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)	EMEA-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 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		0 0 0 0 11 84 0 0 0 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	±	± 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 (± 61.86)	7.59 (± 41.11)	-19.88 (± 49.78)	57.67 (± 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 (± 48.55)	-4.52 (± 50.68)	-29.92 (± 53.19)	3.00 (± 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 (± 47.24)	-3.91 (± 22.31)	-7.25 (± 60.58)	-1.23 (± 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 (± 40.82)	-6.64 (± 32.01)	-20.50 (± 65.08)	-9.95 (± 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 (± 81.88)	-10.88 (± 55.12)	12.57 (± 36.98)	-1.33 (± 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 (± 67.54)	-16.13 (± 81.52)	-23.30 (± 42.36)	-0.50 (± 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 (± 0.22)	0.02 (± 0.16)	-0.03 (± 0.10)	-0.19 (± 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 × fasting insulin (in mcIU/mL) ÷ {[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 × fasting insulin (in mcIU/mL) ÷ {[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 (± 183.17)	-63.88 (± 339.74)	-1860.69 (± 4099.22)	-121.48 (± 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 mcIU/mL) × FPG (in mg/dL) / (22.5×18). 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 (± 31.62)	-0.86 (± 9.02)	-4.46 (± 34.65)	2.58 (± 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 mcIU/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: µIU*hr/mL				
arithmetic mean (standard deviation)	-14.5 (± 128.0)	-32.8 (± 99.9)	141.7 (± 206.1)	-145.6 (± 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: [µIU*hr/mL]/[mg/dL]				
arithmetic mean (standard deviation)	0.0 (± 0.3)	-0.1 (± 0.3)	0.2 (± 0.4)	-0.2 (± 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 (± 97.4)	10.8 (± 58.6)	39.8 (± 50.1)	46.2 (± 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: µIU*hr/mL				
arithmetic mean (standard deviation)	-12.4 (± 89.4)	-19.4 (± 93.6)	87.5 (± 124.5)	-82.8 (± 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: ng*hr/ml				
arithmetic mean (standard deviation)	-1.1 (± 3.1)	-0.4 (± 4.4)	4.1 (± 5.6)	-4.8 (± 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: [µIU*hr/mL]/[mg/dL]				
arithmetic mean (standard deviation)	2.2 (± 9.6)	7.2 (± 17.5)	-2.5 (± 3.2)	1.4 (± 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 (± 5.7)	-6.1 (± 8.2)	1.7 (± 1.0)	-8.9 (± 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: [µIU*hr/mL]/[mg/dL]				
arithmetic mean (standard deviation)	-0.1 (± 0.5)	-0.6 (± 0.8)	-0.0 (± 0.2)	-0.3 (± 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 (± 100.7)	-50.1 (± 79.5)	-49.0 (± 87.5)	-74.0 (± 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: µIU*hr/mL				
arithmetic mean (standard deviation)	-103.8 (± 151.0)	-198.5 (± 263.0)	-40.2 (± 11.5)	-116.6 (± 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: ng*hr/ml				
arithmetic mean (standard deviation)	-1.8 (± 3.0)	-5.2 (± 8.8)	0.9 (± 0.5)	-5.9 (± 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: [µIU*hr/mL]/[mg/dL]				
arithmetic mean (standard deviation)	4.1 (± 13.1)	3.7 (± 5.6)	-2.7 (± 4.3)	1.4 (± 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 (± 2.2)	-0.7 (± 1.9)	-0.8 (± 1.4)	-1.7 (± 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 (± 2.9)	-1.0 (± 2.9)	-0.6 (± 1.3)	-0.3 (± 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 (± 0.5)	-2.0 (± 11.7)	0.0 (± 0.0)	0.0 (± 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 (± 0.6)	-1.9 (± 12.1)	0.0 (± 0.0)	0.3 (± 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 (± 1.4)	-0.2 (± 0.6)	-1.6 (± 2.2)	0.5 (± 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 (± 1.1)	-0.3 (± 0.9)	0.0 (± 0.0)	1.4 (± 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 = ([u-NTx/Creatinine ratio at Week 20] - [baseline u-NTx/Creatinine ratio] ÷ baseline u-NTx/Creatinine ratio) × 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 (± 120.9)	-41.2 (± 148.9)	-98.0 (± 153.0)	12.7 (± 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 = ([u-NTx/Creatinine ratio at Week 54] - [baseline u-NTx/Creatinine ratio] ÷ baseline u-NTx/Creatinine ratio) × 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-NTx/Creatinine ratio at Week 54] - [baseline u-NTx/Creatinine ratio] ÷ baseline u-NTx/Creatinine ratio) × 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-NTx/Creatinine ratio at Week 20] - [baseline u-NTx/Creatinine ratio] ÷ baseline u-NTx/Creatinine ratio) × 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: µg/L				
arithmetic mean (standard deviation)	-20.0 (± 28.4)	-13.5 (± 18.1)	-14.9 (± 10.3)	-6.9 (± 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: µg/L				
arithmetic mean (standard deviation)	-2.2 (± 21.6)	0.1 (± 19.9)	-7.1 (± 0.2)	4.7 (± 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: µg/L				
arithmetic mean (standard deviation)	-16.2 (± 28.0)	-15.0 (± 27.0)	-1.3 (± 0.0)	-15.3 (± 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 = ([IGF-1 value at Week 20] - [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 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 (± 21.9)	11.0 (± 34.0)	-3.2 (± 14.9)	41.4 (± 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 (± 1.9)	0.4 (± 1.8)	1.7 (± 2.3)	-0.8 (± 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 (± 1.1)	1.0 (± 0.6)	1.3 (± 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 (± 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 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 (± 0.6)	0.6 (± 0.7)	()	0.5 (± 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 (± 0.6)	0.1 (± 0.3)	0.2 (± 0.4)	0.3 (± 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 Public Hair at Week 20 - Females

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

End point title	Change from Baseline in Tanner Stage for Public 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 (± 0.7)	0.6 (± 0.5)	()	0.5 (± 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	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 95 (2.11%)	2 / 90 (2.22%)	1 / 9 (11.11%)
occurrences (all)	2	2	1
Respiratory disorder			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 95 (1.05%)	1 / 90 (1.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 95 (4.21%)	3 / 90 (3.33%)	0 / 9 (0.00%)
occurrences (all)	4	3	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 95 (1.05%)	0 / 90 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Tooth fracture			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Cardiac disorders			
Wandering pacemaker			
subjects affected / exposed	0 / 95 (0.00%)	0 / 90 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 95 (3.16%)	2 / 90 (2.22%)	0 / 9 (0.00%)
occurrences (all)	5	2	0
Headache			

subjects affected / exposed	9 / 95 (9.47%)	13 / 90 (14.44%)	2 / 9 (22.22%)
occurrences (all)	9	16	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	0 / 95 (0.00%)	0 / 90 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	16 / 95 (16.84%)	12 / 90 (13.33%)	3 / 9 (33.33%)
occurrences (all)	107	37	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	0 / 5 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gynaecomastia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory disorder			

subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 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) Tooth fracture subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 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) Headache subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 4 1 / 5 (20.00%) 1		
Eye disorders Blepharitis subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 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	0 / 5 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pertussis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	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 ≥7% to ≥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