



Clinical trial results:

A Study to Assess the Pharmacokinetics and the Ability for Pediatric Patients with Type 2 Diabetes to Swallow MK-0431A XR Tablets

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-003731-22 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 29 April 2014 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 04 October 2020 |
| First version publication date | 04 October 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 0431A-296 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01557504 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck Protocol Number: MK-0431A-296 |

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 | 29 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 April 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 April 2014 |
| 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:

- (1) The safety and tolerability of two sitagliptin 50 mg/metformin 1000 mg XR tablets in pediatric participants with type 2 diabetes mellitus (T2DM), aged 10 to 17 years
- (2) The ability of pediatric participants with T2DM, aged 10 to 17 years, to swallow two sitagliptin 50 mg/metformin 1000 mg XR tablets or two matching placebo tablets (excluding marking)
- (3) The pharmacokinetics of sitagliptin and metformin following the administration of two sitagliptin 50 mg/metformin 1000 mg XR tablets to pediatric participants with T2DM, aged 10 to 17 years.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 02 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 25 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 0 |

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) | 1 |
| Adolescents (12-17 years) | 24 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participant is a male or female, between 10 and 17 years of age.

Pre-assignment

Screening details:

1. Female participants of reproductive potential must demonstrate a nongravid state.
2. Participants must have:
 - Type 2 diabetes (T2D) diagnosed by American Diabetes Association (ADA) criteria.
 - No clinically significant abnormality on electrocardiogram (ECG).
 - No clinical or laboratory evidence of type 1 diabetes.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Sitagliptin/Metformin XR Followed by Placebo |

Arm description:

Day 1 (Period 1): participants received a single dose of two sitagliptin/metformin XR tablets with a low-to moderate-fat meal (breakfast). Days 2-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal.

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

Dosage and administration details:

Sitagliptin phosphate 50mg/Metformin hydrochloride 1000mg

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

Dosage and administration details:

0mg/0mg

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

Dosage and administration details:

Concomitant use of thyroid hormone (TH) will also be permitted during the study provided the participant has been receiving a stable dose for at least 12 weeks prior to study drug administration and is euthyroid as documented by thyroid-stimulation hormone (TSH) testing at prestudy. TH should also be held prior to study drug administration and for 24 hours postdose. TH administration can be re-initiated following completion of the 24-hour procedures.

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

Dosage and administration details:

Concomitant use of metformin will be permitted during the study provided the participant has been receiving a stable metformin dose for at least 12 weeks prior to the dose of study drug. Metformin should be held prior to study drug administration and for 24 hours postdose. Metformin administration can be re-initiated following completion of the 24-hour postdose procedures.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Days 1-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal.

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

Dosage and administration details:

0mg/0mg

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

Dosage and administration details:

Concomitant use of metformin will be permitted during the study provided the participant has been receiving a stable metformin dose for at least 12 weeks prior to the dose of study drug. Metformin should be held prior to study drug administration and for 24 hours postdose. Metformin administration can be re-initiated following completion of the 24-hour postdose procedures.

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

Dosage and administration details:

Concomitant use of thyroid hormone (TH) will also be permitted during the study provided the participant has been receiving a stable dose for at least 12 weeks prior to study drug administration and is euthyroid as documented by thyroid-stimulation hormone (TSH) testing at prestudy. TH should also be held prior to study drug administration and for 24 hours postdose. TH administration can be re-initiated following completion of the 24-hour procedures.

| Number of subjects in period 1 | Sitagliptin/Metformin XR Followed by Placebo | Placebo |
|---------------------------------------|--|---------|
| Started | 13 | 12 |
| Completed | 12 | 12 |
| Not completed | 1 | 0 |
| Physician decision | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Sitagliptin/Metformin XR Followed by Placebo |
| Reporting group description: | |
| Day 1 (Period 1): participants received a single dose of two sitagliptin/metformin XR tablets with a low-to moderate-fat meal (breakfast). Days 2-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Days 1-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |

| Reporting group values | Sitagliptin/Metformin XR Followed by Placebo | Placebo | Total |
|--|--|---------|-------|
| Number of subjects | 13 | 12 | 25 |
| 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) | 0 | 1 | 1 |
| Adolescents (12-17 years) | 13 | 11 | 24 |
| 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 | 14.7 | 14.8 | - |
| standard deviation | ± 1.8 | ± 2.0 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 9 | 8 | 17 |
| Male | 4 | 4 | 8 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Sitagliptin/Metformin XR Followed by Placebo |
| Reporting group description: Day 1 (Period 1): participants received a single dose of two sitagliptin/metformin XR tablets with a low-to moderate-fat meal (breakfast). Days 2-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |
| Reporting group title | Placebo |
| Reporting group description: Days 1-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |
| Subject analysis set title | All Treated Participants |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All participants who completed at least one period of treatment and had available data. | |
| Subject analysis set title | Sitagliptin |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Day 1 (Period 1): participants received a single dose of two sitagliptin/metformin XR tablets with a low-to moderate-fat meal (breakfast). Days 2-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |
| Subject analysis set title | Metformin |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Day 1 (Period 1): participants received a single dose of two sitagliptin/metformin XR tablets with a low-to moderate-fat meal (breakfast). Days 2-4 (Period 1): participants received a single dose of two matching placebo tablets. Days 5-9 (Period 2): participants received a single dose of two matching placebo tablets with the evening meal. | |

Primary: Number of Participants Who Successfully Swallowed Study Medication (Med) on Day 2

| | |
|--|--|
| End point title | Number of Participants Who Successfully Swallowed Study Medication (Med) on Day 2 ^[1] |
| End point description: The Swallowing Ability Questionnaire was completed on Day 2 after the participant received two matching placebo tablets (excluding marking) following consumption of a low-to-moderate-fat meal in pediatric participants aged 10 to 17 years. The questionnaire consisted of 5 parts: 1. Could only swallow study med with help; 2. Easy to start swallowing study med; 3. Easy to swallow study med; 4. Felt like study med got stuck in throat, and 5. Had to swallow study med more than once. The number of participants who strongly agreed or agreed in each of the 5 parts is reported. Per protocol population defined as all participants who completed at least one period of treatment and had available data. On Day 2, all participants received matching placebo, so the two treatment groups were pooled on Day 2. | |
| End point type | Primary |
| End point timeframe: Day 2 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned or performed for this endpoint. | |

| End point values | All Treated Participants | | | |
|---|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 24 | | | |
| Units: Participants | | | | |
| Strongly Agreed: 1. Could Swallow Med With Help | 6 | | | |
| Agreed: 1. Could Only Swallow Med With Help | 7 | | | |
| Strongly Agreed: 2. Easy to Start Swallowing Med | 10 | | | |
| Agreed: 2. Easy to Start Swallowing Med | 12 | | | |
| Strongly Agreed: 3. Easy to Swallow Med | 13 | | | |
| Agreed: 3. Easy to Swallow Med | 10 | | | |
| Strongly Agreed: 4. Felt Like Med Stuck in Throat | 0 | | | |
| Agreed: 4. Felt Like Med Got Stuck in Throat | 4 | | | |
| Strongly Agreed: 5. Had to Swallow Med >1 | 2 | | | |
| Agreed: 5. Had to Swallow Med >1 | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Successfully Swallowed Study Med on Day 4

| | |
|-----------------|---|
| End point title | Number of Participants Who Successfully Swallowed Study Med on Day 4 ^[2] |
|-----------------|---|

End point description:

The Swallowing Ability Questionnaire was completed on Day 4 after the participant received two matching placebo tablets (excluding marking) following consumption of a low- to moderate-fat meal in pediatric participants aged 10 to 17 years. The questionnaire consisted of 5 parts: 1. Could only swallow study med with help; 2. Easy to start swallowing study med; 3. Easy to swallow study med; 4. Felt like study med got stuck in throat, and 5. Had to swallow study med more than once. The number of participants who strongly agreed or agreed in each of the 5 parts is reported. Per protocol population defined as all participants who completed at least one period of treatment and had available data. On Day 4, all participants received matching placebo, so the two treatment groups were pooled on Day 4.

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

End point timeframe:

Day 4

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | All Treated Participants | | | |
|---|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 24 | | | |
| Units: Participants | | | | |
| Strongly Agreed: 1. Could Swallow Med With Help | 6 | | | |

| | | | | |
|---|----|--|--|--|
| Agreed: 1. Could Only Swallow Med With Help | 6 | | | |
| Strongly Agreed: 2. Easy to Start Swallowing Med | 8 | | | |
| Agreed: 2. Easy to Start Swallowing Med | 14 | | | |
| Strongly Agreed: 3. Easy to Swallow Med | 8 | | | |
| Agreed: 3. Easy to Swallow Med | 15 | | | |
| Strongly Agreed: 4. Felt Like Med Stuck in Throat | 0 | | | |
| Agreed: 4. Felt Like Med Got Stuck in Throat | 4 | | | |
| Strongly Agreed: 5. Had to Swallow Med >1 | 0 | | | |
| Agreed: 5. Had to Swallow Med >1 | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Successfully Swallowed Study Med on Day 6

| | |
|-----------------|---|
| End point title | Number of Participants Who Successfully Swallowed Study Med on Day 6 ^[3] |
|-----------------|---|

End point description:

The Swallowing Ability Questionnaire was completed on Day 6 after the participant received two matching placebo tablets (excluding marking) following consumption of a low- to moderate-fat meal in pediatric participants aged 10 to 17 years. The questionnaire consisted of 5 parts: 1. Could only swallow study med with help; 2. Easy to start swallowing study med; 3. Easy to swallow study med; 4. Felt like study med got stuck in throat, and 5. Had to swallow study med more than once. The number of participants who strongly agreed or agreed in each of the 5 parts is reported. Per protocol population defined as all participants who completed at least one period of treatment and had available data. On Day 6, all participants received matching placebo, so the two treatment groups were pooled on Day 6.

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

End point timeframe:

Day 6

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | All Treated Participants | | | |
|--|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 24 | | | |
| Units: Participants | | | | |
| Strongly Agreed: 1. Could Swallow Med With Help | 5 | | | |
| Agreed: 1. Could Only Swallow Med With Help | 7 | | | |
| Strongly Agreed: 2. Easy to Start Swallowing Med | 10 | | | |
| Agreed: 2. Easy to Start Swallowing Med | 11 | | | |
| Strongly Agreed: 3. Easy to Swallow Med | 11 | | | |

| | | | | |
|---|----|--|--|--|
| Agreed: 3. Easy to Swallow Med | 12 | | | |
| Strongly Agreed: 4. Felt Like Med Stuck in Throat | 0 | | | |
| Agreed: 4. Felt Like Med Got Stuck in Throat | 3 | | | |
| Strongly Agreed: 5. Had to Swallow Med >1 | 2 | | | |
| Agreed: 5. Had to Swallow Med >1 | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Successfully Swallowed Study Med on Day 9

| | |
|-----------------|---|
| End point title | Number of Participants Who Successfully Swallowed Study Med on Day 9 ^[4] |
|-----------------|---|

End point description:

The Swallowing Ability Questionnaire was completed on Day 9 after the participant received two matching placebo tablets (excluding marking) following consumption of a low- to moderate-fat meal in pediatric participants aged 10 to 17 years. The questionnaire consisted of 5 parts: 1. Could only swallow study med with help; 2. Easy to start swallowing study med; 3. Easy to swallow study med; 4. Felt like study med got stuck in throat, and 5. Had to swallow study med more than once. The number of participants who strongly agreed or agreed in each of the 5 parts is reported. Per protocol population defined as all participants who completed at least one period of treatment and had available data. On Day 9, all participants received matching placebo, so the two treatment groups were pooled on Day 9.

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

End point timeframe:

Day 9

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | All Treated Participants | | | |
|---|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 24 | | | |
| Units: Participants | | | | |
| Strongly Agreed: 1. Could Swallow Med With Help | 9 | | | |
| Agreed: 1. Could Only Swallow Med With Help | 5 | | | |
| Strongly Agreed: 2. Easy to Start Swallowing Med | 9 | | | |
| Agreed: 2. Easy to Start Swallowing Med | 13 | | | |
| Strongly Agreed: 3. Easy to Swallow Med | 12 | | | |
| Agreed: 3. Easy to Swallow Med | 11 | | | |
| Strongly Agreed: 4. Felt Like Med Stuck in Throat | 1 | | | |
| Agreed: 4. Felt Like Med Got Stuck in Throat | 1 | | | |
| Strongly Agreed: 5. Had to Swallow Med >1 | 2 | | | |
| Agreed: 5. Had to Swallow Med >1 | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve 0 to Last (AUC 0-last) of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | Area Under the Curve 0 to Last (AUC 0-last) of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR ^[5] ^[6] |
|-----------------|--|

End point description:

AUC0-last is a measure of the total amount of drug in the plasma from the dose to the last measurable sample at which the concentration is at or above lower limit of quantification (LLQ). In this study, metformin products were withheld 24 hours (hrs.) prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hrs. post study drug administration. Owing to resumption of therapeutic metformin administration 24 hrs. after sitagliptin/metformin XR administration for all participants, metformin pharmacokinetic analyses were restricted to maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and area under the curve 0 to 24 hrs. (AUC0-24hr). Therefore, metformin arm is not included in this endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
|---|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: nM*hr | | | | |
| geometric mean (geometric coefficient of variation) | 5940 (± 25.7) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-24 of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR

| | |
|-----------------|---|
| End point title | AUC 0-24 of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR ^[7] ^[8] |
|-----------------|---|

End point description:

AUC0-24 is a measure of the total amount of drug in the plasma from the dose to 24 hours after the dose. Due different units of measure for sitagliptin and metformin, metformin data are presented in another endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|---|--|--|--|--|
| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: nM*hr | | | | |
| geometric mean (geometric coefficient of variation) | 5310 (\pm 22.4) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-24 of Metformin Following Single Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | AUC 0-24 of Metformin Following Single Administration of Sitagliptin/Metformin XR ^{[9][10]} |
|-----------------|--|

End point description:

AUC0-24 is a measure of the total amount of drug in the plasma from the dose to 24 hours after the dose. In this study, metformin products were withheld 24 hours prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hours post study drug administration. Due different units of measure for sitagliptin and metformin, sitagliptin data are presented in another endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|---|--|--|--|--|
| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: ng*hr/mL | | | | |
| geometric mean (geometric coefficient of variation) | 14200 (\pm 39.7) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve 0 to Infinity (AUC 0- ∞) of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | Area Under the Curve 0 to Infinity (AUC 0- ∞) of Sitagliptin Following Single Administration of Sitagliptin/Metformin XR ^{[11][12]} |
|-----------------|--|

End point description:

AUC0- ∞ is a measure of the mean concentration levels of drug in the plasma after the dose. In this study, metformin products were withheld 24 hours prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hours post study drug administration. Owing to resumption of therapeutic metformin administration 24 hours after sitagliptin/metformin XR administration for all participants, metformin pharmacokinetic analyses were restricted to C_{max}, T_{max} and AUC0-24hr. Therefore, metformin arm is not included in this endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|---|--|--|--|--|
| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: nM*hr | | | | |
| geometric mean (geometric coefficient of variation) | 6020 (\pm 24.8) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Sitagliptin Following Single Dose Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | Cmax of Sitagliptin Following Single Dose Administration of Sitagliptin/Metformin XR ^[13] ^[14] |
|-----------------|--|

End point description:

Cmax is a measure of the maximum amount of drug in the plasma after the dose is given. Due different units of measure for sitagliptin and metformin, metformin data are presented in another endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
|---|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: nM | | | | |
| geometric mean (geometric coefficient of variation) | 757 (± 40.1) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Metformin Following Single Dose Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | Cmax of Metformin Following Single Dose Administration of Sitagliptin/Metformin XR ^[15] ^[16] |
|-----------------|--|

End point description:

Cmax is a measure of the maximum amount of drug in the plasma after the dose is given. Due different units of measure for sitagliptin and metformin, sitagliptin data are presented in another endpoint. In this study, metformin products were withheld 24 hours prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hours post study drug administration. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|---|--|--|--|--|
| End point values | Sitagliptin/Metformin XR Followed by Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1490 (\pm 29.1) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Tmax of Sitagliptin and Metformin Following Single Dose Administration of Sitagliptin/Metformin XR

| | |
|-----------------|--|
| End point title | Tmax of Sitagliptin and Metformin Following Single Dose Administration of Sitagliptin/Metformin XR ^[17] |
|-----------------|--|

End point description:

Tmax is a measure of the time to reach the maximum concentration in the plasma after the drug dose. In this study, metformin products were withheld 24 hours prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hours post study drug administration. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR followed by placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| | | | | |
|-------------------------------|----------------------|----------------------|--|--|
| End point values | Sitagliptin | Metformin | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: Hour | | | | |
| median (full range (min-max)) | 1.52 (0.97 to 3.05) | 5.00 (3.98 to 7.22) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Terminal Half Life (t_{1/2}) of Sitagliptin Following Single Dose Administration of Sitagliptin/Metformin XR

| | |
|-----------------|---|
| End point title | Apparent Terminal Half Life (t _{1/2}) of Sitagliptin Following Single Dose Administration of Sitagliptin/Metformin XR ^[18] |
|-----------------|---|

End point description:

Apparent terminal half-life is the time required to divide the plasma (serum) concentration of drug by two after reaching pseudo-equilibrium. (Note: it is not the time required to eliminate half the administered dose.) In this study, metformin products were withheld 24 hours prior to sitagliptin/metformin XR administration and were permitted to re-initiate 24 hours post study drug administration. Owing to resumption of therapeutic metformin administration 24 hours after sitagliptin/metformin XR administration for all participants, metformin pharmacokinetic analyses were restricted to C_{max}, T_{max}, and AUC_{0-24hr}. Therefore, metformin arm is not included in this endpoint. Per protocol population defined as all participants who completed at least one period of treatment (Sitagliptin/Metformin XR Followed by Placebo arm) and had available data.

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

End point timeframe:

Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours post-dose

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 12 | | | |
| Units: Hour | | | | |
| geometric mean (geometric coefficient of variation) | 10.0 (± 27.3) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Adverse Event (AE)

| | |
|-----------------|--|
| End point title | Number of Participants Who Experienced an Adverse Event (AE) ^[19] |
|-----------------|--|

End point description:

An AE was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered. The analysis population included all participants who received at least one dose of study drug.

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

End point timeframe:

Up to 23 days (including approximately 10 to 14 days after the last dose of study drug)

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin/Metformin XR Followed by Placebo | Placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: Participants | 5 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Abnormal Vital Sign Value

| | |
|-----------------|---|
| End point title | Number of Participants Who Experienced an Abnormal Vital Sign Value ^[20] |
|-----------------|---|

End point description:

Vital sign measurements included blood pressure, heart rate, respiratory rate, and oral temperature. The analysis population included all participants who received at least one dose of study drug.

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

End point timeframe:

Up to 23 days (including approximately 10 to 14 days after the last dose of study drug)

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin/Metformin XR Followed by Placebo | Placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: Participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Drug Due to an AE

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Drug Due to an AE ^[21] |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an IMP, regardless of causal relationship and even if no IMP has been administered. The analysis population included all participants who received at least one dose of study drug.

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

End point timeframe:

Up to 9 days

Notes:

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

Justification: No statistical analysis was planned or performed for this endpoint.

| End point values | Sitagliptin/Metformin XR Followed by Placebo | Placebo | | |
|-----------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 12 | | |
| Units: Participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 23 days (including approximately 10 to 14 days after the last dose of study drug)

Adverse event reporting additional description:

An AE was any untoward medical occurrence of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship or administration. The analysis population included all participants who received at least one dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Sitagliptin/Metformin XR Followed by Placebo |
|-----------------------|--|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events | Sitagliptin/Metformin XR Followed by Placebo | Placebo | |
|---|--|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Sitagliptin/Metformin XR Followed by Placebo | Placebo | |
|---|--|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | 5 / 12 (41.67%) | |
| Investigations | | | |
| Urine analysis abnormal | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | |
| Reproductive system and breast disorders Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Plantar fasciitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 | |
| Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 18 March 2013 | Various changes to diet restrictions and requirements, safety laboratory tests, and other blood draws. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported