



Clinical trial results:

An Exploratory Phase 2a, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of MEDI0382 on Energy Balance in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Summary

EudraCT number	2018-001220-19
Trial protocol	GB
Global end of trial date	22 December 2019

Results information

Result version number	v1
This version publication date	01 January 2021
First version publication date	01 January 2021

Trial information

Trial identification

Sponsor protocol code	D5670C00021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03596177
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	Victoria Parker, MedImmune, LLC, +44 747 1357172, information.center@astrazeneca.com
Scientific contact	Victoria Parker, MedImmune, LLC, +44 747 1357172, 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	30 September 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 December 2019
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 assess the effect of MEDI0382 titrated up to a dose level of 300 µg on body weight versus placebo.

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	26 September 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: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	17
From 65 to 84 years	11

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

The study was conducted in United Kingdom from 26Sep2018 to 22Dec2019.

Pre-assignment

Screening details:

A total of 28 participants were randomized in the study.

Period 1

Period 1 title	Single Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received subcutaneous (SC) injection of placebo for 16 days in the single-blind treatment period, and then SC injection of placebo matched to MEDI0382 for 42 days in double-blind treatment period.

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:

SC injection of placebo for 16 days.

Arm title	MEDI0382
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Arm description:

Participants received SC injection of placebo for 16 days in the single-blind treatment period, and then SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days) in double-blind treatment period.

Arm type	Experimental
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:

SC injection of placebo for 16 days.

Number of subjects in period 1	Placebo	MEDI0382
Started	9	19
Completed	7	18
Not completed	2	1
Consent withdrawn by subject	1	1
Not Specified	1	-

Period 2

Period 2 title	Double Blind Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received subcutaneous (SC) injection of placebo for 16 days in the single-blind treatment period, and then SC injection of placebo matched to MEDI0382 for 42 days in double-blind treatment period.

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:

SC injection of placebo matched to MEDI0382 for 42 days.

Arm title	MEDI0382
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Arm description:

Participants received SC injection of placebo for 16 days in the single-blind treatment period, and then SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days) in double-blind treatment period.

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

Dosage and administration details:

SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days).

Number of subjects in period 2	Placebo	MEDI0382
Started	7	18
Completed	7	12
Not completed	0	6
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1
Not Specified	-	4

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received subcutaneous (SC) injection of placebo for 16 days in the single-blind treatment period, and then SC injection of placebo matched to MEDI0382 for 42 days in double-blind treatment period.	
Reporting group title	MEDI0382
Reporting group description:	
Participants received SC injection of placebo for 16 days in the single-blind treatment period, and then SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days) in double-blind treatment period.	

Reporting group values	Placebo	MEDI0382	Total
Number of subjects	9	19	28
Age categorical			
Units: Participants			
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)	4	13	17
From 65-84 years	5	6	11
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	62.2	59.5	
standard deviation	± 7.2	± 8.4	-
Sex: Female, Male			
Units: Participants			
Female	2	1	3
Male	7	18	25
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	1	0	1
White	8	18	26
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	9	18	27

Unknown or Not Reported	0	1	1
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End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received subcutaneous (SC) injection of placebo for 16 days in the single-blind treatment period, and then SC injection of placebo matched to MEDI0382 for 42 days in double-blind treatment period.	
Reporting group title	MEDI0382
Reporting group description: Participants received SC injection of placebo for 16 days in the single-blind treatment period, and then SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days) in double-blind treatment period.	
Reporting group title	Placebo
Reporting group description: Participants received subcutaneous (SC) injection of placebo for 16 days in the single-blind treatment period, and then SC injection of placebo matched to MEDI0382 for 42 days in double-blind treatment period.	
Reporting group title	MEDI0382
Reporting group description: Participants received SC injection of placebo for 16 days in the single-blind treatment period, and then SC injection of MEDI0382 titrated up to 300 µg for 42 days (100 µg for 4 days, followed by 200 µg for 4 days, and finally 300 µg for 34 days) in double-blind treatment period.	

Primary: Percent Change in Body Weight From Baseline to Day 59

End point title	Percent Change in Body Weight From Baseline to Day 59
End point description: Percent change in body weight is reported. The last observation carried forward (LOCF) analysis was used for missing data imputation for Day 59. Modified intent-to-treat (ITT) population was analysed which included participants in ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.	
End point type	Primary
End point timeframe: Baseline (Day 17) and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	14		
Units: Percent change in body weight				
least squares mean (confidence interval 90%)	-1.40 (-2.66 to -0.13)	-3.98 (-4.85 to -3.10)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.15
upper limit	-1

Secondary: Percent Change in Total Energy Intake From the ad Libitum Lunch From Baseline to Day 32 and Day 59

End point title	Percent Change in Total Energy Intake From the ad Libitum Lunch From Baseline to Day 32 and Day 59
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End point description:

Total energy intake in kilojoules (kJ) were recorded in a food diary after ad libitum lunch on Days 16, 32, and 59. The ad libitum lunch was a standardised solid meal with food of known macronutrient content. Participants were advised to eat freely until they feel comfortably full and the meal duration was flexible according to participant's preference. During the meal, the quantity of food ingested was recorded by study site staff without participants' awareness that food consumption was recorded. Percent change in total energy intake from the ad libitum lunch is reported. The LOCF analysis was used for missing data imputation for Day 59. The mITT population population was analysed whihc included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
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End point timeframe:

Baseline (Day 16), Day 32, and Day 59

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	14		
Units: Percent change in total energy intake				
least squares mean (confidence interval 90%)				
Percent change at Day 32	-5.170 (-23.344 to 13.003)	-50.652 (-63.480 to -37.823)		
Percent change at Day 59	-10.598 (-31.316 to 10.119)	-51.922 (-66.546 to -37.297)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 32
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-45.481
Confidence interval	
level	90 %
sides	2-sided
lower limit	-67.777
upper limit	-23.186

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-41.323
Confidence interval	
level	90 %
sides	2-sided
lower limit	-66.74
upper limit	-15.907

Secondary: Change in Total Energy Intake From the ad Libitum Lunch From Baseline to Day 32 and Day 59

End point title	Change in Total Energy Intake From the ad Libitum Lunch From Baseline to Day 32 and Day 59
End point description:	Total energy intake in kilojoules (kJ) were recorded in a food diary after ad libitum lunch on Days 16, 32, and 59. The ad libitum lunch was a standardised solid meal with food of known macronutrient content. Participants were advised to eat freely until they feel comfortably full and the meal duration was flexible according to participant's preference. During the meal, the quantity of food ingested was recorded by study site staff without participants' awareness that food consumption was recorded. Change in total energy intake from the ad libitum lunch is reported. The LOCF analysis was used for missing data imputation for Day 59. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.
End point type	Secondary
End point timeframe:	
Baseline (Day 16) to Day 32 and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	14		
Units: Kilojoules				
least squares mean (confidence interval 90%)				
Change at Day 32	-126.271 (-647.387 to 394.846)	-1677.465 (-2045.322 to -1309.607)		
Change at Day 59	-410.816 (-1107.896 to 286.263)	-1743.331 (-2235.400 to -1251.261)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 32
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1551.194
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2190.52
upper limit	-911.873

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1332.515
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2187.71
upper limit	-477.318

Secondary: Percent Change in Total Energy Expenditure (TEE) as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Percent Change in Total Energy Expenditure (TEE) as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58
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End point description:

A whole room calorimetry assessment was used to measure gaseous exchange while exercising and therefore indirect estimates of energy expenditure over a 24-hour period. For the assessment, participants had to enter the whole room calorimeter for up to 36 hours and reside inside for this entire duration (this will include toilet visits too). During the time in the calorimeter participants were asked to exercise on an exercise bike for 15-minute intervals at 4 times. During these sessions participants were asked to aim for a heart rate of 65% of maximum (defined as 220 beats per minute minus age) and complete the full 15-minute session. In addition, participants abstained from caffeinated drinks for at least 24 hours prior to measurements as caffeine may increase energy expenditure (EE) and dietary advice was given to ensure participants had a neutral energy balance prior to whole calorimetry assessments. Percent change in TEE is reported. The mITT population was analysed.

End point type	Secondary
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End point timeframe:

Baseline (Day 15) and Day 58

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent change in TEE				
least squares mean (confidence interval 90%)	2.032 (-2.833 to 6.898)	-1.141 (-4.825 to 2.544)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.384
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.173
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.368
upper limit	3.022

Secondary: Change in TEE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Change in TEE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58
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End point description:

A whole room calorimetry assessment was used to measure gaseous exchange while exercising and therefore indirect estimates of energy expenditure over a 24-hour period. For the assessment, participants had to enter the whole room calorimeter for up to 36 hours and reside inside for this entire duration (this will include toilet visits too). During the time in the calorimeter participants were asked to exercise on an exercise bike for 15-minute intervals at 4 times. During these sessions participants were asked to aim for a heart rate of 65% of maximum (defined as 220 beats per minute minus age) and complete the full 15-minute session. In addition, participants abstained from caffeinated drinks for at least 24 hours prior to measurements as caffeine may increase EE and dietary advice was given to ensure participants had a neutral energy balance prior to whole calorimetry assessments. Change in TEE is reported. The mITT population was analysed.

End point type	Secondary
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End point timeframe:

Baseline (Day 15) and Day 58

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: kilojoules/kg fat body mass				
least squares mean (confidence interval 90%)	5.969 (-8.364 to 20.302)	-4.070 (-14.924 to 6.783)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.351
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-10.039
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.287
upper limit	8.209

Secondary: Percent Change in Activity Energy Expenditure (AEE) as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Percent Change in Activity Energy Expenditure (AEE) as
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End point description:

A whole room calorimetry assessment was used to measure gaseous exchange while exercising and therefore indirect estimates of energy expenditure over a 24-hour period. For the assessment, participants had to enter the whole room calorimeter for up to 36 hours and reside inside for this entire duration (this will include toilet visits too). During the time in the calorimeter participants were asked to exercise on an exercise bike for 15-minute intervals at 4 times. During these sessions participants were asked to aim for a heart rate of 65% of maximum (defined as 220 beats per minute minus age) and complete the full 15-minute session. In addition, participants abstained from caffeinated drinks for at least 24 hours prior to measurements as caffeine may increase EE and dietary advice was given to ensure participants had a neutral energy balance prior to whole calorimetry assessments. Percent change in AEE is reported. The mITT population was analysed.

End point type	Secondary
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End point timeframe:

Baseline (Day 15) and Day 58

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent change in AEE				
least squares mean (confidence interval 90%)	-0.446 (-6.836 to 5.943)	-0.261 (-5.139 to 4.618)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.186
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.858
upper limit	8.229

Secondary: Change in AEE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Change in AEE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58
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End point description:

A whole room calorimetry assessment was used to measure gaseous exchange while exercising and

therefore indirect estimates of energy expenditure over a 24-hour period. For the assessment, participants had to enter the whole room calorimeter for up to 36 hours and reside inside for this entire duration (this will include toilet visits too). During the time in the calorimeter participants were asked to exercise on an exercise bike for 15-minute intervals at 4 times. During these sessions participants were asked to aim for a heart rate of 65% of maximum (defined as 220 beats per minute minus age) and complete the full 15-minute session. In addition, participants abstained from caffeinated drinks for at least 24 hours prior to measurements as caffeine may increase EE and dietary advice was given to ensure participants had a neutral energy balance prior to whole calorimetry assessments. Change in AEE is reported. The mITT population was analysed.

End point type	Secondary
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End point timeframe:

Baseline (Day 15) and Day 58

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: kilojoules/kg fat body mass				
least squares mean (confidence interval 90%)	-1.132 (-3.259 to 0.995)	-0.265 (-1.889 to 1.359)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.867
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.81
upper limit	3.545

Secondary: Percent Change in Resting Energy Expenditure (REE) as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Percent Change in Resting Energy Expenditure (REE) as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58
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End point description:

The REE represents the amount of calories required for a 24-hour period by the body during a non-active period and is assessed by whole room indirect calorimetry method. Percent change in REE is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
End point timeframe:	
Baseline (Day 15) and Day 58	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent change in REE				
least squares mean (confidence interval 90%)	8.113 (3.254 to 12.972)	4.468 (0.816 to 8.120)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.645
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.894
upper limit	2.603

Secondary: Change in REE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58

End point title	Change in REE as Measured by Whole Room Indirect Calorimetry From Baseline to Day 58
End point description:	
<p>The REE represents the amount of calories required for a 24-hour period by the body during a non-active period and is assessed by whole room indirect calorimetry method. Change in REE is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.</p>	
End point type	Secondary
End point timeframe:	
Baseline (Day 15) and Day 58	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: kilojoules/kg fat body mass				
least squares mean (confidence interval 90%)	13.237 (4.104 to 22.369)	7.565 (0.701 to 14.429)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 58
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.672
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.415
upper limit	6.072

Secondary: Percent Change in REE as Measured by Hood Indirect Calorimetry From Baseline to Day 32

End point title	Percent Change in REE as Measured by Hood Indirect Calorimetry From Baseline to Day 32
End point description:	
Hood calorimetry assessment was used to measure REE. A large plastic hood is placed over participants head for 20 minutes and measurements of gaseous exchange are undertaken. Participants were rested for at least 1 hour prior to hood calorimetry measures; during a hood calorimetry assessment the participants were asked to remain quiet and rested for 40 minutes in total with 10 minutes before and after the assessment to allow for room air assessment. Percent change in REE is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analyzed according to their randomised treatment group.	
End point type	Secondary
End point timeframe:	
Baseline (Day 16) and Day 32	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent Change in REE				
least squares mean (confidence interval 90%)	1.189 (-5.955 to 8.332)	8.546 (3.138 to 13.954)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 32
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	7.357
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.742
upper limit	16.456

Secondary: Change in REE as Measured by Hood Indirect Calorimetry From Baseline to Day 32

End point title	Change in REE as Measured by Hood Indirect Calorimetry From Baseline to Day 32
End point description:	
Hood calorimetry assessment was used to measure REE. A large plastic hood is placed over participants head for 20 minutes and measurements of gaseous exchange are undertaken. Participants were rested for at least 1 hour prior to hood calorimetry measures; during a hood calorimetry assessment the participants were asked to remain quiet and rested for 40 minutes in total with 10 minutes before and after the assessment to allow for room air assessment. Change in REE is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.	
End point type	Secondary
End point timeframe:	
Baseline (Day 16) and Day 32	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: kilojoules/kg fat body mass				
least squares mean (confidence interval 90%)	3.316 (-11.080 to 17.712)	18.502 (7.604 to 29.400)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 32
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	15.186
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.151
upper limit	33.523

Secondary: Change in Body Weight From Baseline to Day 59

End point title	Change in Body Weight From Baseline to Day 59
End point description:	
Change in body weight is reported. The LOCF analysis was used for missing data imputation for Day 59. The mITT population population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.	
End point type	Secondary
End point timeframe:	
Baseline (Day 17) and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	14		
Units: kg				
least squares mean (confidence interval 90%)	-1.26 (-2.48 to -0.05)	-3.80 (-4.65 to -2.96)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.54
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.05
upper limit	-1.03

Secondary: Percent Change in Total Body fat Mass as Measured by Dual-energy X-ray Absorptiometry (DXA) From Baseline to Day 59

End point title	Percent Change in Total Body fat Mass as Measured by Dual-energy X-ray Absorptiometry (DXA) From Baseline to Day 59
End point description:	
The total body fat mass was measured in kilograms (kg) using DXA. Participants body was scanned using DXA scanner and total body fat mass was determined. Percent change in total body fat mass is reported. The mITT population population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.	
End point type	Secondary
End point timeframe:	
Baseline (Day -1) and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent change in total body fat mass				
least squares mean (confidence interval 90%)	-4.218 (-8.249 to -0.186)	-9.340 (-12.343 to -6.337)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.122
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.364
upper limit	0.119

Secondary: Change in Total Body fat Mass as Measured by DXA From Baseline to Day 59

End point title	Change in Total Body fat Mass as Measured by DXA From Baseline to Day 59
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End point description:

The total body fat mass was measured in kg using DXA. Participants body was scanned using DXA scanner and total body fat mass was determined. Change in total body fat mass is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
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End point timeframe:

Baseline (Day -1) and Day 59

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Kg				
least squares mean (confidence interval 90%)	-1.455 (-2.806 to -0.103)	-3.303 (-4.310 to -2.296)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.848

Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.605
upper limit	-0.091

Secondary: Percent Change in Total Body fat Mass: Lean Mass Ratio as Measured by DXA From Baseline to Day 59

End point title	Percent Change in Total Body fat Mass: Lean Mass Ratio as Measured by DXA From Baseline to Day 59
End point description:	
The total body fat mass and lean body mass was measured in kg using DXA. Participants body was scanned using DXA scanner and total body fat mass and lean mass was determined. Percent change in total body fat mass:lean mass (TBFM:LM) ratio is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.	
End point type	Secondary
End point timeframe:	
Baseline (Day -1) and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percent change in TBFM:LM ratio				
least squares mean (confidence interval 90%)	-1.667 (-4.934 to 1.600)	-4.827 (-7.298 to -2.355)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.204
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.159
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.326
upper limit	1.007

Secondary: Change in Total Body fat Mass: Lean Mass Ratio as Measured by DXA From Baseline to Day 59

End point title	Change in Total Body fat Mass: Lean Mass Ratio as Measured by DXA From Baseline to Day 59
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End point description:

The total body fat mass and lean body mass was measured in kg using DXA. Participants body was scanned using DXA scanner and total body fat mass and lean mass was determined. Change in total body fat mass:lean mass (TBFM:LM) ratio is reported. The mITT population population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
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End point timeframe:

Baseline (Day -1) and Day 59

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Ratio				
least squares mean (confidence interval 90%)	-0.010 (-0.027 to 0.007)	-0.029 (-0.042 to -0.016)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.019
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.041
upper limit	0.003

Secondary: Change in Fasting Glucose During a Mixed-meal Tolerance Test (MMTT) from Baseline to Day 59

End point title	Change in Fasting Glucose During a Mixed-meal Tolerance Test (MMTT) from Baseline to Day 59
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End point description:

The MMTT involves consumption of a standardized solid breakfast meal within 5 minutes, following a minimum 12 hours fast, and timed serial blood samples are obtained for measurement of glucose levels through 240 minutes with no additional food intake during this time. Change in fasting glucose is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
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End point timeframe:

Baseline (Day -1) and Day 59

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: mg/dL				
least squares mean (confidence interval 90%)	-12.600 (-21.673 to -3.527)	-38.601 (-45.360 to -31.842)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-26.001
Confidence interval	
level	90 %
sides	2-sided
lower limit	-37.801
upper limit	-14.201

Secondary: Percent Change in Glucose Area Under the Concentration-time Curve at 0 to 4 hours (AUC0-4hrs) During a MMTT From Baseline to Day 59

End point title	Percent Change in Glucose Area Under the Concentration-time Curve at 0 to 4 hours (AUC0-4hrs) During a MMTT From Baseline to Day 59
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End point description:

The MMTT involves consumption of a standardized solid breakfast meal within 5 minutes, following a minimum 12 hours fast, and timed serial blood samples are obtained for measurement of glucose levels through 240 minutes with no additional food intake during this time. Percent change in glucose AUC0-4hrs during MMTT is reported. The mITT population was analysed which included participants in the ITT population (who received any study drug) who received at least one dose of the study drug in the double-blind treatment period, and analysed according to their randomized treatment group.

End point type	Secondary
End point timeframe:	
Baseline (Day -1) and Day 59	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Percentage change in glucose AUC0-4hrs				
least squares mean (confidence interval 90%)	-6.773 (-12.528 to -1.018)	-19.105 (-23.434 to -14.777)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 59
Comparison groups	Placebo v MEDI0382
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-12.332
Confidence interval	
level	90 %
sides	2-sided
lower limit	-19.726
upper limit	-4.938

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)
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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, and congenital anomaly. 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. Participants who received any study drug in the double-blind treatment period and were analysed according to the treatment they received were analysed for this end point.

End point type	Secondary
End point timeframe:	
Day 17 through 28 days post last dose (approximately 14 months)	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	18		
Units: Participants				
Any TEAEs	5	17		
Any TESAEs	0	2		

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
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End point description:

Number of participants with clinical laboratory abnormalities reported as TEAEs are reported. Clinical laboratory abnormalities are defined as any abnormal findings in analysis of serum chemistry, hematology, and urinalysis. Participants who received any study drug in the double-blind treatment period and were analysed according to the treatment they received were analysed for this end point.

End point type	Secondary
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End point timeframe:

Day 17 through 28 days post last dose (approximately 14 months)

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	18		
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
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End point description:

Number of participants with abnormal vital signs reported as TEAEs are reported. Abnormal vital signs reported as TEAEs included any abnormal findings in body temperature, blood pressure, pulse rate, and respiratory rate. Participants who received any study drug in the double-blind treatment period and were analysed according to the treatment they received were analysed for this end point.

End point type	Secondary
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End point timeframe:

Day 17 through 28 days post last dose (approximately 14 months)

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	18		
Units: Participants	0	0		

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
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End point description:

Number of participants with abnormal ECG reported as TEAEs are reported. Participants who received any study drug in the double-blind treatment period and were analysed according to the treatment they received were analysed for this end point.

End point type	Secondary
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End point timeframe:

Day 17 through 28 days post last dose (approximately 14 months)

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	18		
Units: Participants				
Electrocardiogram T wave amplitude decreased	0	4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Positive Anti-drug Antibodies (ADAs) to MEDI0382
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End point description:

Number of participants with positive ADA to MEDI0382 are reported. Treatment-boosted ADA is defined as baseline ADA titer that was boosted to a 4-fold or higher level following drug administration. Treatment-emergent ADA is defined as the sum of treatment-induced ADA (post-baseline positive only)

and treatment-boosted ADA. Participants who received any study drug in the double-blind treatment period and were analysed according to the treatment they received were considered for this end point. Participants with post-baseline ADA results were analysed.

End point type	Secondary
End point timeframe:	
Day 17 (predose), Day 32 (predose), Day 59; and 28 days post last dose (approximately 14 months)	

End point values	Placebo	MEDI0382		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	14		
Units: Participants				
ADA positive post-BL	0	3		
Treatment-boosted ADA	0	0		
Treatment-emergent ADA	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 17 through 28 days post last dose (approximately 14 months)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	MEDI0382
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Reporting group description: -

Serious adverse events	Placebo	MEDI0382	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	2 / 18 (11.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Coronary artery thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	MEDI0382	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	16 / 18 (88.89%)	
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all) Injection site haemorrhage subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	2 / 18 (11.11%) 2 1 / 18 (5.56%) 1	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Reproductive system and breast disorders Coital bleeding subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	
Investigations Electrocardiogram T wave amplitude decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	4 / 18 (22.22%) 4	
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 18 (16.67%) 4	
Eye contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Skin abrasion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 18 (11.11%) 2	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 18 (11.11%) 2	
Headache subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 5	2 / 18 (11.11%) 2	
Lethargy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 18 (16.67%) 3	
Restless legs syndrome subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 18 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 18 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 18 (11.11%) 2	
Breath odour subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Constipation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 18 (16.67%) 5	
Dental caries			

subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	4 / 7 (57.14%)	3 / 18 (16.67%)	
occurrences (all)	5	6	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Eructation			
subjects affected / exposed	0 / 7 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	13 / 18 (72.22%)	
occurrences (all)	2	19	
Retching			
subjects affected / exposed	1 / 7 (14.29%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	4 / 18 (22.22%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 7 (14.29%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Back pain			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 18 (0.00%) 0	
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 18 (5.56%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 18 (0.00%) 0	
Tooth abscess subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 18 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	5 / 18 (27.78%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2018	Inclusion criteria was amended and additional text sections were revised to allow the inclusion of participants using sodium-glucose co-transporter inhibitors. Exclusion criteria was amended to allow the use of chronic kidney disease-epidemiology collaboration to estimate impaired renal function. Text describing manual randomisation procedures was amended to use an interactive voice/web response system. Double-blind study drug administration row was added to the treatment period study procedures table. Two additional time points for in clinic administration of study drugs were added for Visit 4. Text describing the administration of study drug procedures was updated. Text describing the timing of samples from intravenous glucose tolerance test was amended. Blood volume estimations were updated. New section added that allowed for and described procedures for early discontinuation or unscheduled study visits. Text describing discontinuation of study drug in the event of unblinding of study drug allocation was removed.
17 July 2018	Text was added clarifying the procedures in the event of severe persistent hyperglycemia. Specific amylase and lipase values were added to exclusion criterion. Pancreatic lipase and amylase assessments were added to the Schedule of Screening Procedures. Serum pregnancy test was added to the Schedule of Screening Procedures, Days -1 and 17 of the Treatment Period Study Procedures table, and to the clinical laboratory tests section. Pregnancy test was clarified as a urine pregnancy test in the Early Discontinuation Visit or Unscheduled Study Visit table. The time period for the collection of AEs was changed to start from the time of signature of informed consent.
20 August 2018	Updated exercise times for when participants were to be inside the whole room calorimeter in Treatment Period Study Procedures table footnote. Amended Treatment Period Study Procedures table footnote to remove sentence around pre and post meal and to clarify that it was the visual analog scale questionnaire that is to be repeated during the day. Added Day 15/16 to clarify the timing of the collection of urine for protein estimation. Additional paragraph added to describe measures that were taken to ensure the blind.
31 August 2018	Replaced carbon dioxide 'consumption' with 'production' in an exploratory endpoint. Removed instruction relating to study drug in Treatment Period Study Procedures table footnote. Changed the time of doubly labelled water urine collection from 1 to 3 hours in Treatment Period Study Procedures table footnote.
20 March 2019	The secondary objective and related endpoint pertaining to the effect of placebo treatment on ad libitum lunchtime energy intake was removed. The rationale for the single group crossover analyses was removed. Text describing which participants were to be included in the treatment groups for certain endpoints was removed. Analysis populations were added and revised. The analysis populations were changed for the efficacy and patient reported outcome (PRO) analyses. Added information related to ADA samples to be taken pre-dose on Day 17 and 32. ADA ligand binding 'bridging' assay details removed. Association of ADA positive status with efficacy and safety data added. Dose escalation text altered to state time period for placebo or cotadutide treatment following the single blind placebo treatment period. Minor procedural changes were made regarding the randomised treatment period, muscle biopsy, and IVGTT. Storage of residual blood samples from main study 'for future analysis' modified to 'potential future analysis'. Processes for evaluation of Hy's Law were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The analysis of endpoints change and percent change in TEE measured by doubly labelled water is not yet complete, so results of these endpoints will be reported post finalization of addendum Clinical Study Report.

Notes: