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 asses 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 (AUCT) of MEDI0382 at 300 µg

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

End point description:

Area under the plasma concentration time curve over a dosing duration (AUCT) 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 (Cmax) of MEDI0382 at 300 µg

End point title	Maximum Observed Serum Concentration (Cmax) of MEDI0382 at 300 µg[2]

End point description:

Maximum observed serum concentration (Cmax) 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 (Ctrough) of MEDI0382

End point title	Trough Plasma Concentration (Ctrough) 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 (Ctrough) 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	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradyarrhythmia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bundle branch block left			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bundle branch block right			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 21 (9.52%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Carotid artery stenosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	
occurrences (all)	3	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vertigo positional			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	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	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin fissures			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin swelling			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 21 (14.29%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Otitis media			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	3	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