



Clinical trial results:

A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin).

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-003583-20 |
| Trial protocol | DE GB |
| Global end of trial date | 17 September 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 25 March 2020 |
| First version publication date | 25 March 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------------------------|
| Sponsor protocol code | 0431A-170 and 0431A-289 |
|-----------------------|-------------------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01472367 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | EudraCT Number: 2012-004035-23, NCT Number: NCT01760447, EudraCT Number: 2011-002529-23 |

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) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 September 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to the addition of placebo on glycated hemoglobin (A1C), and the safety and tolerability of the addition of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

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 individual study was in place for the protection of trial subjects: Insulin as glycemic rescue therapy. In protocol MK-0431A-170, the type of insulin used as glycemic rescue therapy was at the investigator's discretion during Weeks 0-20, but only insulin glargine was used as glycemic rescue therapy during Weeks 20-54. In protocol MK-0431A-289, only insulin glargine was used as glycemic rescue therapy throughout Weeks 0-54.

Background therapy:

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

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 07 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | Brazil: 1 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Chile: 4 |
| Country: Number of subjects enrolled | Colombia: 2 |
| Country: Number of subjects enrolled | Costa Rica: 4 |
| Country: Number of subjects enrolled | Dominican Republic: 10 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Guatemala: 8 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Italy: 4 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Malaysia: 22 |
| Country: Number of subjects enrolled | Mauritius: 6 |
| Country: Number of subjects enrolled | Mexico: 30 |
| Country: Number of subjects enrolled | Philippines: 4 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Saudi Arabia: 6 |
| Country: Number of subjects enrolled | South Africa: 1 |
| Country: Number of subjects enrolled | Sri Lanka: 23 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Thailand: 4 |
| Country: Number of subjects enrolled | Ukraine: 8 |
| Country: Number of subjects enrolled | United Arab Emirates: 4 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | United States: 31 |
| Worldwide total number of subjects | 223 |
| EEA total number of subjects | 16 |

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) | 21 |
| Adolescents (12-17 years) | 202 |
| 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 28 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 metformin with sitagliptin/metformin placebo or metformin XR with sitagliptin/metformin XR placebo each day.

Period 1

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

Arms

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

Arm description:

Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1700mg or 2000 mg of metformin. Dosage of metformin was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to metformin.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

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

Arm description:

Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 1000 mg, 1700 mg or 2000 mg of metformin. Dosage was based on each participant's daily metformin dose prior to enrollment.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Placebo to sitagliptin plus metformin |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to sitagliptin plus metformin.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| | |
|------------------|--------------------------|
| Arm title | Sitagliptin/Metformin XR |
|------------------|--------------------------|

Arm description:

Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1500mg or 2000 mg of metformin. Dosage of metformin XR was based on each participant's daily metformin dose prior to enrollment.

| | |
|--|-------------------------|
| Investigational medicinal product name | Placebo to metformin XR |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to metformin XR.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

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

Arm description:

Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to sitagliptin plus metformin XR |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A XR |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to sitagliptin plus metformin XR.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 1000 mg, 1500 mg or 2000 mg of metformin XR. Dosage was based on each participant's daily metformin dose prior to enrollment.

| Number of subjects in period 1 | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR |
|---------------------------------------|-----------------------|-----------|--------------------------|
| Started | 63 | 62 | 47 |
| Completed | 62 | 62 | 45 |
| Not completed | 1 | 0 | 2 |
| Randomized but not treated | 1 | - | 2 |

| Number of subjects in period 1 | Metformin XR |
|---------------------------------------|--------------|
| Started | 51 |

| | |
|----------------------------|----|
| Completed | 51 |
| 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/Metformin |

Arm description:

Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1700mg or 2000 mg of metformin. Dosage of metformin was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to metformin.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

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

Arm description:

Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 1000 mg, 1700 mg or 2000 mg of metformin. Dosage was based on each participant's daily metformin dose prior to enrollment.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Placebo to sitagliptin plus metformin |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to sitagliptin plus metformin.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| | |
|------------------|--------------------------|
| Arm title | Sitagliptin/Metformin XR |
|------------------|--------------------------|

Arm description:

Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1500mg or 2000 mg of metformin. Dosage of metformin XR was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| | |
|--|-------------------------|
| Investigational medicinal product name | Placebo to metformin XR |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to metformin XR.

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

Arm description:

Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to sitagliptin plus metformin XR |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A XR |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to sitagliptin plus metformin XR.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 1000 mg, 1500 mg or 2000 mg of metformin XR. Dosage was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

Notes:

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

Justification: Period 1 includes all participants randomized. Period 2 includes all participants who were both randomized and treated with study medication, which is the population used for baseline characteristics.

| Number of subjects in period 2^[2] | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR |
|---|-----------------------|-----------|--------------------------|
| Started | 62 | 62 | 45 |
| Treated | 62 | 62 | 45 |
| Completed | 59 | 62 | 42 |
| Not completed | 3 | 0 | 3 |
| Consent withdrawn by subject | 2 | - | 1 |
| Lost to follow-up | 1 | - | 1 |

| | | | |
|--------------------------------------|---|---|---|
| Consent withdrawn by Parent/Guardian | - | - | 1 |
|--------------------------------------|---|---|---|

| Number of subjects in period 2 ^[2] | Metformin XR |
|---|--------------|
| Started | 51 |
| Treated | 51 |
| Completed | 47 |
| Not completed | 4 |
| Consent withdrawn by subject | - |
| Lost to follow-up | 1 |
| Consent withdrawn by Parent/Guardian | 3 |

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: The baseline period used all participants both randomized and treated with study medication rather than all participants randomized, which was used as the worldwide total.

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/Metformin |

Arm description:

Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1700mg or 2000 mg of metformin. Dosage of metformin was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to metformin.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

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

Arm description:

Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal, to provide a total daily dose of 1000 mg, 1700 mg or 2000 mg of metformin. Dosage was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Placebo to sitagliptin plus metformin |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, one taken with a morning meal and one taken with an evening meal. Each tablet contained placebo to sitagliptin plus metformin.

| | |
|------------------|--------------------------|
| Arm title | Sitagliptin/Metformin XR |
|------------------|--------------------------|

Arm description:

Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-289.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 100 mg of sitagliptin and 1000mg, 1500mg or 2000 mg of metformin. Dosage of metformin XR was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| | |
|--|-------------------------|
| Investigational medicinal product name | Placebo to metformin XR |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to metformin XR.

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

Arm description:

Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-289.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to sitagliptin plus metformin XR |
| Investigational medicinal product code | |
| Other name | Placebo to MK-0431A XR |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal. Each tablet contained placebo to sitagliptin plus metformin XR.

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

Dosage and administration details:

Participants received 2 tablets daily, both taken together with a meal, to provide a total daily dose of 1000 mg, 1500 mg or 2000 mg of metformin XR. Dosage was based on each participant's daily metformin dose prior to enrollment.

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

Dosage and administration details:

Participants who met protocol-specific glycemic rescue criteria received insulin glargine as glycemic rescue therapy; participants on background insulin had their insulin dose increased for glycemic rescue.

| Number of subjects in period 3^[3] | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR |
|---|-----------------------|-----------|--------------------------|
| Started | 28 | 30 | 42 |
| Completed | 25 | 28 | 39 |
| Not completed | 3 | 2 | 3 |
| Consent withdrawn by subject | 2 | 1 | 1 |
| Lost to follow-up | - | - | 1 |
| Consent withdrawn by Parent/Guardian | 1 | 1 | 1 |

| Number of subjects in period 3^[3] | Metformin XR |
|---|--------------|
| Started | 47 |
| Completed | 43 |
| Not completed | 4 |
| Consent withdrawn by subject | 2 |
| Lost to follow-up | 2 |
| Consent withdrawn by Parent/Guardian | - |

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants who completed the Weeks 0-20 Period continued in the Weeks 20-54 Period. In protocol MK-0431A-170, participants were required to re-consent to enter the Weeks 20-54 period, and many did not do so.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Sitagliptin/Metformin |
|-----------------------|-----------------------|

Reporting group description:

Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

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

Reporting group description:

Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170.

| | |
|-----------------------|--------------------------|
| Reporting group title | Sitagliptin/Metformin XR |
|-----------------------|--------------------------|

Reporting group description:

Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

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

Reporting group description:

Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289.

| Reporting group values | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR |
|--|-----------------------|-----------|--------------------------|
| Number of subjects | 62 | 62 | 45 |
| 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) | 10 | 7 | 3 |
| Adolescents (12-17 years) | 52 | 55 | 42 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 14.4 | 13.9 | 14.8 |
| standard deviation | ± 2.2 | ± 1.8 | ± 1.9 |
| Gender Categorical Units: Subjects | | | |
| Female | 41 | 40 | 32 |
| Male | 21 | 22 | 13 |
| Race Units: Subjects | | | |
| American Indian Or Alaska Native | 0 | 1 | 3 |
| Asian | 21 | 22 | 15 |

| | | | |
|---|--------|--------|--------|
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 |
| Black or African American | 2 | 2 | 2 |
| White | 24 | 23 | 22 |
| More than one race | 14 | 13 | 3 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 23 | 23 | 11 |
| Not Hispanic or Latino | 35 | 36 | 29 |
| Unknown or Not Reported | 4 | 3 | 5 |
| 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 | 8.13 | 7.87 |
| standard deviation | ± 1.22 | ± 1.08 | ± 0.94 |

| Reporting group values | Metformin XR | Total | |
|--|--------------|-------|--|
| Number of subjects | 51 | 220 | |
| 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) | 1 | 21 | |
| Adolescents (12-17 years) | 50 | 199 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 14.9 | | |
| standard deviation | ± 1.6 | - | |
| Gender Categorical Units: Subjects | | | |
| Female | 32 | 145 | |
| Male | 19 | 75 | |
| Race Units: Subjects | | | |
| American Indian Or Alaska Native | 9 | 13 | |
| Asian | 6 | 64 | |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | |
| Black or African American | 4 | 10 | |
| White | 27 | 96 | |
| More than one race | 5 | 35 | |
| Ethnicity Units: Subjects | | | |

| | | | |
|---|--------|-----|--|
| Hispanic or Latino | 20 | 77 | |
| Not Hispanic or Latino | 28 | 128 | |
| Unknown or Not Reported | 3 | 15 | |
| 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 | 7.97 | | |
| standard deviation | ± 1.05 | - | |

Subject analysis sets

| | |
|----------------------------|---|
| Subject analysis set title | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This analysis set contains the pooled population of treated participants from the experimental-drug groups "Sitagliptin/Metformin" (from protocol MK-0431A-170) and "Sitagliptin/Metformin XR" (from protocol MK-0431A-289).

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Metformin and Metformin XR Pooled |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This analysis set contains the pooled population of treated participants from the placebo groups "Metformin" (from protocol MK-0431A-170) and "Metformin XR" (from protocol MK-0431A-289).

| Reporting group values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | |
|--|---|-----------------------------------|--|
| Number of subjects | 107 | 113 | |
| 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) | 13 | 8 | |
| Adolescents (12-17 years) | 94 | 105 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 14.5 | 14.4 | |
| standard deviation | ± 2.1 | ± 1.8 | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 73 | 72 | |
| Male | 34 | 41 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian Or Alaska Native | 3 | 10 | |

| | | | |
|---|--------|--------|--|
| Asian | 36 | 28 | |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | |
| Black or African American | 4 | 6 | |
| White | 46 | 50 | |
| More than one race | 17 | 18 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 34 | 43 | |
| Not Hispanic or Latino | 64 | 64 | |
| Unknown or Not Reported | 9 | 6 | |
| 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 | 7.96 | 8.06 | |
| standard deviation | ± 1.11 | ± 1.07 | |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Sitagliptin/Metformin |
| Reporting group description: Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Metformin |
| Reporting group description: Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Sitagliptin/Metformin XR |
| Reporting group description: Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289. | |
| Reporting group title | Metformin XR |
| Reporting group description: Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289. | |
| Reporting group title | Sitagliptin/Metformin |
| Reporting group description: Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Metformin |
| Reporting group description: Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Sitagliptin/Metformin XR |
| Reporting group description: Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289. | |
| Reporting group title | Metformin XR |
| Reporting group description: Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 0-20. Participants in this arm were enrolled in protocol MK-0431A-289. | |
| Reporting group title | Sitagliptin/Metformin |
| Reporting group description: Participants received one tablet of sitagliptin/metformin and one tablet of metformin-placebo, administered twice daily prior to the morning and evening meals, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Metformin |
| Reporting group description: Participants received one tablet of metformin and one tablet of placebo to sitagliptin/metformin, administered twice daily prior to the morning and evening meals, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-170. | |
| Reporting group title | Sitagliptin/Metformin XR |
| Reporting group description: Participants received two tablets of sitagliptin/metformin XR and two tablets of metformin XR placebo, administered once daily with a meal, during Weeks 20-54. Participants in this arm were enrolled in | |

protocol MK-0431A-289.

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

Reporting group description:

Participants received two tablets of metformin XR and two tablets of placebo to sitagliptin/metformin XR, administered once daily with a meal, during Weeks 20-54. Participants in this arm were enrolled in protocol MK-0431A-289.

| | |
|----------------------------|---|
| Subject analysis set title | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled |
|----------------------------|---|

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

Subject analysis set description:

This analysis set contains the pooled population of treated participants from the experimental-drug groups "Sitagliptin/Metformin" (from protocol MK-0431A-170) and "Sitagliptin/Metformin XR" (from protocol MK-0431A-289).

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Metformin and Metformin XR Pooled |
|----------------------------|-----------------------------------|

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

Subject analysis set description:

This analysis set contains the pooled population of treated participants from the placebo groups "Metformin" (from protocol MK-0431A-170) and "Metformin XR" (from protocol MK-0431A-289).

Primary: Change from Baseline in A1C at Week 20

| | |
|-----------------|--|
| End point title | Change from Baseline in A1C at Week 20 |
|-----------------|--|

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. Mean change from baseline at Week 20 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 of A1C. Per protocol, only the pooled analysis groups were analyzed for this primary endpoint.

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

End point timeframe:

Baseline and Week 20

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|--|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Percentage | | | | |
| Least squares mean (confidence interval 95%) | | | | |
| Change from Baseline at Week 20 | -0.58 (-0.94 to -0.22) | -0.09 (-0.43 to 0.26) | | |

Statistical analyses

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

Statistical analysis description:

The Least Squares (LS) Mean for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled."

| | |
|-------------------|---|
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
|-------------------|---|

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | -0.09 |

Primary: Number of participants who experienced ≥ 1 Adverse Event During Weeks 0-20

| | |
|---|---|
| End point title | Number of participants who experienced ≥ 1 Adverse Event During Weeks 0-20 |
| End point description: | |
| The number of participants experiencing ≥ 1 adverse event during Weeks 0-20 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 20 | |

| End point values | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR | Metformin XR |
|-----------------------------|-----------------------|-----------------|--------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 62 | 45 | 51 |
| Units: Participants | 42 | 46 | 29 | 30 |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Participants | 71 | 76 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in Percentage |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Difference in Percentage |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.9 |
| upper limit | 11.3 |

Notes:

[1] - The percentage of participants who experienced ≥ 1 adverse event for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled."

Primary: Number of Participants Who Discontinued Study Drug Due to Experiencing an Adverse Event During Weeks 0-20

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Drug Due to Experiencing an Adverse Event During Weeks 0-20 |
|-----------------|---|

End point description:

The number of participants who discontinued from study drug due to an adverse event during Weeks 0-20 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 20

| End point values | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR | Metformin XR |
|-----------------------------|-----------------------|-----------------|--------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 62 | 45 | 51 |
| Units: Participants | 1 | 2 | 2 | 2 |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Participants | 3 | 4 | | |

Statistical analyses

| Statistical analysis title | Difference in Percentage |
|---|---|
| Statistical analysis description: The percentage of participants who discontinued study drug due to experiencing an adverse event for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.2 |
| upper limit | 5 |

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 |
| End point description: The number of participants experiencing ≥1 adverse event during Weeks 0-56 were 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 and continued in the study beyond Week 20. | |
| End point type | Primary |
| End point timeframe: Up to approximately Week 56 | |

| End point values | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR | Metformin XR |
|-----------------------------|-----------------------|-----------------|--------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 | 30 | 42 | 47 |
| Units: Participants | 26 | 27 | 36 | 39 |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: Participants | 62 | 66 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in Percentage |
| Statistical analysis description: The percentage of participants who experienced ≥ 1 adverse event for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.9 |
| upper limit | 14.4 |

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

| | |
|--|---|
| End point title | Number of Participants Who Discontinued Study Drug Due to Experiencing an Adverse Event During Weeks 0-54 |
| 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 and continued in the study beyond Week 20. | |
| End point type | Primary |
| End point timeframe: Up to Week 54 | |

| End point values | Sitagliptin/Metformin | Metformin | Sitagliptin/Metformin XR | Metformin XR |
|-----------------------------|-----------------------|-----------------|--------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 28 | 30 | 42 | 47 |
| Units: Participants | 1 | 1 | 1 | 3 |

| | | | | |
|-----------------------------|---|-----------------------------------|--|--|
| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: Participants | 2 | 4 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Difference in Percentage |
| Statistical analysis description: | |
| The percentage of participants who discontinued study drug due to experiencing an adverse event for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.1 |
| upper limit | 5.8 |

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. Mean change from baseline at Week 54 was estimated from a longitudinal data analysis model. The analysis population includes all randomized participants who received ≥1 dose of study medication, had at least 1 measurement of A1C, and continued in the study beyond Week 20. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|--|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: Percentage | | | | |
| least squares mean (confidence interval 95%) | 0.35 (-0.48 to 1.19) | 0.73 (-0.08 to 1.54) | | |

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. Mean change from baseline at Week 20 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 of FPG. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 20 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|--|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | -2.5 (-16.7 to 11.7) | 8.3 (-5.0 to 21.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in Change from Baseline |
| Statistical analysis description: The Least Squares (LS) Mean for the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.159 |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -10.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.9 |
| upper limit | 4.3 |

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. Mean change from baseline at Week 54 was estimated from a longitudinal data analysis model. The analysis population includes all randomized participants who received ≥ 1 dose of study medication, had at least 1 measurement of FPG, and continued in the study beyond Week 20. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 54 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|--|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | 16.8 (-8.4 to 42.0) | 16.9 (-7.0 to 40.8) | | |

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: | |
| Percentage of participants with A1C at goal (<7.0%) at Week 20 was presented. The analysis population includes all randomized participants who received ≥ 1 dose of study medication. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |

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

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Percentage | | | | |
| number (not applicable) | 43.0 | 31.0 | | |

Statistical analyses

| Statistical analysis title | Difference in Percentage |
|--|---|
| Statistical analysis description: | |
| The percentage of participants with A1C at the A1C goal (<7.0%) in the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." For estimating the treatment difference, when the A1C result for a participant at Week 20 was not available, a multiple imputation method was used to impute whether the participant had met the goal. | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 28.9 |

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: | |
| Percentage of participants with A1C at goal (<6.5%) at Week 20 was presented. The analysis population includes all randomized participants who received ≥1 dose of study medication. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 20 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Percentage | | | | |
| number (not applicable) | 29.0 | 20.4 | | |

Statistical analyses

| Statistical analysis title | Difference in Percentage |
|--|---|
| Statistical analysis description: | |
| The percentage of participants with A1C at the A1C goal (<6.5%) in the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled." For estimating the treatment difference, when the A1C result for a participant at Week 20 was not available, a multiple imputation method was used to impute whether the participant had met the goal. | |
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 |
| Method | Miettinen and Nurminen |
| Parameter estimate | Difference in Percentage |
| Point estimate | 12.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 24.8 |

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: | |
| Percentage of participants with A1C at goal (<7.0%) at Week 54 was presented. The analysis population includes all randomized participants who received ≥1 dose of study medication and continued in the study beyond Week 20. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 54 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: Percentage | | | | |
| number (not applicable) | 31.4 | 27.3 | | |

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: Percentage of participants with A1C at goal (<6.5%) at Week 54 was presented. The analysis population includes all randomized participants who received ≥ 1 dose of study medication and continued in the study beyond Week 20. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: Week 54 | |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 77 | | |
| Units: Percentage | | | | |
| number (not applicable) | 18.6 | 19.5 | | |

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:

Percentage of participants who initiated glycemic rescue therapy prior to Week 20 was reported. The analysis population includes 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/Metformin | Metformin | Sitagliptin/Metformin XR | Metformin XR |
|-----------------------------|-----------------------|-----------------|--------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 62 | 45 | 51 |
| Units: Percentage | | | | |
| number (not applicable) | 3.2 | 19.4 | 4.4 | 13.7 |

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 107 | 113 | | |
| Units: Percentage | | | | |
| number (not applicable) | 3.7 | 16.8 | | |

Statistical analyses

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

Statistical analysis description:

The percentage of participants initiating glycemic rescue therapy in the arm "Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled" is compared against that of "Metformin and Metformin XR Pooled."

| | |
|---|---|
| Comparison groups | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled v Metformin and Metformin XR Pooled |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Log-Rank Test |
| Parameter estimate | Kaplan-Meier Difference in Percentage |
| Point estimate | -13.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.1 |
| upper limit | -5.3 |

Secondary: Percentage of Participants Initiating Insulin Glargine During Weeks 20-54

| | |
|-----------------|---|
| End point title | Percentage of Participants Initiating Insulin Glargine During Weeks 20-54 |
|-----------------|---|

End point description:

Percentage of participants who initiated insulin glargine therapy from Weeks 20 through 54 was reported. The analysis population includes all randomized participants who received ≥ 1 dose of study medication and continued in the study beyond Week 20 without initiating glycemic rescue therapy before Week 20. Per protocol, only the pooled analysis groups were analyzed for this secondary endpoint.

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

End point timeframe:

Week 20 up to Week 54

| End point values | Sitagliptin/Metformin and Sitagliptin/Metformin XR Pooled | Metformin and Metformin XR Pooled | | |
|-----------------------------|---|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 66 | 64 | | |
| Units: Percentage | | | | |
| number (not applicable) | 22.7 | 26.6 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 56 weeks for non serious adverse events. Up to approximately 8 years for serious adverse events and deaths.

Adverse event reporting additional description:

"Pooled Sita/Met FDC" = "Sita/Met IR FDC" plus "Sita/Met XR FDC." "Pooled Metformin" = "Metformin IR" plus "Metformin XR."

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Sita/Met IR FDC |
|-----------------------|-----------------|

Reporting group description: -

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

Reporting group description: -

| | |
|-----------------------|-----------------|
| Reporting group title | Sita/Met XR FDC |
|-----------------------|-----------------|

Reporting group description: -

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

Reporting group description: -

| | |
|-----------------------|---------------------|
| Reporting group title | Pooled Sita/Met FDC |
|-----------------------|---------------------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events | Sita/Met IR FDC | Metformin IR | Sita/Met XR FDC |
|---|-----------------|----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 3 / 62 (4.84%) | 3 / 45 (6.67%) |
| 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 | 0 / 62 (0.00%) | 1 / 62 (1.61%) | 0 / 45 (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 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 62 (1.61%) | 0 / 45 (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 |

| | | | |
|--|----------------|----------------|----------------|
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Immune system disorders | | | |
| Type I hypersensitivity | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 62 (0.00%) | 0 / 45 (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 | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 62 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 62 (0.00%) | 0 / 45 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 62 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 62 (1.61%) | 0 / 45 (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 |

| Serious adverse events | Metformin XR | Pooled Sita/Met FDC | Pooled Metformin |
|---|----------------|---------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 7 / 107 (6.54%) | 6 / 113 (5.31%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood glucose increased | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Type I hypersensitivity | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (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 | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (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 |
| H1N1 influenza | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 107 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 107 (0.93%) | 0 / 113 (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 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 107 (0.00%) | 2 / 113 (1.77%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Sita/Met IR FDC | Metformin IR | Sita/Met XR FDC |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 62 (54.84%) | 40 / 62 (64.52%) | 30 / 45 (66.67%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 62 (4.84%) | 3 / 45 (6.67%) |
| occurrences (all) | 3 | 3 | 3 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 1 / 62 (1.61%) | 3 / 45 (6.67%) |
| occurrences (all) | 3 | 1 | 3 |
| Blood glucose increased | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 0 / 62 (0.00%) | 2 / 45 (4.44%) |
| occurrences (all) | 4 | 0 | 2 |
| Creatinine renal clearance increased | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 0 / 62 (0.00%) | 0 / 45 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Urine albumin/creatinine ratio increased | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 2 / 62 (3.23%) | 0 / 45 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 8 / 62 (12.90%) | 2 / 45 (4.44%) |
| occurrences (all) | 4 | 10 | 4 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 4 / 62 (6.45%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 4 | 4 |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 62 (1.61%) | 2 / 62 (3.23%) | 0 / 45 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 62 (11.29%) | 4 / 62 (6.45%) | 1 / 45 (2.22%) |
| occurrences (all) | 8 | 4 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 5 / 62 (8.06%) | 4 / 45 (8.89%) |
| occurrences (all) | 5 | 5 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 3 / 62 (4.84%) | 3 / 45 (6.67%) |
| occurrences (all) | 2 | 4 | 3 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 1 / 62 (1.61%) | 3 / 45 (6.67%) |
| occurrences (all) | 2 | 1 | 3 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 3 / 62 (4.84%) | 3 / 45 (6.67%) |
| occurrences (all) | 6 | 3 | 3 |
| Influenza | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 4 / 62 (6.45%) | 2 / 45 (4.44%) |
| occurrences (all) | 1 | 5 | 3 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 62 (11.29%) | 7 / 62 (11.29%) | 1 / 45 (2.22%) |
| occurrences (all) | 11 | 7 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 3 / 62 (4.84%) | 1 / 45 (2.22%) |
| occurrences (all) | 1 | 3 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 62 (14.52%) | 6 / 62 (9.68%) | 5 / 45 (11.11%) |
| occurrences (all) | 11 | 8 | 9 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 5 / 62 (8.06%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 6 | 3 |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|------------------|----------------|-----------------|
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 5 / 62 (8.06%) | 3 / 45 (6.67%) |
| occurrences (all) | 3 | 6 | 3 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 10 / 62 (16.13%) | 6 / 62 (9.68%) | 9 / 45 (20.00%) |
| occurrences (all) | 106 | 15 | 70 |

| Non-serious adverse events | Metformin XR | Pooled Sita/Met FDC | Pooled Metformin |
|---|------------------|---------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 51 (70.59%) | 64 / 107 (59.81%) | 76 / 113 (67.26%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 5 / 107 (4.67%) | 6 / 113 (5.31%) |
| occurrences (all) | 3 | 6 | 6 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 6 / 107 (5.61%) | 2 / 113 (1.77%) |
| occurrences (all) | 1 | 6 | 2 |
| Blood glucose increased | | | |
| subjects affected / exposed | 3 / 51 (5.88%) | 5 / 107 (4.67%) | 3 / 113 (2.65%) |
| occurrences (all) | 5 | 6 | 5 |
| Creatinine renal clearance increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 4 / 107 (3.74%) | 0 / 113 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Urine albumin/creatinine ratio increased | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 4 / 107 (3.74%) | 2 / 113 (1.77%) |
| occurrences (all) | 0 | 5 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | 5 / 107 (4.67%) | 18 / 113 (15.93%) |
| occurrences (all) | 15 | 8 | 25 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 6 / 107 (5.61%) | 8 / 113 (7.08%) |
| occurrences (all) | 4 | 6 | 8 |
| Abdominal pain upper | | | |

| | | | |
|--|----------------------|-------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 4 | 1 / 107 (0.93%) 2 | 5 / 113 (4.42%) 6 |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 10 | 8 / 107 (7.48%) 9 | 7 / 113 (6.19%) 14 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 3 | 6 / 107 (5.61%) 11 | 7 / 113 (6.19%) 8 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 5 / 107 (4.67%) 5 | 5 / 113 (4.42%) 6 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 6 | 5 / 107 (4.67%) 5 | 2 / 113 (1.77%) 7 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 2 | 8 / 107 (7.48%) 9 | 5 / 113 (4.42%) 5 |
| Influenza subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 5 | 3 / 107 (2.80%) 4 | 7 / 113 (6.19%) 10 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 51 (3.92%) 3 | 8 / 107 (7.48%) 13 | 9 / 113 (7.96%) 10 |
| Pharyngitis subjects affected / exposed occurrences (all) | 5 / 51 (9.80%) 6 | 2 / 107 (1.87%) 2 | 8 / 113 (7.08%) 9 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 51 (5.88%) 5 | 14 / 107 (13.08%) 20 | 9 / 113 (7.96%) 13 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 51 (1.96%) 1 | 3 / 107 (2.80%) 3 | 6 / 113 (5.31%) 7 |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|------------------|-------------------|-------------------|
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 51 (7.84%) | 6 / 107 (5.61%) | 9 / 113 (7.96%) |
| occurrences (all) | 4 | 6 | 10 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 10 / 51 (19.61%) | 19 / 107 (17.76%) | 16 / 113 (14.16%) |
| occurrences (all) | 45 | 176 | 60 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 21 September 2012 | MK-0431A-170 AM01 (Base study): Incorporated procedural and administrative changes. |
| 17 April 2014 | MK-0431A-170 AM02 (Base study): Updated analyses to reflect the pooled analysis. Reduced the sample size from 240 to 90 participants and analysis was combined with study MK-0431A-289 with adequate power for the primary analysis at Week 20. The timeframe required for participants to be off insulin therapy before Visit 1 was reduced from 6 months to 12 weeks. A1C lower limit for inclusion changed from $\geq 7.0\%$ to $\geq 6.5\%$. |
| 17 April 2014 | MK-0431A-170 AM03 (Extension study): Created the 34-week extension study. |
| 17 April 2014 | MK-0431A-289 AM04: Modified the timeframe for prior treatment with insulin from 6 months to 12 weeks. A1C lower limit for inclusion changed from $\geq 7\%$ to $\geq 6.5\%$. Sample size was reduced from 240 to 90 participants and analysis was combined with study MK-0431A-170 with adequate power for the primary analysis at Week 20. |
| 09 January 2015 | MK-0431A-170 AM04 (Base study): Included participants on background insulin. |
| 09 January 2015 | MK-0431A-170 AM05 (Extension study): Included participants on background insulin. |
| 20 January 2015 | MK-0431A-289 AM05: Included participants on background insulin. |
| 10 April 2015 | MK-0431A-170 AM07 (Base study): Changed "adverse experience" to "adverse event." |
| 10 April 2015 | MK-0431A-170 AM08 (Extension study): Changed "adverse experience" to "adverse event." |
| 09 September 2015 | MK-0431A-289 AM07: Changed "adverse experience" to "adverse event." Complied with recommendations from the FDA to minimize missing data. |
| 04 November 2015 | MK-0431A-170 AM11 (Base study): Complied with recommendations from the FDA to minimize missing data. Updated sample size from approximately 90 participants to approximately 130 participants. |
| 04 November 2015 | MK-0431A-170 AM12 (Extension study): Complied with recommendations from the FDA to minimize missing data. Updated sample size from approximately 90 participants to approximately 130 participants. |
| 12 April 2018 | MK-0431A-289 AM10: 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. |
| 12 April 2018 | MK-0431A-170 AM15 (Base study): Modified sample size. Beginning and end of study were defined. Clarified statistical methods for analyses using the Treatment Effect estimand. Added analyses using the Treatment Policy estimand. |
| 12 April 2018 | MK-0431A-170 AM16 (Extension study): Modified sample size. Beginning and end of study were defined. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported