9) | -1.0 (\pm 2.9) | -0.6 (\pm 1.3) | -0.3 (\pm 1.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in CD26 at Week 20

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in CD26 at Week 20 |
|-----------------|---|

End point description:

The percent change from baseline in CD26 = ([CD26 value at Week 20] - [baseline CD26 value] ÷ baseline CD26 value) × 100. The analysis population included all randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

End point type Secondary

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 68 | 57 | 4 | 3 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 4.06 (± 19.25) | -1.78 (± 17.18) | 4.89 (± 1.90) | 14.57 (± 15.46) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in CD26 at Week 54

End point title Percent Change from Baseline in CD26 at Week 54

End point description:

The percent change from baseline in CD26 = ([CD26 value at Week 54] - [baseline CD26 value] ÷ baseline CD26 value) × 100. The analysis population included all randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

End point type Secondary

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 56 | 55 | 5 | 3 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 4.74 (± 17.18) | 4.27 (± 18.24) | 12.63 (± 13.02) | -5.30 (± 4.19) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Calcitonin at Week 20 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Calcitonin at Week 20 - Females |
|-----------------|---|

End point description:

Calcitonin, along with parathyroid hormone, is a hormone that regulates calcium and bone metabolism. This change from baseline was Week 20 calcitonin minus the Week 0 calcitonin. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-------------------|--------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 46 | 4 | 2 |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | -0.1 (\pm 0.5) | -2.0 (\pm 11.7) | 0.0 (\pm 0.0) | 0.0 (\pm 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Calcitonin at Week 54 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Calcitonin at Week 54 - Females |
|-----------------|---|

End point description:

Calcitonin, along with parathyroid hormone, is a hormone that regulates calcium and bone metabolism. This change from baseline was Week 54 calcitonin minus the Week 0 calcitonin. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 43 | 3 | 2 |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | -0.1 (\pm 0.6) | -1.9 (\pm 12.1) | 0.0 (\pm 0.0) | 0.3 (\pm 0.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Calcitonin at Week 20 - Males

| | |
|-----------------|---|
| End point title | Change from Baseline in Calcitonin at Week 20 - Males |
|-----------------|---|

End point description:

Calcitonin, along with parathyroid hormone, is a hormone that regulates calcium and bone metabolism. This change from baseline was Week 20 calcitonin minus the Week 0 calcitonin. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 35 | 25 | 2 | 2 |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | 0.2 (\pm 1.4) | -0.2 (\pm 0.6) | -1.6 (\pm 2.2) | 0.5 (\pm 0.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Calcitonin at Week 54 - Males

| | |
|-----------------|---|
| End point title | Change from Baseline in Calcitonin at Week 54 - Males |
|-----------------|---|

End point description:

Calcitonin, along with parathyroid hormone, is a hormone that regulates calcium and bone metabolism. This change from baseline was Week 54 calcitonin minus the Week 0 calcitonin. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 33 | 21 | 1 | 2 |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | 0.1 (\pm 1.1) | -0.3 (\pm 0.9) | 0.0 (\pm 0.0) | 1.4 (\pm 0.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Urine N-terminal Cross-linking Telopeptide of Bone Collagen [u-NTx]/Creatinine Ratio at Week 20 - Females

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Urine N-terminal Cross-linking Telopeptide of Bone Collagen [u-NTx]/Creatinine Ratio at Week 20 - Females |
|-----------------|---|

End point description:

Urine N-terminal cross-linking telopeptide of bone collagen [u-NTx]/creatinine ratio is a biochemical marker of bone turnover/resorption. The percent change from baseline in u-NTx/Creatinine ratio = $([\text{u-NTx/Creatinine ratio at Week 20}] - [\text{baseline u-NTx/Creatinine ratio}] \div \text{baseline u-NTx/Creatinine ratio}) \times 100$. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 33 | 31 | 4 | 3 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -28.7 (\pm 120.9) | -41.2 (\pm 148.9) | -98.0 (\pm 153.0) | 12.7 (\pm 29.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline u-NTx/Creatinine Ratio at Week 20 - Males

| | |
|-----------------|--|
| End point title | Percent Change from Baseline u-NTx/Creatinine Ratio at Week 20 - Males |
|-----------------|--|

End point description:

Urine N-terminal cross-linking telopeptide of bone collagen [u-NTx]/creatinine ratio is a biochemical marker of bone turnover/resorption. The percent change from baseline in u-NTx/Creatinine ratio = $([\text{u-NTx/Creatinine ratio at Week 54}] - [\text{baseline u-NTx/Creatinine ratio}] \div \text{baseline u-NTx/Creatinine ratio}) \times 100$. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 31 | 21 | 1 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -30.9 (± 167.2) | -69.8 (± 162.1) | 62.0 (± 0.0) | -29.0 (± 32.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in u-NTx/Creatinine Ratio at Week 54 - Females

| | |
|---|---|
| End point title | Percent Change from Baseline in u-NTx/Creatinine Ratio at Week 54 - Females |
| End point description: Urine N-terminal cross-linking telopeptide of bone collagen [u-NTx]/creatinine ratio is a biochemical marker of bone turnover/resorption. The percent change from baseline in u-NTx/Creatinine ratio = $([u\text{-NTx/Creatinine ratio at Week 54}] - [\text{baseline u-NTx/Creatinine ratio}] \div \text{baseline u-NTx/Creatinine ratio}) \times 100$. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 30 | 4 | 3 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -88.4 (± 102.6) | -61.2 (± 137.6) | -80.3 (± 208.5) | -17.0 (± 13.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in u-NTx/Creatinine Ratio at Week 54 - Males

| | |
|---|---|
| End point title | Percent Change from Baseline in u-NTx/Creatinine Ratio at Week 54 - Males |
| End point description: Urine N-terminal cross-linking telopeptide of bone collagen [u-NTx]/creatinine ratio is a biochemical marker of bone turnover/resorption. The percent change from baseline in u-NTx/Creatinine ratio = $([u\text{-NTx/Creatinine ratio at Week 20}] - [\text{baseline u-NTx/Creatinine ratio}] \div \text{baseline u-NTx/Creatinine ratio}) \times 100$. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 16 | 0 ^[40] | 1 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -78.2 (± 166.9) | -102.4 (± 267.7) | () | -30.0 (± 0.0) |

Notes:

[40] - All participants in this arm were missing baseline or Week 54 measurements.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 20 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 20 - Females |
|-----------------|---|

End point description:

Bone-specific alkaline phosphatase is a biochemical marker of bone turnover. This change from baseline was Week 20 bone-specific alkaline phosphatase minus the Week 0 bone-specific alkaline phosphatase. The analysis population included all female randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 | 52 | 5 | 3 |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | -6.0 (± 13.7) | -4.2 (± 9.9) | -9.7 (± 7.7) | 10.7 (± 9.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 54 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 54 - Females |
|-----------------|---|

End point description:

Bone-specific alkaline phosphatase is a biochemical marker of bone turnover. This change from baseline was Week 54 bone-specific alkaline phosphatase minus the Week 0 bone-specific alkaline phosphatase. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 43 | 4 | 3 |
| Units: $\mu\text{g/L}$ | | | | |
| arithmetic mean (standard deviation) | -20.0 (\pm 28.4) | -13.5 (\pm 18.1) | -14.9 (\pm 10.3) | -6.9 (\pm 9.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 20 - Males

| | |
|-----------------|---|
| End point title | Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 20 - Males |
|-----------------|---|

End point description:

Bone-specific alkaline phosphatase is a biochemical marker of bone turnover. This change from baseline was Week 20 bone-specific alkaline phosphatase minus the Week 0 bone-specific alkaline phosphatase. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|--------------------|-------------------|-------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 25 | 2 | 2 |
| Units: $\mu\text{g/L}$ | | | | |
| arithmetic mean (standard deviation) | -2.2 (\pm 21.6) | 0.1 (\pm 19.9) | -7.1 (\pm 0.2) | 4.7 (\pm 8.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 54 - Males

| | |
|---|---|
| End point title | Change from Baseline in Bone-Specific Alkaline Phosphatase at Week 54 - Males |
| End point description: Bone-specific alkaline phosphatase is a biochemical marker of bone turnover. This change from baseline was Week 54 bone-specific alkaline phosphatase minus the Week 0 bone-specific alkaline phosphatase. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 33 | 20 | 1 | 2 |
| Units: $\mu\text{g/L}$ | | | | |
| arithmetic mean (standard deviation) | -16.2 (\pm 28.0) | -15.0 (\pm 27.0) | -1.3 (\pm 0.0) | -15.3 (\pm 12.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Insulin-like Growth Factor-1 (IGF-1) at Week 20 - Females

| | |
|---|---|
| End point title | Percent Change from Baseline in Insulin-like Growth Factor-1 (IGF-1) at Week 20 - Females |
| End point description: IGF-1 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-1 = $([\text{IGF-1 value at Week 20}] - [\text{baseline IGF-1 value}] \div \text{baseline IGF-1 value}) \times 100$. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-------------------|--------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 49 | 5 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 0.5 (\pm 21.9) | 11.0 (\pm 34.0) | -3.2 (\pm 14.9) | 41.4 (\pm 31.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-1 at Week 54 - Females

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in IGF-1 at Week 54 - Females |
|-----------------|--|

End point description:

IGF-1 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-1 = ([IGF-1 value at Week 54] - [baseline IGF-1 value] ÷ baseline IGF-1 value) × 100. The analysis population included all female randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 42 | 4 | 1 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -1.5 (± 34.4) | 7.2 (± 57.6) | -11.9 (± 13.4) | -13.5 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-1 at Week 20 - Males

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in IGF-1 at Week 20 - Males |
|-----------------|--|

End point description:

IGF-1 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-1 = ([IGF-1 value at Week 20] - [baseline IGF-1 value] ÷ baseline IGF-1 value) × 100. The analysis population included all male randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 20 | 2 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -2.7 (± 22.1) | 9.3 (± 29.6) | 7.6 (± 17.4) | 5.3 (± 16.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-1 at Week 54 - Males

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in IGF-1 at Week 54 - Males |
|-----------------|--|

End point description:

IGF-1 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-1 = ([IGF-1 value at Week 54] - [baseline IGF-1 value] ÷ baseline IGF-1 value) × 100. The analysis population included all male randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 32 | 18 | 1 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | -4.9 (± 33.5) | 29.6 (± 99.8) | 18.8 (± 0.0) | -6.8 (± 22.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Insulin-like Growth Factor Binding Protein 3 (IGF-BP3) at Week 20 - Females

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Insulin-like Growth Factor Binding Protein 3 (IGF-BP3) at Week 20 - Females |
|-----------------|---|

End point description:

IGF-BP3 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-BP3 = ([IGF-BP3 value at Week 20] - [baseline IGF-BP3 value] ÷ baseline IGF-BP3 value) × 100. The analysis population included all female randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 50 | 6 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 3.5 (± 18.2) | 3.8 (± 13.8) | 8.4 (± 12.9) | -0.7 (± 24.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-BP3 at Week 54 - Females

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in IGF-BP3 at Week 54 - Females |
|-----------------|--|

End point description:

IGF-BP3 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-BP3 = ([IGF-BP3 value at Week 54] - [baseline IGF-BP3 value] ÷ baseline IGF-BP3 value) × 100. The analysis population included all female randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 45 | 4 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 2.0 (± 16.7) | 4.5 (± 17.0) | 11.4 (± 17.4) | -13.4 (± 9.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-BP3 at Week 20 - Males

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in IGF-BP3 at Week 20 - Males |
|-----------------|--|

End point description:

IGF-BP3 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-BP3 = ([IGF-BP3 value at Week 20] - [baseline IGF-BP3 value] ÷ baseline IGF-BP3 value) × 100. The analysis population included all male randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 36 | 24 | 2 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 5.6 (± 13.3) | 10.2 (± 18.6) | 3.3 (± 0.5) | 14.2 (± 50.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in IGF-BP3 at Week 54 - Males

| | |
|---|--|
| End point title | Percent Change from Baseline in IGF-BP3 at Week 54 - Males |
| End point description: IGF-BP3 is a biochemical marker of growth hormone action and growth. The percent change from baseline in IGF-BP3 = ([IGF-BP3 value at Week 54] - [baseline IGF-BP3 value] ÷ baseline IGF-BP3 value) × 100. The analysis population included all male randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 32 | 21 | 1 | 2 |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 5.4 (± 18.4) | 18.2 (± 43.1) | -2.9 (± 0.0) | 22.5 (± 8.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 20 - Females

| | |
|---|--------------------------------------|
| End point title | Growth Velocity at Week 20 - Females |
| End point description: Growth Velocity = change from baseline in height/change from baseline in chronologic age. The analysis population included all female randomized participants who received ≥1 dose of study medication and had height data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |

End point timeframe:

Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 46 | 53 | 6 | 3 |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 3.2 (± 8.2) | 1.9 (± 2.7) | 5.0 (± 6.8) | 0.6 (± 1.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 54 - Females

| | |
|---|--------------------------------------|
| End point title | Growth Velocity at Week 54 - Females |
| End point description: Growth Velocity = change from baseline in height/change from baseline in chronologic age. The analysis population included all female randomized participants who received ≥1 dose of study medication and had height data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 48 | 5 | 3 |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 2.1 (± 3.7) | 1.2 (± 1.8) | 2.4 (± 2.9) | 0.7 (± 1.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 20 - Males

| | |
|---|------------------------------------|
| End point title | Growth Velocity at Week 20 - Males |
| End point description: Growth Velocity = change from baseline in height/change from baseline in chronologic age. The analysis population included all male randomized participants who received ≥1 dose of study medication and had height data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |

End point timeframe:

Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 29 | 2 | 2 |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 2.6 (± 2.7) | 3.6 (± 3.2) | -1.0 (± 1.3) | 1.7 (± 2.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Velocity at Week 54 - Males

End point title Growth Velocity at Week 54 - Males

End point description:

Growth Velocity = change from baseline in height/change from baseline in chronologic age. The analysis population included all male randomized participants who received ≥1 dose of study medication and had height data for the analysis endpoint at both baseline and timepoint measurements.

End point type Secondary

End point timeframe:

Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 35 | 25 | 1 | 2 |
| Units: cm/year | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 2.5) | 2.8 (± 2.1) | 1.7 (± 0.0) | 2.8 (± 4.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal Maturation at Week 20 - Females

End point title Skeletal Maturation at Week 20 - Females

End point description:

Skeletal Maturation = change from baseline in bone age/change from baseline in chronologic age. Bone age was determined from an X-ray of left hand and wrist. The analysis population included all female randomized participants who received ≥1 dose of study medication and had bone age data for the analysis endpoint at both baseline and timepoint measurements.

End point type Secondary

End point timeframe:

Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 17 | 18 | 3 | 2 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 0.6 (\pm 1.9) | 0.4 (\pm 1.8) | 1.7 (\pm 2.3) | -0.8 (\pm 5.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal Maturation at Week 54 - Females

| | |
|-----------------|--|
| End point title | Skeletal Maturation at Week 54 - Females |
|-----------------|--|

End point description:

Skeletal Maturation = change from baseline in bone age/change from baseline in chronologic age. Bone age was determined from X-ray of left hand and wrist. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had bone age data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 14 | 3 | 0 ^[41] |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 1.3 (\pm 1.1) | 1.0 (\pm 0.6) | 1.3 (\pm 2.2) | () |

Notes:

[41] - All participants in this arm were missing baseline or Week 54 measurements.

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal Maturation at Week 20 - Males

| | |
|-----------------|--|
| End point title | Skeletal Maturation at Week 20 - Males |
|-----------------|--|

End point description:

Skeletal Maturation = change from baseline in bone age/change from baseline in chronologic age. Bone age was determined from X-ray of left hand and wrist. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had bone age data for the analysis endpoint at both baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 17 | 1 | 1 |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 1.6 (± 1.7) | 1.2 (± 1.1) | 0.4 (± 0.0) | 2.4 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal Maturation at Week 54 - Males

| | |
|--|--|
| End point title | Skeletal Maturation at Week 54 - Males |
| End point description: | |
| Skeletal Maturation = change from baseline in bone age/change from baseline in chronologic age. Bone age was determined from X-ray of left hand and wrist. The analysis population included all male randomized participants who received ≥1 dose of study medication and had bone age data for the analysis endpoint at both baseline and timepoint measurements. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11 | 10 | 0 ^[42] | 0 ^[43] |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | 1.3 (± 0.9) | 1.3 (± 0.6) | () | () |

Notes:

[42] - All participants in this arm were missing baseline or Week 54 measurements.

[43] - All participants in this arm were missing baseline or Week 54 measurements.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Staging for Genitalia at Week 20 - Males

| | |
|--|---|
| End point title | Change from Baseline in Tanner Staging for Genitalia at Week 20 - Males |
| End point description: | |
| Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in male participants. Tanner staging includes an assessment of genital | |

development (males) with a score of range 1 to 5 where 1=no development and 5=adult genitals. This change from baseline was Week 20 Tanner Staging for Genitalia minus the Week 0 Tanner Staging for Genitalia. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 20 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 31 | 29 | 1 | 2 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.3 (\pm 0.5) | 0.2 (\pm 0.4) | 0.0 (\pm 0.0) | 0.5 (\pm 0.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Staging for Genitalia at Week 54 - Males

| | |
|-----------------|---|
| End point title | Change from Baseline in Tanner Staging for Genitalia at Week 54 - Males |
|-----------------|---|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in male participants. Tanner staging includes an assessment of genital development (males) with a score of range 1 to 5 where 1=no development and 5=adult genitals. This change from baseline was Week 54 Tanner Staging for Genitalia minus the Week 0 Tanner Staging for Genitalia. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 23 | 0 ^[44] | 2 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.5 (\pm 0.6) | 0.6 (\pm 0.7) | () | 0.5 (\pm 0.7) |

Notes:

[44] - All participants in this arm were missing baseline or Week 54 measurements.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Staging for Breasts at Week 20 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Tanner Staging for Breasts at Week 20 - Females |
|-----------------|---|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in female participants. Tanner staging includes an assessment of breast development (females). Tanner stage (breast) is a score of range 1 to 5 where 1=no development and 5=adult breast. This change from baseline was Week 20 Tanner Staging for Breasts minus the Week 0 Tanner Staging for Breasts. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|------------------|-------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 44 | 5 | 3 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | 0.2 (\pm 0.6) | 0.1 (\pm 0.3) | 0.2 (\pm 0.4) | 0.3 (\pm 0.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Staging for Breasts at Week 54 - Females

| | |
|-----------------|---|
| End point title | Change from Baseline in Tanner Staging for Breasts at Week 54 - Females |
|-----------------|---|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in female participants. Tanner staging includes an assessment of breast development (females). Tanner stage (breast) is a score of range 1 to 5 where 1=no development and 5=adult breast. This change from baseline was Week 54 Tanner Staging for Breasts minus the Week 0 Tanner Staging for Breasts. The analysis population included all female randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 36 | 4 | 3 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | 0.5 (± 0.7) | 0.4 (± 0.6) | 0.5 (± 1.0) | 0.7 (± 0.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Stage for Pubic Hair at Week 20 - Females

| | |
|-----------------|--|
| End point title | Change from Baseline in Tanner Stage for Pubic Hair at Week 20 - Females |
|-----------------|--|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in female participants. Tanner staging includes an assessment of pubic hair development. Tanner stage (pubic hair) is a score of range 1 to 5 where 1=no development and 5=adult pubic hair. This change from baseline was Week 20 Tanner Staging for Pubic Hair minus the Week 0 Tanner Staging for Pubic Hair. The analysis population included all female randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 43 | 5 | 3 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.4) | 0.1 (± 0.3) | 0.2 (± 0.4) | 0.0 (± 0.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Stage for Pubic Hair at Week 54 - Females

| | |
|-----------------|--|
| End point title | Change from Baseline in Tanner Stage for Pubic Hair at Week 54 - Females |
|-----------------|--|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in female participants. Tanner staging includes an assessment of pubic hair development with a score of range 1 to 5 where 1=no development and 5=adult pubic hair. This change from baseline was Week 54 Tanner Staging for Pubic Hair minus the Week 0 Tanner Staging for Pubic Hair. The analysis population included all female randomized participants who received ≥1 dose of study

medication and had data for the analysis endpoint at both baseline and timepoint measurements.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 35 | 4 | 3 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.5 (± 0.6) | 0.3 (± 0.5) | 0.8 (± 1.5) | 0.3 (± 0.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Stage for Pubic Hair at Week 20 - Males

| | |
|-----------------|--|
| End point title | Change from Baseline in Tanner Stage for Pubic Hair at Week 20 - Males |
|-----------------|--|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in male participants. Tanner staging includes an assessment of pubic hair development with a score of range 1 to 5 where 1=no development and 5=adult pubic hair. This change from baseline was Week 20 Tanner Staging for Pubic Hair minus the Week 0 Tanner Staging for Pubic Hair. The analysis population included all male randomized participants who received ≥1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 29 | 1 | 2 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.3 (± 0.5) | 0.2 (± 0.4) | 0.0 (± 0.0) | 0.5 (± 0.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tanner Stage for Pubic Hair at Week 54 - Males

| | |
|-----------------|--|
| End point title | Change from Baseline in Tanner Stage for Pubic Hair at Week 54 - Males |
|-----------------|--|

End point description:

Participant's stage of sexual maturation was assessed using the Tanner staging measure for determining pubertal development in male participants. Tanner staging includes an assessment of pubic hair development with a score of range 1 to 5 where 1=no development and 5=adult pubic hair. This change from baseline was Week 54 Tanner Staging for Pubic Hair minus the Week 0 Tanner Staging for Pubic Hair. The analysis population included all male randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at both baseline and timepoint measurements.

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

End point timeframe:

Baseline and Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 23 | 0 ^[45] | 2 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.5 (\pm 0.7) | 0.6 (\pm 0.5) | () | 0.5 (\pm 0.7) |

Notes:

[45] - All participants in this arm were missing baseline or Week 54 measurements.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Worsening in Dental Status at Week 20

| | |
|-----------------|---|
| End point title | Percentage of Participants with Worsening in Dental Status at Week 20 |
|-----------------|---|

End point description:

Participants were evaluated with a visual oral exam; a subset had dental photographs. Teeth worsening included participants with worsening of tooth fracture, tooth discoloration, or enamel defect as determined by the independent reviewer. Worsening in these categories was a change in dental defect assessments made by comparing Week 20 dental assessments versus Baseline dental assessments. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Week 20

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|-----------------|-------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 88 | 85 | 8 | 5 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Participants with a dental assessment | 69.3 | 71.8 | 25.0 | 40.0 |
| 1. With ≥ 1 tooth with worsening in any category | 36.4 | 29.4 | 12.5 | 0 |
| 2. With ≥ 1 tooth with worsening fracture | 5.7 | 5.9 | 0 | 0 |

| | | | | |
|---|------|------|------|---|
| 3. With ≥ 1 tooth with worsening discoloration | 33.0 | 27.1 | 0 | 0 |
| 4. With ≥ 1 tooth with worsening enamel defect | 8.0 | 4.7 | 12.5 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Worsening in Dental Status at Week 54

| | |
|-----------------|---|
| End point title | Percentage of Participants with Worsening in Dental Status at Week 54 |
|-----------------|---|

End point description:

Participants were evaluated with a visual oral exam; a subset had dental photographs. Teeth worsening included participants with worsening of tooth fracture, tooth discoloration, or enamel defect as determined by the independent reviewer. Worsening in these categories was a change in dental defect assessments made by comparing Week 20 dental assessments versus Baseline dental assessments. The analysis population included all randomized participants who received ≥ 1 dose of study medication and had data for the analysis endpoint at timepoint measurements.

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

End point timeframe:

Week 54

| End point values | Sitagliptin | Placebo/Metformin | Metformin | Placebo/Sitagliptin |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79 | 78 | 8 | 5 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Participants with a dental assessment | 74.7 | 75.6 | 25.0 | 40.0 |
| 1. With ≥ 1 tooth with worsening in any category | 62.0 | 64.1 | 25.0 | 0 |
| 2. With ≥ 1 tooth with worsening fracture | 16.5 | 19.2 | 12.5 | 0 |
| 3. With ≥ 1 tooth with worsening discoloration | 57.0 | 61.5 | 25.0 | 0 |
| 4. With ≥ 1 with worsening enamel defect | 16.5 | 16.7 | 12.5 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: Up to approximately Week 56. Deaths and SAEs: Up to approximately 93 months.

Adverse event reporting additional description:

The analysis population consisted of all participants who received ≥ 1 dose of study medication and included all post-randomization follow-ups. One participant in the Sitagliptin treatment arm died after the treatment phases of the study at approximately 93 months.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Sitagliptin |
|-----------------------|-------------|

Reporting group description:

Participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Participants continued to receive 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54.

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo/Metformin |
|-----------------------|-------------------|

Reporting group description:

Participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54.

| | |
|-----------------------|-----------|
| Reporting group title | Metformin |
|-----------------------|-----------|

Reporting group description:

Participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Participants continued to receive 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Metformin treatment arm, but ongoing participants in this arm continued in this arm during Weeks 0-54.

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo/Sitagliptin |
|-----------------------|---------------------|

Reporting group description:

Participants received 1 tablet of placebo matching sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 0-20. Participants received 1 tablet of sitagliptin 100 mg prior to the morning meal and 2 tablets of placebo matching metformin 500 mg prior to both the morning and evening meals during Weeks 20-54. Amendment 5 of the protocol ended enrollment in the Placebo/Sitagliptin arm, but ongoing participants in this arm continued in this arm during Weeks 0-54.

| Serious adverse events | Sitagliptin | Placebo/Metformin | Metformin |
|---|------------------|-------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 95 (10.53%) | 7 / 90 (7.78%) | 1 / 9 (11.11%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|----------------|----------------|---------------|
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (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 |
| Leukaemia | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| Social circumstances | | | |
| Sexual abuse | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (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 |

| | | | | |
|--|---|----------------|----------------|----------------|
| Skin and subcutaneous tissue disorders Erythema nodosum | subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Psychiatric disorders Affect lability | subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 0 / 9 (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 Acute kidney injury | subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| | | | | |
| Nephrolithiasis | subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 0 / 9 (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 |
| | | | | |
| Infections and infestations Abscess soft tissue | subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (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 |
| | | | | |
| Appendicitis | subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 1 / 9 (11.11%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Dengue fever | subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| | | | | |
| Gastroenteritis viral | | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 0 / 90 (0.00%) | 0 / 9 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 1 / 90 (1.11%) | 0 / 9 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo/Sitagliptin | | |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |

| | | | |
|---|---------------|--|--|
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Social circumstances | | | |
| Sexual abuse | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema nodosum | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Affect lability | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess soft tissue | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---------------|--|--|
| Dehydration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Sitagliptin | Placebo/Metformin | Metformin |
|---|------------------|-------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 62 / 95 (65.26%) | 53 / 90 (58.89%) | 7 / 9 (77.78%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 95 (2.11%) | 2 / 90 (2.22%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 2 | 1 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 4 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 6 / 90 (6.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 2 / 95 (2.11%) | 1 / 90 (1.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Gynaecomastia | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hyperventilation subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 95 (2.11%) 2 | 2 / 90 (2.22%) 2 | 1 / 9 (11.11%) 1 |
| Respiratory disorder subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 95 (1.05%) 1 | 1 / 90 (1.11%) 1 | 0 / 9 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 95 (4.21%) 4 | 3 / 90 (3.33%) 3 | 0 / 9 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 95 (1.05%) 1 | 0 / 90 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Tooth fracture subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Cardiac disorders | | | |
| Wandering pacemaker subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 95 (3.16%) 5 | 2 / 90 (2.22%) 2 | 0 / 9 (0.00%) 0 |
| Headache | | | |

| | | | |
|--|---------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 9 / 95 (9.47%) 9 | 13 / 90 (14.44%) 16 | 2 / 9 (22.22%) 5 |
| Eye disorders | | | |
| Blepharitis | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye pain | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 95 (8.42%) | 7 / 90 (7.78%) | 1 / 9 (11.11%) |
| occurrences (all) | 10 | 10 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 95 (8.42%) | 11 / 90 (12.22%) | 2 / 9 (22.22%) |
| occurrences (all) | 9 | 14 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 2 / 90 (2.22%) | 1 / 9 (11.11%) |
| occurrences (all) | 6 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 5 / 95 (5.26%) | 4 / 90 (4.44%) | 1 / 9 (11.11%) |
| occurrences (all) | 5 | 5 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 95 (6.32%) | 7 / 90 (7.78%) | 0 / 9 (0.00%) |
| occurrences (all) | 9 | 8 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue | | | |

| | | | |
|-----------------------------------|------------------|------------------|----------------|
| disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 3 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 95 (1.05%) | 1 / 90 (1.11%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 1 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 95 (3.16%) | 7 / 90 (7.78%) | 1 / 9 (11.11%) |
| occurrences (all) | 4 | 10 | 1 |
| Influenza | | | |
| subjects affected / exposed | 2 / 95 (2.11%) | 6 / 90 (6.67%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 7 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 95 (15.79%) | 6 / 90 (6.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 19 | 6 | 0 |
| Pertussis | | | |
| subjects affected / exposed | 0 / 95 (0.00%) | 0 / 90 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 6 / 95 (6.32%) | 6 / 90 (6.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 7 | 6 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 95 (12.63%) | 12 / 90 (13.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 15 | 13 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 95 (4.21%) | 9 / 90 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 4 | 11 | 0 |
| Viral infection | | | |

| | | | |
|---|-------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 95 (0.00%) 0 | 0 / 90 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 16 / 95 (16.84%) 107 | 12 / 90 (13.33%) 37 | 3 / 9 (33.33%) 65 |

| | | | |
|---|---|--|--|
| Non-serious adverse events | Placebo/Sitagliptin | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 4 / 5 (80.00%) | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 | | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) Gynaecomastia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Hyperventilation subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Respiratory disorder | 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Tooth fracture subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Cardiac disorders Wandering pacemaker subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 4 | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Eye disorders Blepharitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Eye pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|--|--|
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |

| | | | |
|---|---|--|--|
| Infections and infestations Anal abscess subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pertussis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 1 / 5 (20.00%) 4 | | |
| Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 May 2013 | AM1 - Global amendment. Procedural and administrative changes. |
| 25 February 2014 | AM5 - Global amendment: Lengthened the Phase A placebo-controlled portion from 16 weeks to 20 weeks. Modified visit schedule to reduce the total number of visits from 13 to 11. Removed the metformin group and the placebo/sitagliptin group from the study. Based on revised power calculations, the sample size for the entire study was reduced from 360 participants to 170 participants – 2 treatment groups (sitagliptin or placebo) with 85 participants/group. Changed inclusion criterion of A1C from $\geq 7\%$ to $\geq 6.5\%$. Modified the timeframe for prior treatment with insulin from 6 months to 12 weeks. |
| 12 February 2015 | AM7 - Global amendment. Included participants on background insulin. |
| 01 December 2015 | AM9 - Global amendment. Changed “adverse experience” to “adverse event.” Complied with recommendations from the US FDA to minimize missing data. |
| 03 February 2017 | AM12 - Global amendment. Added the dental substudy. |
| 18 July 2018 | AM16 - Global amendment. Complied with the recommendations from a health authority. Increased sample size. Clarified statistical methods for analyses using the Treatment Effect estimand. Added analyses using the Treatment Policy estimand. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported