



Clinical trial results:

A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MEDI0382 in Subjects with Type 2 Diabetes Mellitus and Renal Impairment

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2018-000019-26 |
| Trial protocol | GB |
| Global end of trial date | 04 February 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 |
| This version publication date | 03 April 2020 |
| First version publication date | 28 February 2020 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D5670C00013 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03550378 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | MedImmune, a wholly owned subsidiary of AstraZeneca |
| Sponsor organisation address | Milstein Building, Granta Park, Cambridge, United Kingdom, CB21 6GH |
| Public contact | Lars Hansen, MedImmune, a wholly owned subsidiary of AstraZeneca, +1 301-398-4563, information.center@astrazeneca.com |
| Scientific contact | Lars Hansen, MedImmune, a wholly owned subsidiary of AstraZeneca, +1 301-398-4563, information.center@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | |
| 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? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 August 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 04 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety and efficacy of MEDI0382 titrated up to a dose level of 300 µg on glucose control versus Placebo after 32 days of treatment in participants with type 2 diabetes mellitus (T2DM) and renal impairment.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 29 June 2018 |
| 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 Kingdom: 9 |
| Country: Number of subjects enrolled | Germany: 32 |
| Worldwide total number of subjects | 41 |
| EEA total number of subjects | 41 |

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) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|----|
| Adults (18-64 years) | 5 |
| From 65 to 84 years | 36 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in the United Kingdom and Germany between 29Jun2018 and 04Feb2019.

Pre-assignment

Screening details:

A total of 41 participants were randomized to the study.

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

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

Arm description:

Participants received subcutaneous dose (SC) dose of placebo matched to MEDI0382 once daily for 32 days.

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

Dosage and administration details:

Subcutaneous (SC) dose of placebo matched to MEDI0382 once daily for 32 days.

| | |
|------------------|----------|
| Arm title | MEDI0382 |
|------------------|----------|

Arm description:

Participants received SC dose of MEDI0382 titrated from 50 µg upto 300 µg (50 µg once daily for 4 days, followed by 100 µg daily for 7 days, 200 µg daily for 7 days, and 300 µg daily for 14 days) for 32 days.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MEDI0382 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The SC dose of MEDI0382 titrated from 50 µg upto 300 µg (50 µg once daily for 4 days, followed by 100 µg daily for 7 days, 200 µg daily for 7 days, and 300 µg daily for 14 days) for 32 days.

| Number of subjects in period 1 | Placebo | MEDI0382 |
|---------------------------------------|---------|----------|
| Started | 20 | 21 |
| Completed | 20 | 20 |
| Not completed | 0 | 1 |
| Adverse event, serious fatal | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received subcutaneous dose (SC) dose of placebo matched to MEDI0382 once daily for 32 days. | |
| Reporting group title | MEDI0382 |
| Reporting group description: | |
| Participants received SC dose of MEDI0382 titrated from 50 µg upto 300 µg (50 µg once daily for 4 days, followed by 100 µg daily for 7 days, 200 µg daily for 7 days, and 300 µg daily for 14 days) for 32 days. | |

| Reporting group values | Placebo | MEDI0382 | Total |
|--|---------|----------|-------|
| Number of subjects | 20 | 21 | 41 |
| 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 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 1 | 4 | 5 |
| From 65-84 years | 19 | 17 | 36 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 70.9 | 71.1 | - |
| standard deviation | ± 4.7 | ± 7.4 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 11 | 9 | 20 |
| Male | 9 | 12 | 21 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 0 | 0 | 0 |
| White | 20 | 20 | 40 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 20 | 21 | 41 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | Placebo |
| Reporting group description: Participants received subcutaneous dose (SC) dose of placebo matched to MEDI0382 once daily for 32 days. | |
| Reporting group title | MEDI0382 |
| Reporting group description: Participants received SC dose of MEDI0382 titrated from 50 µg upto 300 µg (50 µg once daily for 4 days, followed by 100 µg daily for 7 days, 200 µg daily for 7 days, and 300 µg daily for 14 days) for 32 days. | |

Primary: Percent Change From Baseline in Plasma Glucose Area Under the Concentration Time-curve From Time 0 to 4 hours (AUC0-4 hrs) as Measured by Mixed-meal Tolerance Test (MMTT) to Day 32

| | |
|---|--|
| End point title | Percent Change From Baseline in Plasma Glucose Area Under the Concentration Time-curve From Time 0 to 4 hours (AUC0-4 hrs) as Measured by Mixed-meal Tolerance Test (MMTT) to Day 32 |
| End point description: The MMTT involved the consumption of a standardised liquid meal (a nutritional supplement containing the components of fat, carbohydrate, and protein, which make up a standard MMTT) within 15 minutes, and timed serial blood samples obtained for measurement of glucose and parameters related to glucose metabolism through 240 minutes after consumption of the standardised meal (with no additional food intake during this time). Intent-to-treat (ITT) population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group. | |
| End point type | Primary |
| End point timeframe: Zero minutes before and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after consumption of the standardised meal on Day -5 (Baseline) and Day 32 | |

| End point values | Placebo | MEDI0382 | | |
|--|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 18 | | |
| Units: Percent change in plasma glucose | | | | |
| least squares mean (confidence interval 90%) | 3.678 (-3.793 to 11.149) | -26.706 (-34.584 to -18.828) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Comparison in percent change of glucose AUC |
| Comparison groups | Placebo v MEDI0382 |

| | |
|---|--------------------|
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -30.384 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -41.27 |
| upper limit | -19.498 |

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

| | |
|-----------------|--|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) |
|-----------------|--|

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Day 1 through Day 60

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | | | | |
| TEAEs | 13 | 20 | | |
| TESAEs | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Vital Signs Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Participants With Abnormal Vital Signs Reported as TEAEs |
|-----------------|--|

End point description:

Number of participants with abnormal vital signs reported as TEAEs is reported. Vital sign measurements were obtained after the participant had rested in the supine position for at least 10 minutes at the recording time. Abnormal vital signs is defined as any abnormal finding in the vital sign parameters (blood pressure, pulse rate, body temperature, and respiratory rate). As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Day 1 through Day 60

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Postural Blood Pressure

| | |
|-----------------|---|
| End point title | Change From Baseline in Postural Blood Pressure |
|-----------------|---|

End point description:

The change difference is the change from Day 1 to Day 32 in the difference between blood pressure values in standing and supine positions. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received. Participants who had the blood pressure (systolic and diastolic) values of both standing and supine position on Day 1 and Day 32 were analysed for this end point.

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

End point timeframe:

Day 1 through Day 32

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 18 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic Blood Pressure (n = 17, 18) | 0.1 (± 9.3) | 8.9 (± 14.2) | | |
| Diastolic Blood Pressure (n = 17, 17) | 1.8 (± 6.3) | 0.8 (± 5.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Electrocardiograms (ECGs) Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Participants With Abnormal Electrocardiograms (ECGs) Reported as TEAEs |
|-----------------|--|

End point description:

Number of participants with abnormal ECGs reported as TEAEs is reported. Abnormal ECGs is defined as any abnormal findings in heart rate, RR interval, PR interval, QRS, axis, ST-T morphology, and QT intervals from the primary lead of the digital 12-lead ECG. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Day 1 through Day 60

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | | | | |
| Bradyarrhythmia | 1 | 0 | | |
| Bundle branch block left | 1 | 0 | | |
| Bundle branch block right | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

| | |
|-----------------|---|
| End point title | Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs |
|-----------------|---|

End point description:

Number of participants with abnormal clinical laboratory parameters reported as TEAEs is reported. Abnormal clinical laboratory parameters defined as any abnormal finding during analysis of serum chemistry, hematology, and urine. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Day 1 through Day 60

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | | | | |
| Hypoglycaemia | 1 | 3 | | |
| Alanine aminotransferase increased | 1 | 0 | | |
| Aspartate aminotransferase increased | 1 | 0 | | |
| Glomerular filtration rate decreased | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events of Special Interest (TEAESIs)

| | |
|-----------------|---|
| End point title | Number of Participants With Treatment-emergent Adverse Events of Special Interest (TEAESIs) |
|-----------------|---|

End point description:

An adverse event of special interest (AESI) was one of scientific and medical interest specific to understanding of the study drug and may require close monitoring and rapid communication by the investigator to the sponsor. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Day 1 through Day 60

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean 24-hrs Pulse Rate to the End of Each Dosing Level

| | |
|-----------------|--|
| End point title | Change From Baseline in Mean 24-hrs Pulse Rate to the End of Each Dosing Level |
|-----------------|--|

End point description:

Change from baseline in mean 24-hrs pulse rate to the end of each dosing levels. End of dosing: Day 5 for 50 µg; Day 12 for 100 µg, Day 19 for 200 µg, and Day 32 for 300 µg. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received. Here, "n" signifies only the participants with available data were analysed for the specified time points.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day -5 (Baseline) and on Days 5, 12, 19, and 32 | |

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Beats/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 5 (n= 12, 13) | -0.73 (± 4.13) | 6.40 (± 5.53) | | |
| Day 12 (n= 11, 12) | 1.04 (± 5.07) | 9.01 (± 7.73) | | |
| Day 19 (n= 14, 13) | 1.32 (± 5.28) | 12.72 (± 8.93) | | |
| Day 32 (n= 11, 10) | -0.92 (± 4.51) | 11.85 (± 8.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean 24-hrs Systolic and Diastolic Blood Pressure to the end of Each Dosing Level

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean 24-hrs Systolic and Diastolic Blood Pressure to the end of Each Dosing Level |
|-----------------|---|

End point description:

Change from baseline in mean 24-hrs systolic and diastolic blood pressure to the end of each dosing levels. End of dosing: Day 5 for 50 µg; Day 12 for 100 µg, Day 19 for 200 µg, and Day 32 for 300 µg. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received. Here, "n" signifies only the participants with available data were analyzed for the specified time points.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day -5 (Baseline) and on Days 5, 12, 19, and 32 | |

| End point values | Placebo | MEDI0382 | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 5: Systolic Blood Pressure (n=12,13) | -3.11 (± 9.97) | -1.69 (± 9.06) | | |
| Day 12: Systolic Blood Pressure (n=11,12) | -2.67 (± 12.30) | -4.34 (± 11.46) | | |
| Day 19: Systolic Blood Pressure (n=14,13) | -3.56 (± 10.15) | -4.72 (± 11.65) | | |
| Day 32: Systolic Blood Pressure (n=11,10) | 2.21 (± 7.24) | -1.15 (± 18.43) | | |

| | | | | |
|--|----------------|---------------|--|--|
| Day 5: Diastolic Blood Pressure (n=12,13) | -0.07 (± 3.19) | 1.15 (± 3.64) | | |
| Day 12: Diastolic Blood Pressure (n=11,12) | -0.55 (± 5.17) | 1.28 (± 5.22) | | |
| Day 19: Diastolic Blood Pressure (n=14,13) | -0.44 (± 3.85) | 0.76 (± 3.75) | | |
| Day 32: Diastolic Blood Pressure (n=11,10) | 1.84 (± 1.79) | 2.54 (± 5.34) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haemoglobin A1c (HbA1c) to Day 32

| | |
|-----------------|---|
| End point title | Change From Baseline in Haemoglobin A1c (HbA1c) to Day 32 |
|-----------------|---|

End point description:

Change from baseline in haemoglobin A1c (HbA1c) is reported. An ITT population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group.

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

End point timeframe:

Day 1 (Baseline) and Day 32

| End point values | Placebo | MEDI0382 | | |
|--|----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: Percent | | | | |
| least squares mean (confidence interval 90%) | 0.01 (-0.15 to 0.17) | -0.65 (-0.82 to -0.49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Glucose to Day 32

| | |
|-----------------|---|
| End point title | Change From Baseline in Fasting Glucose to Day 32 |
|-----------------|---|

End point description:

Change from baseline in fasting glucose is reported. An ITT population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group.

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

End point timeframe:

Day 1 (Baseline) and Day 32

| End point values | Placebo | MEDI0382 | | |
|--|------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 90%) | 0.60 (-12.89 to 14.08) | -19.55 (-33.39 to -5.71) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percentage of Time Spent Within a Target Glucose Range Over a 7-day Period to the Final Week of Treatment

| | |
|-----------------|---|
| End point title | Change From Baseline in Percentage of Time Spent Within a Target Glucose Range Over a 7-day Period to the Final Week of Treatment |
|-----------------|---|

End point description:

Change from baseline in percentage of time spent within a target glucose range over a 7-day period to the final week of treatment is reported. Target glucose range was considered as 70 mg/dL (3.9 mmol/L) to 180 mg/dL (10 mmol/L). An ITT population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group. Here, "n" signifies only the participants with available data were analyzed for the specified time points.

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

End point timeframe:

Baseline (Days -8 to -2), Days 5 to 11, Days 12 to 18, Days 19 to 25, and Days 26 to 32 (final week of treatment)

| End point values | Placebo | MEDI0382 | | |
|--|--------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Percentage of time | | | | |
| least squares mean (confidence interval 90%) | | | | |
| Days 5 - 11 (n=17,19) | -10.49 (-20.77 to -0.20) | 12.25 (2.52 to 21.98) | | |
| Days 12 - 18 (n=18,19) | -5.34 (-12.77 to 2.10) | 15.62 (8.39 to 22.86) | | |
| Days 19 - 25 (n=18,18) | -16.05 (-25.02 to -7.08) | 19.18 (10.21 to 28.15) | | |
| Days 26 - 32 (n=18,17) | -21.23 (-33.13 to -9.32) | 14.79 (2.54 to 27.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change Frome Baseline in Body Weight to Day 33

| | |
|-----------------|--|
| End point title | Percent Change Frome Baseline in Body Weight to Day 33 |
|-----------------|--|

End point description:

Percent change from baseline in body weight is reported. An ITT population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group.

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

End point timeframe:

Day 1 (Baseline) and Day 33

| End point values | Placebo | MEDI0382 | | |
|--|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: Percent change in body weight | | | | |
| least squares mean (confidence interval 90%) | -0.21 (-1.05 to 0.62) | -3.69 (-4.55 to -2.83) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Absolute Body Weight to Day 33

| | |
|-----------------|--|
| End point title | Change From Baseline in Absolute Body Weight to Day 33 |
|-----------------|--|

End point description:

Change from baseline in absolute body weight is reported. An ITT population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to their randomised treatment group.

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

End point timeframe:

Day 1 (Baseline) and Day 33

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: Kg | | | | |
| arithmetic mean (standard deviation) | -0.15 (± 1.84) | -3.39 (± 2.16) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve Over a Dosing Duration (AUC_T) of MEDI0382 at 300 µg

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Time Curve Over a Dosing Duration (AUC _T) of MEDI0382 at 300 µg ^[1] |
|-----------------|--|

End point description:

Area under the plasma concentration time curve over a dosing duration (AUC_T) of MEDI0382 at 300 µg is reported. Pharmacokinetic (PK) population was analysed for this endpoint, which included all participants who received at least 1 dose of study drug and had at least one PK sample collected with a value above the lower limit of quantitation.

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

End point timeframe:

Predose and at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdose on Day 32

Notes:

[1] - 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: Only those baseline period arms for which analysis was planned were reported in the end point

| End point values | MEDI0382 | | | |
|---------------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: ng.hr/mL | | | | |
| geometric mean (full range (min-max)) | 285.93 (124.08 to 669.17) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (C_{max}) of MEDI0382 at 300 µg

| | |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (C _{max}) of MEDI0382 at 300 µg ^[2] |
|-----------------|---|

End point description:

Maximum observed serum concentration (C_{max}) of MEDI0382 at 300 µg is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of study drug and had at least one PK sample collected with a value above the lower limit of quantitation.

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

End point timeframe:

Predose and at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdose on Day 32

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those baseline period arms for which analysis was planned were reported in the end point

| | | | | |
|---------------------------------------|----------------------|--|--|--|
| End point values | MEDI0382 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | 16.93 (5.17 to 35.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Observed Maximum Serum Concentration (Tmax) of MEDI0382 at 300 µg

| | |
|-----------------|--|
| End point title | Time to Observed Maximum Serum Concentration (Tmax) of MEDI0382 at 300 µg ^[3] |
|-----------------|--|

End point description:

Time to observed maximum serum concentration (Tmax) of MEDI0382 at 300 µg is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of study drug and had at least one PK sample collected with a value above the lower limit of quantitation.

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

End point timeframe:

Predose and at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdose on Day 32

Notes:

[3] - 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: Only those baseline period arms for which analysis was planned were reported in the end point

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | MEDI0382 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: Hours | | | | |
| median (full range (min-max)) | 5.6 (4 to 24) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctough) of MEDI0382

| | |
|-----------------|---|
| End point title | Trough Plasma Concentration (Ctough) of MEDI0382 ^[4] |
|-----------------|---|

End point description:

Trough concentration is the lowest concentration reached by a drug before the next dose is administered. Trough plasma concentration (Ctough) of MEDI0382 reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of study drug and had at least one PK sample collected with a value above the lower limit of quantitation. Here, "n" signifies only the participants with available data were analysed for the specified time points. Here, the arbitrary number "9999" signifies that the data is not reported as no participants were evaluable for the specified time point.

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

End point timeframe:

Days 1, 5, 12, and 19: Predose; and Day 32: Predose and at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdose (Day 33)

Notes:

[4] - 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: Only those baseline period arms for which analysis was planned were reported in the end point

| End point values | MEDI0382 | | | |
|---------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 1 (n=0) | 9999 (9999 to 9999) | | | |
| Day 5 (n=19) | 1.44 (0.48 to 2.58) | | | |
| Day 12 (n=19) | 2.03 (0.63 to 3.75) | | | |
| Day 19 (n=20) | 3.68 (0.59 to 8.86) | | | |
| Day 32 (n=17) | 5.86 (1.3 to 19.4) | | | |
| Day 33 (n=19) | 5.96 (2.43 to 19.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug antibodies (ADA) Titre to MEDI0382

| | |
|-----------------|---|
| End point title | Number of Participants With Positive Anti-drug antibodies (ADA) Titre to MEDI0382 |
|-----------------|---|

End point description:

Number of participants with positive Anti-drug antibodies (ADA) Titre to MEDI0382 is reported. As-treated population was analysed for this endpoint, which included all participants who received any dose of study drug and analysed according to the treatment they actually received.

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

End point timeframe:

Pre-dose on Days 1, 12, and 32 and on Day 60

| End point values | Placebo | MEDI0382 | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Participants | | | | |
| Positive at baseline | 0 | 0 | | |
| Positive post-baseline | 0 | 2 | | |
| Positive at baseline and post-baseline | 0 | 0 | | |

| | | | | |
|--|---|---|--|--|
| Not detected at baseline; positive post-baseline | 0 | 2 | | |
| Positive at baseline; not detected post-baseline | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 60

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | MEDI0382 |
|-----------------------|----------|

Reporting group description:

Participants received SC dose of MEDI0382 titrated from 50 µg upto 300 µg (50 µg once daily for 4 days, followed by 100 µg daily for 7 days, 200 µg daily for 7 days, and 300 µg daily for 14 days) for 32 days.

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

Reporting group description:

Participants received subcutaneous dose (SC) dose of placebo matched to MEDI0382 once daily for 32 days.

| Serious adverse events | MEDI0382 | Placebo | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 20 (10.00%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

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

| Non-serious adverse events | MEDI0382 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 21 (90.48%) | 13 / 20 (65.00%) | |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Nervousness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Glomerular filtration rate decreased | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 20 (0.00%) 0 | |
| Injury, poisoning and procedural complications Face injury subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 | 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 | |
| Cardiac disorders Bradyarrhythmia subjects affected / exposed occurrences (all) Bundle branch block left subjects affected / exposed occurrences (all) Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 1 / 21 (4.76%) 1 | 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Carotid artery stenosis subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 0 / 21 (0.00%) 0 2 / 21 (9.52%) 3 | 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 2 / 20 (10.00%) 3 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) Vertigo positional subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 1 / 21 (4.76%) 1 | 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 0 / 20 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 1 / 20 (5.00%) | |
| occurrences (all) | 6 | 1 | |
| Eructation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 20 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 4 / 20 (20.00%) | |
| occurrences (all) | 19 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 1 / 20 (5.00%) | |
| occurrences (all) | 18 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Night sweats | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Skin fissures subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 20 (0.00%) 0 | |
| Skin swelling subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 20 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 2 / 20 (10.00%) 2 | |
| Otitis media subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 20 (0.00%) 0 | |
| Pyelonephritis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 20 (10.00%) 2 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 0 / 20 (0.00%) 0 | |
| Hypoglycaemia unawareness | | | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 20 (5.00%) | |
| occurrences (all) | 8 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 28 February 2018 | Addition of weight to schedule of assessments on Day 32. Text modified to state electrocardiogram (ECG) is from lead II on V2. Added a prohibited concomitant medication. Added a prohibited concomitant medication. |
| 06 April 2018 | Changes to discontinuation of study drug criteria. Updated to add a 2-hour post-dose ECG on Days 1 and 32. Added amylase and lipase sampling at Days 5, 12 and 19. Updated that all deaths (including those that are clearly the result of disease progression) reported as a serious adverse event (SAE). |
| 11 October 2018 | Planned interim analysis was removed. |
| 12 November 2018 | "At least" was changed to "Approximately" in regard to eligible participants in the estimated glomerular filtration rate 30 to 45 mL/min/1.73 m ² category. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported