



Clinical trial results:

An Exploratory Phase 2a Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of MEDI0382 versus Placebo in Overweight/Obese Subjects with Type 2 Diabetes Mellitus Treated with Dapagliflozin and Metformin

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-002817-78 |
| Trial protocol | HU DE |
| Global end of trial date | 06 December 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 21 December 2019 |
| First version publication date | 21 December 2019 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D5670C00007 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03444584 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | MedImmune, LLC |
| Sponsor organisation address | Milstein Building, Granta Park, Cambridge, United Kingdom, CB21 6GH |
| Public contact | Armando Flor, MedImmune, LLC, +1 3013981955, information.center@astrazeneca.com |
| Scientific contact | Armando Flor, MedImmune, LLC, +1 3013981955, information.center@astrazeneca.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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 December 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 December 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the change in glucose area under the concentration time-curve (AUC) as measured by a standardized mixed-meal tolerance test (MMTT) in participants treated with dapagliflozin and metformin receiving MEDI0382 or placebo for 28 days.

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 | 08 May 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 | Germany: 25 |
| Country: Number of subjects enrolled | Hungary: 24 |
| Worldwide total number of subjects | 49 |
| EEA total number of subjects | 49 |

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) | 32 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Germany and Hungary between 08May2018 and 06Dec2018.

Pre-assignment

Screening details:

A total of 128 participants consented to participate in the study, of which 79 were screen failures. A total of 49 participants were randomised 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 of placebo matched to MEDI0382 daily for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period.

| | |
|--|------------------------|
| Arm type | Active comparator |
| 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 daily for 28 days.

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

Dosage and administration details:

Oral metformin tablet (Maximum tolerated dose >1 g) throughout the study including screening period (up to 60 days), 4-week run-in period (for 28 days), and study treatment period for 28 days.

| | |
|--|--------------------|
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral dapagliflozin 10 mg per day was provided during the 4-week run-in period (for 28 days) for participants treated with metformin monotherapy during the screening period (up to 60 days). During the study treatment period, oral dapagliflozin 10 mg per day was provided for all participants for 28 days.

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

Arm description:

Participants received subcutaneous dose of MEDI0382 daily (titrated up from 100 µg for 7 days to 200

µg for 7 days and to 300 µg for 14 days) for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period.

| | |
|--|------------------------|
| 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:

Subcutaneous (SC) dose of MEDI0382 daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and to 300 µg for 14 days) for 28 days.

| | |
|--|--------------------|
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral dapagliflozin 10 mg per day was provided during the 4-week run-in period (for 28 days) for participants treated with metformin monotherapy during the screening period (up to 60 days). During the study treatment period, oral dapagliflozin 10 mg per day was provided for all participants for 28 days.

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

Dosage and administration details:

Oral metformin tablet (Maximum tolerated dose >1 g) throughout the study including screening period (up to 60 days), 4-week run-in period (for 28 days), and study treatment period for 28 days.

| Number of subjects in period 1 | Placebo | MEDI0382 |
|---------------------------------------|---------|----------|
| Started | 24 | 25 |
| Completed | 24 | 23 |
| Not completed | 0 | 2 |
| Consent withdrawn by subject | - | 1 |
| Not specified | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received subcutaneous dose of placebo matched to MEDI0382 daily for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period. | |
| Reporting group title | MEDI0382 |
| Reporting group description: | |
| Participants received subcutaneous dose of MEDI0382 daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and to 300 µg for 14 days) for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period. | |

| Reporting group values | Placebo | MEDI0382 | Total |
|--|---------|----------|-------|
| Number of subjects | 24 | 25 | 49 |
| 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) | 16 | 16 | 32 |
| From 65-84 years | 8 | 9 | 17 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 58.4 | 61.0 | |
| standard deviation | ± 10.0 | ± 8.2 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 12 | 10 | 22 |
| Male | 12 | 15 | 27 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 24 | 25 | 49 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 23 | 25 | 48 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | Placebo |
| Reporting group description: Participants received subcutaneous dose of placebo matched to MEDI0382 daily for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period. | |
| Reporting group title | MEDI0382 |
| Reporting group description: Participants received subcutaneous dose of MEDI0382 daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and to 300 µg for 14 days) for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period. | |

Primary: Change From Baseline to Day 28 in Plasma Glucose Area Under the Concentration Time-curve From Time 0 to 4 Hours (AUC0-4hrs) as Measured by Mixed-meal Tolerance Test (MMTT)

| | |
|---|---|
| End point title | Change From Baseline to Day 28 in Plasma Glucose Area Under the Concentration Time-curve From Time 0 to 4 Hours (AUC0-4hrs) as Measured by Mixed-meal Tolerance Test (MMTT) |
| End point description: The MMTT test involved the consumption of a standardised liquid meal (nutritional supplement of fat, carbohydrate, and protein) within 5 minutes. On Day -1 and on Day 28, following a minimum 10-hour fast, serial of blood samples were obtained prior and through 240 minutes after consumption of standardized meal for the measurement of glucose metabolism (with no additional food intake during this time). Intent-to-treat (ITT) population was analysed which included all participants who received any dose of study drugs analysed according to their randomized treatment group. Here, number of participants analysed "N" signifies participants who were analyzed for the specified end point. | |
| 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 -1 (Baseline) and Day 28 | |

| End point values | Placebo | MEDI0382 | | |
|--|--------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 24 | | |
| Units: hr·mg/dL | | | | |
| least squares mean (confidence interval 95%) | -11.28 (-51.05 to 28.50) | -154.37 (-192.45 to -116.29) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v MEDI0382 |

| | |
|---|--------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -143.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -198.2 |
| upper limit | -87.98 |

Primary: Percent Change From Baseline to Day 28 in Plasma Glucose AUC0-4hrs as Measured by MMTT

| | |
|-----------------|--|
| End point title | Percent Change From Baseline to Day 28 in Plasma Glucose AUC0-4hrs as Measured by MMTT |
|-----------------|--|

End point description:

The MMTT test involved the consumption of a standardised liquid meal (nutritional supplement of fat, carbohydrate, and protein) within 5 minutes. On Day -1 and on Day 28, following a minimum 10-hour fast, serial of blood samples were obtained prior and through 240 minutes after consumption of standardized meal for the measurement of glucose metabolism (with no additional food intake during this time). An ITT population was analysed which included all participants who received any dose of study drugs analysed according to their randomised treatment group. Here, number of participants analysed "N" signifies participants who were analysed for the specified end point.

| | |
|----------------|---------|
| 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 -1 (Baseline) and Day 28

| End point values | Placebo | MEDI0382 | | |
|--|-----------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 24 | | |
| Units: Percent change in Glucose AUC0-4hrs | | | | |
| least squares mean (confidence interval 95%) | -0.13 (-5.96 to 5.69) | -22.30 (-27.88 to -16.73) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v MEDI0382 |

| | |
|---|--------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS mean difference |
| Point estimate | -22.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.24 |
| upper limit | -14.1 |

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 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 28 days after the last dose of MEDI0382 (approximately 8 weeks)

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | | | | |
| TEAEs | 14 | 13 | | |
| TESAEs | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal 12-lead Electrocardiogram (ECG) Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Participants With Abnormal 12-lead Electrocardiogram (ECG) Reported as TEAEs |
|-----------------|--|

End point description:

Number of participants with abnormal 12-lead ECG reported as TEAEs are reported. As-treated population was analysed 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 28 days after the last dose of MEDI0382 (approximately 8 weeks)

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | 0 | 0 | | |

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 are reported. As-treated population was analysed 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 28 days after the last dose of MEDI0382 (approximately 8 weeks)

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | | | | |
| Tachycardia | 2 | 1 | | |
| Tachycardia paroxysmal | 1 | 0 | | |
| Palpitations | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Physical Examinations Reported as TEAEs

| | |
|---|--|
| End point title | Number of Participants With Abnormal Physical Examinations Reported as TEAEs |
| End point description: Number of participants with abnormal physical examinations reported as TEAEs are reported. As-treated population was analysed 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 28 days after the last dose of MEDI0382 (approximately 8 weeks) | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Placebo | MEDI0382 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | 0 | 0 | | |

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 are reported. As-treated population was analysed 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 28 days after the last dose of MEDI0382 (approximately 8 weeks) | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Placebo | MEDI0382 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | | | | |
| Hypoglycemia | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero to

Infinity (AUC [0-∞]) of MEDI0382

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC [0-∞]) of MEDI0382 ^[1] |
|-----------------|--|

End point description:

Area under the plasma concentration time curve from time zero to infinity (AUC [0-∞]) of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

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 | 25 | | | |
| Units: ng.hr/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n=9) | 106.4 (57.7 to 251.8) | | | |
| Day 14 (MEDI0382 200 µg) (n=9) | 196.7 (99.4 to 472.0) | | | |
| Day 28 (MEDI0382 300 µg) (n=9) | 314.6 (211.0 to 537.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC [0-∞]) of Dapagliflozin

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC [0-∞]) of Dapagliflozin |
|-----------------|--|

End point description:

Area under the plasma concentration time curve from time zero to infinity (AUC [0-∞]) of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: ng.hr/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day -1 (n= 20, 24) | 432.6 (271.5 to 918.6) | 473.8 (288.8 to 1073.2) | | |
| Day 7 (n=15, 12) | 410.2 (209.9 to 1024.2) | 438.0 (222.2 to 833.6) | | |
| Day 14 (n=16, 8) | 421.0 (219.0 to 1327.8) | 448.6 (247.0 to 615.9) | | |
| Day 28 (n=15, 16) | 405.7 (261.1 to 799.5) | 523.4 (319.5 to 946.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve During the Dosing Period (AUCtau) of MEDI0382

| | |
|-----------------|---|
| End point title | Area Under the Plasma Concentration-time Curve During the Dosing Period (AUCtau) of MEDI0382 ^[2] |
|-----------------|---|

End point description:

Area under the plasma concentration-time curve during the dosing period (AUCtau) of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

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 | 25 | | | |
| Units: ng.hr/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n=23) | 89.6 (43.1 to 199.4) | | | |
| Day 14 (MEDI0382 200 µg) (n=23) | 165.0 (86.9 to 365.5) | | | |
| Day 28 (MEDI0382 300 µg) (n=22) | 265.9 (101.7 to 795.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve During the Dosing Period (AUCtau) of Dapagliflozin

| | |
|-----------------|---|
| End point title | Area Under the Plasma Concentration-time Curve During the Dosing Period (AUCtau) of Dapagliflozin |
|-----------------|---|

End point description:

Area under the plasma Concentration-time curve during the dosing period (AUCtau) of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: ng.hr/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day -1 (n= 24, 24) | 400.9 (182.4 to 1011.5) | 430.3 (252.5 to 815.2) | | |
| Day 7 (n=24, 25) | 377.5 (76.4 to 910.7) | 406.8 (211.5 to 1142.6) | | |
| Day 14 (n= 23, 23) | 417.1 (209.0 to 1107.7) | 396.8 (215.4 to 669.7) | | |
| Day 28 (n= 23, 24) | 423.1 (180.6 to 977.3) | 463.8 (284.3 to 1245.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of MEDI0382

| | |
|-----------------|--|
| End point title | Maximum Observed Serum Concentration (Cmax) of |
|-----------------|--|

End point description:

Maximum observed serum concentration (Cmax) of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

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 | 25 | | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n = 25) | 5.2 (2.7 to 11.9) | | | |
| Day 14 (MEDI0382 200 µg) (n= 24) | 10.1 (4.4 to 21.7) | | | |
| Day 28 (MEDI0382 300 µg) (n= 22) | 17.2 (6.1 to 45.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Dapagliflozin

| | |
|-----------------|--|
| End point title | Maximum Observed Serum Concentration (Cmax) of Dapagliflozin |
|-----------------|--|

End point description:

Maximum observed serum concentration (Cmax) of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: ng/mL | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day -1 (n= 24,25) | 110.1 (46.3 to 208.3) | 116.7 (38.2 to 206.8) | | |
| Day 7 (n= 24, 25) | 92.0 (5.2 to 256.7) | 84.4 (24.1 to 211.7) | | |
| Day 14 (n= 23, 24) | 95.6 (33.5 to 280.7) | 61.1 (15.8 to 149.9) | | |
| Day 28 (n= 23, 24) | 112.2 (47.0 to 235.4) | 94.2 (25.2 to 182.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Serum Concentration (Tmax) of

MEDI0382

| | |
|-----------------|--|
| End point title | Time to Reach Maximum Observed Serum Concentration (Tmax) of MEDI0382 ^[4] |
|-----------------|--|

End point description:

Time to reach maximum observed serum concentration (Tmax) of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

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 | 25 | | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 25) | 5.5 (2 to 8) | | | |
| Day 14 (MEDI0382 200 µg) (n= 24) | 5.1 (2 to 8) | | | |
| Day 28 (MEDI0382 300 µg) (n= 22) | 4 (1.9 to 8.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Serum Concentration (Tmax) of Dapagliflozin

| | |
|-----------------|--|
| End point title | Time to Reach Maximum Observed Serum Concentration (Tmax) of Dapagliflozin |
|-----------------|--|

End point description:

Time to reach maximum observed serum concentration (Tmax) of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28

| End point values | Placebo | MEDI0382 | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day -1 (n= 24, 25) | 1 (0.5 to 2) | 1 (0.4 to 23.9) | | |
| Day 7 (n= 24, 25) | 1 (0.5 to 11.4) | 1 (0.5 to 4) | | |
| Day 14 (23, 24) | 1.1 (0.5 to 6) | 1 (0 to 8.1) | | |
| Day 28 (23, 24) | 1 (0.2 to 1.8) | 1 (0.5 to 8.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-life ($t_{1/2}$) of MEDI0382

| | |
|-----------------|---|
| End point title | Terminal Elimination Half-life ($t_{1/2}$) of MEDI0382 ^[5] |
|-----------------|---|

End point description:

Terminal half-life is the time required for the plasma concentration to fall by 50% during the terminal phase. The $t_{1/2}$ of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: 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 | 25 | | | |
| Units: Hours | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 9) | 8.8 (6.1 to 11.9) | | | |
| Day 14 (MEDI0382 200 µg) (n= 9) | 9 (5.6 to 11.8) | | | |
| Day 28 (MEDI0382 300 µg) (n= 9) | 9.1 (5.1 to 11.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-life ($t_{1/2}$) of Dapagliflozin

| | |
|-----------------|---|
| End point title | Terminal Elimination Half-life ($t_{1/2}$) of Dapagliflozin |
|-----------------|---|

End point description:

Terminal half-life is the time required for the plasma concentration to fall by 50% during the terminal phase. The $t_{1/2}$ of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Hours | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day -1 (n= 20, 24) | 8.2 (5.3 to 11.2) | 7.8 (5.4 to 11.3) | | |
| Day 7 (n= 15, 12) | 7.9 (4.1 to 10.4) | 8.3 (5.8 to 11.1) | | |
| Day 14 (n= 16, 8) | 7.0 (5.1 to 11.4) | 8.5 (7 to 10) | | |
| Day 28 (15, 16) | 7.6 (5.8 to 11.0) | 9.1 (6.1 to 11.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of MEDI0382

| | |
|-----------------|--|
| End point title | Apparent clearance (CL/F) of MEDI0382 ^[6] |
|-----------------|--|

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. The CL/F of MEDI0382 is reported. MEDI0382 pharmacokinetic (PK) population was analysed which included all participants who received at least 1 dose of MEDI0382 and had at least 1 MEDI0382 PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days 7, 14, and 28

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: 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 | 25 | | | |
| Units: L/hr | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 9) | 1.1 (0.5 to 1.9) | | | |
| Day 14 (MEDI0382 200 µg) (n= 9) | 1.3 (0.5 to 2.2) | | | |
| Day 28 (MEDI0382 300 µg) (n= 9) | 1.2 (0.8 to 1.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of Dapagliflozin

| | |
|---|--|
| End point title | Apparent clearance (CL/F) of Dapagliflozin |
| End point description: | |
| Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. The CL/F of Dapagliflozin is reported. Dapagliflozin PK population was analysed which included all participants who received at least 1 dose of dapagliflozin and had at least 1 dapagliflozin PK sample above the lower limit of quantitation. Here, number analysed "n" signifies participants who were analysed for the specified day. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose on Days -1, 7, 14, and 28 | |

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: L/Hr | | | | |
| geometric mean (full range (min-max)) | | | | |
| Day -1 (n= 20, 24) | 25.5 (13.3 to 38.9) | 23.3 (12.3 to 39.6) | | |
| Day 7 (n= 15, 12) | 26.7 (11.0 to 52.8) | 25.7 (14.2 to 47.3) | | |
| Day 14 (n= 16, 8) | 25.9 (9.0 to 47.7) | 25.5 (18.8 to 46.4) | | |
| Day 28 (n= 15, 16) | 26.8 (13.8 to 40.2) | 22.2 (13.4 to 35.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) Titer to MEDI0382

| | |
|-----------------|---|
| End point title | Number of Participants With Positive Anti-drug Antibodies |
|-----------------|---|

End point description:

Number of participants with positive Anti-drug antibodies (ADA) titer to MEDI0382 are reported. Immunogenicity population included was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to the treatment they actually received and had at least one serum sample for immunogenicity testing. Here, number analysed "n" signifies participants who were analysed for the specified day.

End point type

Secondary

End point timeframe:

Day 1 (pre-dose), on Day 29 , and 28 days post last dose (end of study visit; approximately 8 weeks)

| End point values | Placebo | MEDI0382 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Participants | | | | |
| Day 1 (n= 24, 25) | 0 | 3 | | |
| Day 29 (n= 24, 24) | 0 | 1 | | |
| End of Study (n= 24, 24) | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Glucose AUC24-hrs to the end of Each Dosing Level as Measured by Continuous Glucose Monitoring (CGM)

End point title

Change From Baseline in Plasma Glucose AUC24-hrs to the end of Each Dosing Level as Measured by Continuous Glucose Monitoring (CGM)

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

End point type

Secondary

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: hr.mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | 49.14 (± 667.30) | -832.66 (± 506.22) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 57.30 (± 379.95) | -666.05 (± 647.63) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | 229.47 (± 589.19) | -726.85 (± 710.71) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean 24-hrs Plasma Glucose to the end of Each Dosing Level as Measured by CGM

| | |
|-----------------|---|
| End point title | Change From Baseline in Mean 24-hrs Plasma Glucose to the end of Each Dosing Level as Measured by CGM |
|-----------------|---|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | 2.59 (± 28.96) | -34.74 (± 20.34) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 2.83 (± 17.01) | -28.34 (± 27.12) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | 9.70 (± 24.73) | -30.55 (± 29.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Standard Deviation of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM

| | |
|-----------------|---|
| End point title | Change From Baseline in Standard Deviation of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM |
|-----------------|---|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | -3.01 (± 13.84) | -7.21 (± 11.05) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 1.38 (± 9.47) | -7.52 (± 9.73) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -4.39 (± 10.67) | -9.76 (± 10.18) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Coefficient of Variation of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM

| | |
|-----------------|---|
| End point title | Change From Baseline in Coefficient of Variation of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM |
|-----------------|---|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Percent of coefficient of variation | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | -2.37 (± 9.06) | -0.45 (± 6.68) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 0.96 (± 8.74) | -2.06 (± 6.59) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -4.26 (± 7.16) | -3.21 (± 7.25) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Amplitude of Glucose Excursions (MAGE) of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM

| | |
|-----------------|--|
| End point title | Change From Baseline in Mean Amplitude of Glucose Excursions (MAGE) of 24-hrs Plasma Glucose Readings to the end of Each Dosing Level as Measured by CGM |
|-----------------|--|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | -13.46 (± 32.07) | -25.74 (± 35.06) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 18.05 (± 47.60) | -26.59 (± 25.60) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -8.09 (± 27.68) | -27.92 (± 23.17) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within the Euglycemic Range to the end of Each Dosing as Measured by CGM

| | |
|-----------------|---|
| End point title | Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within the Euglycemic Range to the end of Each Dosing as Measured by CGM |
|-----------------|---|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. Euglycemic range is defined as glucose levels of ≥ 70 mg/dL (≥ 3.9 mmol/L) and ≤ 180 mg/dL (≤ 10.0 mmol/L). An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Percent of Euglycemic Range | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | -5.61 (± 19.65) | 7.12 (± 20.60) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | -2.79 (± 10.16) | 5.31 (± 17.71) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -4.17 (± 15.80) | 6.54 (± 24.37) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within the Hyperglycemic Range to the end of Each Dosing as Measured by CGM

| | |
|-----------------|--|
| End point title | Change From Baseline in the Percentage of 24-hrs Glucose |
|-----------------|--|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. Hyperglycemic (high glucose) range is defined as glucose levels of >180 mg/dL (> 10.0 mmol/L). An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|---------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Percent of hyperglycemic range | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | 3.62 (± 17.80) | -13.99 (± 14.95) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 0.36 (± 10.50) | -9.81 (± 13.68) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | 6.08 (± 16.96) | -9.72 (± 20.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within the Hypoglycemic Range to the end of Each Dosing as Measured by CGM

| | |
|-----------------|---|
| End point title | Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within the Hypoglycemic Range to the end of Each Dosing as Measured by CGM |
|-----------------|---|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. Hypoglycemic range is defined as glucose levels of < 70 mg/dL (< 3.9 mmol/L). An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Percent of hypoglycemic range | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | 1.17 (± 5.64) | 6.08 (± 10.36) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 2.00 (± 3.79) | 3.44 (± 12.72) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -2.08 (± 4.14) | 2.84 (± 12.20) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within Clinically Significant Hypoglycemic Range to the end of Each Dosing as Measured by CGM

| | |
|-----------------|--|
| End point title | Change From Baseline in the Percentage of 24-hrs Glucose Readings That Falls Within Clinically Significant Hypoglycemic Range to the end of Each Dosing as Measured by CGM |
|-----------------|--|

End point description:

Continuous glucose monitoring is a minimally invasive device applied to the skin in the upper arm that provides a measure of interstitial glucose levels every 15 minutes. Continuous glucose monitoring measures glucose excursions during different meals and at different times of the day. End of dosing: Day 7 for MEDI0382 100 µg; Day 14 for MEDI0382 200 µg; and Day 28 for MEDI0382 300 µg. Clinically significant hypoglycemic range is defined as glucose levels of < 54 mg/dL (3.0 mmol/L). An ITT population was analysed which included all participants who received any dose of study drug (MEDI0382 or placebo) and analysed according to their randomized treatment group. Here, number analysed "n" signifies participants who were analysed for the specified day.

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

End point timeframe:

Day -1 (Baseline) through Day 7 for MEDI0382 100 µg, Day 14 for MEDI0382 200 µg, and Day 28 for MEDI0382 300 µg

| End point values | Placebo | MEDI0382 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 25 | | |
| Units: Percent of hypoglycemic range | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 (MEDI0382 100 µg) (n= 10, 12) | 0.76 (± 3.64) | 1.61 (± 5.03) | | |
| Day 14 (MEDI0382 200 µg) (n= 9, 13) | 0.27 (± 1.19) | -0.06 (± 2.18) | | |
| Day 28 (MEDI0382 300 µg) (n= 12, 18) | -0.26 (± 0.90) | 0.93 (± 4.91) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day -2 through 28 days post last dose (approximately 07 months)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Participants received subcutaneous dose of MEDI0382 daily (titrated up from 100 µg for 7 days to 200 µg for 7 days and to 300 µg for 14 days) for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period.

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

Reporting group description:

Participants received subcutaneous dose of placebo matched to MEDI0382 daily for 28 days. Participants were on metformin and dapagliflozin background dual therapy during the treatment period.

| Serious adverse events | MEDI0382 | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 24 (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 | MEDI0382 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 25 (52.00%) | 14 / 24 (58.33%) | |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Procedural nausea | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |

| | | | |
|--|----------------------|---------------------|--|
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | 2 / 24 (8.33%) 2 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | 0 / 24 (0.00%) 0 | |
| Tachycardia paroxysmal subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 5 | 1 / 24 (4.17%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 24 (0.00%) 0 | |
| General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 5 | 0 / 24 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 0 / 24 (0.00%) 0 | |
| Diarrhoea | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 2 / 24 (8.33%) 2 | |
| Nausea subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 7 | 2 / 24 (8.33%) 4 | |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 6 | 0 / 24 (0.00%) 0 | |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 0 / 24 (0.00%) 0 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 24 (4.17%) 1 | |
| Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | |
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| Pruritus genital subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 24 (8.33%) 2 | |
| Rash pruritic | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 1 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | 3 / 24 (12.50%) | |
| occurrences (all) | 3 | 3 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 24 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 1 | |
| Genital infection fungal | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 1 | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 1 | 1 | |
| Food craving | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 2 | |
| Hypoglycaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 24 (4.17%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 08 December 2017 | Amended rationale for conducting the study, schedule of treatment period procedures, treatment regimen, and schedule of treatment period procedures. Updated selection of participants with type 2 diabetes mellitus with a glycated haemoglobin (Range of 7.0% to 10.0%). Added Inclusion criteria allowing participants on stable doses of metformin (maximum tolerated dose [MTD] > 1 g) with canagliflozin (maximum dose of 300 mg/day) or metformin (MTD > 1 g) with empagliflozin (maximum dose of 25 mg/day) for at least 3 months prior to screening to enter the study, after switching to dapagliflozin 10 mg at least 2 weeks prior to Day -2. Updated exclusion criterion to clarify that investigational sodium-glucose cotransporter-2 (SGLT2)-containing preparations (excluding canagliflozin and empagliflozin) within the last 30 days or 5 half-lives of the drug (whichever is longest) at the time of screening are exclusionary. Corrected schedule of run-in period procedures. Added Day -2 for training of participant on glucose and ketone monitoring. Added triglycerides test (screening only) to the serum chemistry and "Plasma glucose" was amended to "FPG". The starting point for AE and SAE collection was changed from "the time of admission to the clinic (Day -2)" to "from the time of informed consent". |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported