Clinical trial results:
A Randomised Controlled Trial for People with Established Type 2 Diabetes during Ramadan: Canagliflozin (Invokana™) vs. standard dual therapy regimen: The 'Can Do Ramadan' Study

Summary

EudraCT number	2015-002104-91
Trial protocol	GB
Global end of trial date	13 September 2018

Results information

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

Trial information

Trial identification

Sponsor protocol code	UNOLE0527

Additional study identifiers

ISRCTN number	ISRCTN14964201
ClinicalTrials.gov id (NCT number)	NCT02694263
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research & Enterprise Division, University of Leicester, Leicester General Hospital, Leicester , United Kingdom, LE5 4PW
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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	13 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2018
Global end of trial reached?	Yes
Global end of trial date	13 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to achieve the double composite endpoint of a reduction in HbA1c (≥ 0.3%) and weight loss (≥1kg) 3-4 weeks post-Ramadan.

Protection of trial subjects:

All study participants were required to read a patient Information Sheet (PIS) about the trial (including trial treatments and any known side-effects) and sign an Informed Consent Form (ICF). Patients were monitored regularly throughout the trial duration.

Background therapy:

Patients taking monotherapy (Metformin) or standard second line therapy (Metformin plus other glucose lowering therapy (comparator)) were recruited into the trial.

Evidence for comparator:

There have been significant advances in glucose lowering therapies in T2DM and their availability, thus offering a greater choice of therapies to people with diabetes with the potential for supporting safer fasting. Three new classes of therapy have been licensed for the treatment of T2DM in the UK in the past 10 years. The most recent class that has been introduced are the Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2 inhibitors).

Canagliflozin (Invokana™) is one of a number of SGLT2 inhibitors that have been licensed within the UK. Phase III trials of this novel agent have reported reductions in HbA1c, body weight and systolic blood pressure reduction. Canagliflozin has a low intrinsic propensity to cause hypoglycaemia. Importantly this drug is reported to be well-tolerated and has a good safety profile in patients with inadequately controlled T2DM, as monotherapy or in combination with other glucose lowering therapy including sulphonylureas and metformin.

Exploration in advent of novel therapies such as Canagliflozin which could potentially provide positive health outcomes to those who wish to participate in Ramadan is required.

The aim in the present study was to determine if the addition of Canagliflozin therapy to monotherapy of metformin was more effective at achieving the double composite endpoint of a reduction in HbA1c (≥ 0.3%) and weight loss (≥1kg) 3-4 weeks post-Ramadan. Patients currently on dual therapy (specifically metformin plus a sulphonylurea or pioglitazone or repaglinide or DPP-4 inhibitor) were included to determine whether switching to metformin plus Canagliflozin is more effective at achieving the composite endpoint compared to those remaining on previous dual therapy.

Actual start date of recruitment	15 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 25

Worldwide total number of subjects	25
EEA total number of subjects	25

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)	22
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sponsor Greenlight was issued on 11/07/2016. The First Patient First Visit (FPFV) date was 15/08/2016 and the Last Patient Last Visit (LPLV) date was 13/09/2018. Participants took part in the study at one of two sites in the UK (Leicester and Birmingham).

Pre-assignment

Screening details:

Participants with Type 2 Diabetes Mellitus planning to fast during Ramadan were enrolled. Participants on monotherapy at entry were randomised 1:1 to metformin + Canagliflozin or metformin + other glucose lowering therapy. Participants on dual therapy at entry were randomised 1:1 to metformin + Canagliflozin or to existing dual therapy combination

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Drug (IMP)

Arm description:

Canagliflozin (Invokana™) 100mg or 300mg, orally, once daily.

Arm type	Experimental
Investigational medicinal product name	Canagliflozin (Invokana™)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

There was a lead-in period for this study of 4 weeks to ensure that the correct dose was achieved for each participant. Titration of study treatment Canagliflozin (Invokana™) oral hyperglycaemic agent began with a starting dose of 100mg once daily. Those participants that tolerated this dose well for 14 days +/- 3 days had this increased to 300mg once daily by telephone consultation. The best tolerated dose was then maintained until the participant's final study visit. Conversely, if participants experienced tolerability issues such as recurrent hypoglycaemia or postural hypotension or they exceeded the HbA1c target, they did not have the study treatment titrated.

Arm title	Comparator (other glucose lowering therapy)

Arm description:

Standard second-line therapy (a sulphonylurea or pioglitazone or repaglinide or DPP-4 inhibitor) in line with NICE guidelines as the preferred second-line therapy after metformin.

Arm type	Active comparator
Investigational medicinal product name	Sulphonylurea
Investigational medicinal product code	
Other name	Gliclazide and glimepiride
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Gliclazide and glimepiride were the sulphonylureas chosen to be prescribed to participants in this study. Gliclazide dose was started at 40-80 mg once daily, up to maximum dose of 160mg twice daily. Glimepiride was initially administered as 1mg once daily, up to a maximum dose of 4mg once daily.

Investigational medicinal product name	Repaglinide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

An initial dose of 0.5mg once daily where no prior treatment has been given was prescribed. However, where prior treatment was in place, an initial dose of 1-2mg once daily was started and this was titrated up to a maximum dose of 4mg daily.

Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

An initial dose of 15mg or 30mg once daily was prescribed. If the response was inadequate, the maximum daily dosage was increased to 45mg once daily.

Investigational medicinal product name	DPP4 inhibitor
Investigational medicinal product code	
Other name	Sitagliptin, Vildagliptin, Saxagliptin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The study clinicians did not actively prescribe DPP-4 inhibitors. If participants were taking metformin and a DPP-4 inhibitor at baseline and were randomised to continuation of their current prescribed second line therapy (control arm), they remained on a DPP-4 inhibitor. If they were randomised to the intervention arm, they were prescribed metformin and Canagliflozin (Invokana™).

Number of subjects in period 1	Study Drug (IMP)	Comparator (other glucose lowering therapy)
Started	12	13
Completed	8	8
Not completed	4	5
Physician decision	1	2
Lost to follow-up	1	1
Voluntary withdrawal	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Study Drug (IMP)
Reporting group description:	
Canagliflozin (Invokana™) 100mg or 300mg, orally, once daily.	

Reporting group title	Comparator (other glucose lowering therapy)
Reporting group description:	
Standard second-line therapy (a sulphonylurea or pioglitazone or repaglinide or DPP-4 inhibitor) in line with NICE guidelines as the preferred second-line therapy after metformin.	

Reporting group values	Study Drug (IMP)	Comparator (other glucose lowering therapy)	Total
Number of subjects	12	13	25
Age categorical			
25 participants, with type 2 diabetes, above 25 years of age were enrolled into the main study across two sites. 21 were included in the physical activity (PA) sub-study.			
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)	10	12	22
From 65-84 years	2	1	3
85 years and over	0	0	0
Age continuous			
In the main study of 25 participants, the mean age was 53.6 years.			
Units: years			
arithmetic mean	54.6	52.7	
standard deviation	± 9.4	± 9.7	-
Gender categorical Units: Subjects			
Female	1	3	4
Male	11	10	21
Ethnicity Units: Subjects			
South Asian	10	12	22
Other	2	1	3
Smoking Status Units: Subjects			
Current smoker	3	0	3
Ex-smoker	3	4	7
Never smoked	6	9	15

Systolic blood pressure			
The combined main study population had a mean systolic blood pressure of 125.8mmHg.			
Units: mmHg			
arithmetic mean	122.5	128.8	
standard deviation	± 13.7	± 11.6	-
Diastolic blood pressure			
The combined main study population had a mean diastolic blood pressure of 79.1 mmHg.			
Units: mmHg			
arithmetic mean	74.8	83.0	
standard deviation	± 10.5	± 9.3	-
Heart Rate			
The combined main study population had a mean heart rate of 78.6 (bpm).			
Units: bpm			
arithmetic mean	72.8	83.8	
standard deviation	± 9.1	± 13.2	-
Standing Systolic blood pressure			
The combined main study population had a mean standing systolic blood pressure of 129.6mmHg.			
Units: mmHg			
arithmetic mean	127.4	131.7	
standard deviation	± 16.4	± 11.8	-
Standing Diastolic blood pressure			
The combined main study population had a mean standing diastolic blood pressure of 83.2mmHg.			
Units: mmHg			
arithmetic mean	79.0	87.1	
standard deviation	± 9.1	± 10.7	-
Standing heart rate			
The combined main study population had a mean standing heart rate of 84.5 bpm.			
Units: mmHg			
arithmetic mean	78.8	89.7	
standard deviation	± 8.6	± 14.0	-
Weight			
The combined main study population had an average weight of 75.9kg.			
Units: Kg			
arithmetic mean	68.7	82.4	
standard deviation	± 8.0	± 23.4	-
BMI			
The combined main study population had a mean BMI of 27.3kg/m^2			
Units: kg/m^2			
arithmetic mean	25.6	28.9	
standard deviation	± 2.7	± 5.8	-
Body fat			
The combined main study population had a mean body fat of 25.6%.			
Units: percentage			
arithmetic mean	20.3	30.5	
standard deviation	± 6.1	± 6.5	-
Muscle Mass			
The combined main study population had a mean muscle mass of 53.2kg.			
Units: kg			
arithmetic mean	52.0	54.3	
standard deviation	± 7.8	± 13.2	-
Fat free mass			
The combined main study population had a mean fat free mass of 55.9 kg.			

Units: kg			
arithmetic mean	54.7	56.9	
standard deviation	± 8.2	± 13.9	-
Waist Circumference			
The combined main study population had a mean waist circumference of 96.8cm.			
Units: cm			
arithmetic mean	90.9	102.3	
standard deviation	± 4.3	± 14.4	-
Hip Circumference			
The combined main study population had a mean hip circumference of 100.6cm.			
Units: cm			
arithmetic mean	96.3	104.7	
standard deviation	± 6.6	± 10.2	-
Visceral rating			
Visceral fat rating on a scale from 1 to 59 (This is for an age range between 18 years to 99 years). 1-12 is healthy, 13-59 is an excess level of visceral fat.			
Units: Visceral fat rating scale			
arithmetic mean	9.2	11.8	
standard deviation	± 1.5	± 6.1	-
Height			
Units: cm			
arithmetic mean			
standard deviation	±	±	-
Valid days			
Number of days with valid accelerometer data.			
Units: number			
arithmetic mean			
standard deviation	±	±	-
Overall activity level			
Units: mg			
arithmetic mean			
standard deviation	±	±	-
Total MVPA			
MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean			
standard deviation	±	±	-
MVPA in 1-min bouts			
MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean			
standard deviation	±	±	-
MVPA in 5-min bouts			
MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean			
standard deviation	±	±	-
MVPA in 10-min bouts			
MVPA = moderate to vigorous physical activity			
Units: minute/day			
arithmetic mean			
standard deviation	±	±	-

Subject analysis sets	
Subject analysis set title	PA sub-study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who had a valid GeneActiv recording as part of the GeneActiv sub-study.	
Subject analysis set title	PA sub-study pre-Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pre-Ramadan period for patients in the PA GeneActiv sub-study	
Subject analysis set title	PA sub-study during Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
During-Ramadan period for patients in the PA GeneActiv sub-study.	
Subject analysis set title	PA sub-study post-Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Post-Ramadan period for patients in the PA GeneActiv sub-study.	

Reporting group values	PA sub-study	PA sub-study pre-Ramadan	PA sub-study during Ramadan
Number of subjects	21	21	11
Age categorical			
25 participants, with type 2 diabetes, above 25 years of age were enrolled into the main study across two sites. 21 were included in the physical activity (PA) sub-study.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
In the main study of 25 participants, the mean age was 53.6 years.			
Units: years			
arithmetic mean	52.4		
standard deviation	± 8.6	±	±
Gender categorical			
Units: Subjects			
Female	3		
Male	18		

Ethnicity Units: Subjects			
South Asian Other			
Smoking Status Units: Subjects			
Current smoker Ex-smoker Never smoked	3 7 11		
Systolic blood pressure			
The combined main study population had a mean systolic blood pressure of 125.8mmHg.			
Units: mmHg arithmetic mean standard deviation	 126.4 ± 11.6	 ±	 ±
Diastolic blood pressure			
The combined main study population had a mean diastolic blood pressure of 79.1 mmHg.			
Units: mmHg arithmetic mean standard deviation	 80.9 ± 9.9	 ±	 ±
Heart Rate			
The combined main study population had a mean heart rate of 78.6 (bpm).			
Units: bpm arithmetic mean standard deviation	 78.1 ± 11.1	 ±	 ±
Standing Systolic blood pressure			
The combined main study population had a mean standing systolic blood pressure of 129.6mmHg.			
Units: mmHg arithmetic mean standard deviation	 129.8 ± 14.0	 ±	 ±
Standing Diastolic blood pressure			
The combined main study population had a mean standing diastolic blood pressure of 83.2mmHg.			
Units: mmHg arithmetic mean standard deviation	 84.4 ± 10.8	 ±	 ±
Standing heart rate			
The combined main study population had a mean standing heart rate of 84.5 bpm.			
Units: mmHg arithmetic mean standard deviation	 84.7 ± 10.9	 ±	 ±
Weight			
The combined main study population had an average weight of 75.9kg.			
Units: Kg arithmetic mean standard deviation	 76.8 ± 19.6	 ±	 ±
BMI			
The combined main study population had a mean BMI of 27.3kg/m^2			
Units: kg/m^2 arithmetic mean standard deviation	 27.6 ± 4.9	 ±	 ±
Body fat			
The combined main study population had a mean body fat of 25.6%.			
Units: percentage			

arithmetic mean	25.8		
standard deviation	± 7.7	±	±
Muscle Mass			
The combined main study population had a mean muscle mass of 53.2kg.			
Units: kg			
arithmetic mean	52.6		
standard deviation	± 10.9	±	±
Fat free mass			
The combined main study population had a mean fat free mass of 55.9 kg.			
Units: kg			
arithmetic mean	56.4		
standard deviation	± 11.4	±	±
Waist Circumference			
The combined main study population had a mean waist circumference of 96.8cm.			
Units: cm			
arithmetic mean	96.9		
standard deviation	± 12.7	±	±
Hip Circumference			
The combined main study population had a mean hip circumference of 100.6cm.			
Units: cm			
arithmetic mean	100.6		
standard deviation	± 9.5	±	±
Visceral rating			
Visceral fat rating on a scale from 1 to 59 (This is for an age range between 18 years to 99 years). 1-12 is healthy, 13-59 is an excess level of visceral fat.			
Units: Visceral fat rating scale			
arithmetic mean	10.9		
standard deviation	± 4.7	±	±
Height			
Units: cm			
arithmetic mean	166.1		
standard deviation	± 10.8	±	±
Valid days			
Number of days with valid accelerometer data.			
Units: number			
arithmetic mean		6.7	
standard deviation	±	± 0.8	±
Overall activity level			
Units: mg			
arithmetic mean		29.0	
standard deviation	±	± 8.0	±
Total MVPA			
MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean		110.5	
standard deviation	±	± 53.6	±
MVPA in 1-min bouts			
MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean		39.6	
standard deviation	±	± 27.4	±
MVPA in 5-min bouts			

MVPA = moderate to vigorous physical activity			
Units: min/day			
arithmetic mean		18.3	
standard deviation	±	± 20.0	±
MVPA in 10-min bouts			
MVPA = moderate to vigorous physical activity			
Units: minute/day			
arithmetic mean		8.8	
standard deviation	±	± 11.5	±

Reporting group values	PA sub-study post-Ramadan		
Number of subjects	9		
Age categorical			
25 participants, with type 2 diabetes, above 25 years of age were enrolled into the main study across two sites. 21 were included in the physical activity (PA) sub-study.			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
In the main study of 25 participants, the mean age was 53.6 years.			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
South Asian			
Other			
Smoking Status			
Units: Subjects			
Current smoker			
Ex-smoker			
Never smoked			
Systolic blood pressure			
The combined main study population had a mean systolic blood pressure of 125.8mmHg.			
Units: mmHg			
arithmetic mean			
standard deviation	±		
Diastolic blood pressure			

The combined main study population had a mean diastolic blood pressure of 79.1 mmHg.			
Units: mmHg arithmetic mean standard deviation	±		
Heart Rate			
The combined main study population had a mean heart rate of 78.6 (bpm).			
Units: bpm arithmetic mean standard deviation	±		
Standing Systolic blood pressure			
The combined main study population had a mean standing systolic blood pressure of 129.6mmHg.			
Units: mmHg arithmetic mean standard deviation	±		
Standing Diastolic blood pressure			
The combined main study population had a mean standing diastolic blood pressure of 83.2mmHg.			
Units: mmHg arithmetic mean standard deviation	±		
Standing heart rate			
The combined main study population had a mean standing heart rate of 84.5 bpm.			
Units: mmHg arithmetic mean standard deviation	±		
Weight			
The combined main study population had an average weight of 75.9kg.			
Units: Kg arithmetic mean standard deviation	±		
BMI			
The combined main study population had a mean BMI of 27.3kg/m^2			
Units: kg/m^2 arithmetic mean standard deviation	±		
Body fat			
The combined main study population had a mean body fat of 25.6%.			
Units: percentage arithmetic mean standard deviation	±		
Muscle Mass			
The combined main study population had a mean muscle mass of 53.2kg.			
Units: kg arithmetic mean standard deviation	±		
Fat free mass			
The combined main study population had a mean fat free mass of 55.9 kg.			
Units: kg arithmetic mean standard deviation	±		
Waist Circumference			
The combined main study population had a mean waist circumference of 96.8cm.			
Units: cm			

arithmetic mean standard deviation	±		
Hip Circumference			
The combined main study population had a mean hip circumference of 100.6cm.			
Units: cm arithmetic mean standard deviation	±		
Visceral rating			
Visceral fat rating on a scale from 1 to 59 (This is for an age range between 18 years to 99 years). 1-12 is healthy, 13-59 is an excess level of visceral fat.			
Units: Visceral fat rating scale arithmetic mean standard deviation	±		
Height Units: cm arithmetic mean standard deviation	±		
Valid days			
Number of days with valid accelerometer data.			
Units: number arithmetic mean standard deviation	±		
Overall activity level Units: mg arithmetic mean standard deviation	±		
Total MVPA			
MVPA = moderate to vigorous physical activity			
Units: min/day arithmetic mean standard deviation	±		
MVPA in 1-min bouts			
MVPA = moderate to vigorous physical activity			
Units: min/day arithmetic mean standard deviation	±		
MVPA in 5-min bouts			
MVPA = moderate to vigorous physical activity			
Units: min/day arithmetic mean standard deviation	±		
MVPA in 10-min bouts			
MVPA = moderate to vigorous physical activity			
Units: minute/day arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Study Drug (IMP)
Reporting group description:	
Canagliflozin (Invokana™) 100mg or 300mg, orally, once daily.	

Reporting group title	Comparator (other glucose lowering therapy)
Reporting group description:	
Standard second-line therapy (a sulphonylurea or pioglitazone or repaglinide or DPP-4 inhibitor) in line with NICE guidelines as the preferred second-line therapy after metformin.	
Subject analysis set title	PA sub-study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who had a valid GeneActiv recording as part of the GeneActiv sub-study.	
Subject analysis set title	PA sub-study pre-Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pre-Ramadan period for patients in the PA GeneActiv sub-study	
Subject analysis set title	PA sub-study during Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
During-Ramadan period for patients in the PA GeneActiv sub-study.	
Subject analysis set title	PA sub-study post-Ramadan
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Post-Ramadan period for patients in the PA GeneActiv sub-study.	

Primary: Reduction in HbA1c and weight 3-4 weeks post-Ramadan

End point title	Reduction in HbA1c and weight 3-4 weeks post-Ramadan[1]
End point description:	
The primary outcome is the achievement of the double composite endpoint of a reduction in HbA1c (at least 0.3%) and weight loss (of at least 1kg) 3-4 weeks post-Ramadan.	
End point type	Primary
End point timeframe:	
3-4 weeks post Ramadan.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: 50% of participants on Canagliflozin (IMP) achieved planned primary outcome compared to 12.5% on standard second line therapy (control). Underpowered to test statistical significance of this trend.

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[2]	8[3]		
Units: Number of patients achieving outcome				
Achieved	4	1		

Not achieved	4	7		

Notes:

[2] - 8 patients had valid HbA1c and weight values pre- and post-Ramadan.

[3] - 8 patients had valid HbA1c and weight values pre- and post-Ramadan.

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction or maintenance of HbA1c, reduction in weight and no self-reported hypoglycaemic events (blood glucose < 3.1 mmol/L)

End point title	Reduction or maintenance of HbA1c, reduction in weight and no self-reported hypoglycaemic events (blood glucose < 3.1 mmol/L)

End point description:

Triple composite endpoint of a reduction or maintenance of HbA1c, reduction in weight (at least 1kg) and no self-reported hypoglycaemic events (capillary blood glucose of 3.1 mmol/L or lower) between baseline and 3-4 weeks post-Ramadan.

End point type	Secondary

End point timeframe:

Between baseline and 3-4 weeks post-Ramadan.

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Number of patients achieving outcome				
Achieved Not achieved				

Notes:

[4] - Only 4 patients had results at more than one time point - therefore not feasible to include results.

[5] - Only 4 patients had results at more than one time point - therefore not feasible to include results.

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction or maintenance of HbA1c, reduction in weight and no self-reported hypoglycaemic events (blood glucose < 3.9 mmol/L)

End point title	Reduction or maintenance of HbA1c, reduction in weight and no self-reported hypoglycaemic events (blood glucose < 3.9 mmol/L)

End point description:

Triple composite outcome of a reduction or maintenance of HbA1c, reduction in weight (≥1kg) and no self-reported hypoglycaemic events (capillary blood glucose ≤ 3.9mmol/L).

End point type	Secondary

End point timeframe:

Between baseline and 3-4 weeks post-Ramadan.

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Number of patients achieving outcome				
Achieved Not achieved				

Notes:

[6] - Only 4 patients had results at more than one time point - therefore not feasible to include results.

[7] - Only 4 patients had results at more than one time point - therefore not feasible to include results.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in weight from baseline to follow-up

End point title	Change in weight from baseline to follow-up

End point description:

Change in weight between baseline and 3-4 weeks post-Ramadan.

End point type	Secondary

End point timeframe:

Between baseline and 3-4 weeks post-Ramadan.

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: kg				
arithmetic mean (standard deviation)	-3.2 (± 3.2)	0.9 (± 2.4)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-1.1

Secondary: Change in HbA1c from baseline to follow-up

End point title	Change in HbA1c from baseline to follow-up
End point description:	
Change in HbA1c from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe:	
Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: Percent %				
arithmetic mean (standard deviation)	-0.6 (± 0.6)	-0.4 (± 0.7)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.6

Secondary: Change in fructosamine from baseline to follow-up	
End point title	Change in fructosamine from baseline to follow-up
End point description: Change in fructosamine level from baseline and 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: µmol/L				
arithmetic mean (standard deviation)	-2.7 (± 29.4)	15.4 (± 42.7)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Comparator (other glucose lowering therapy) v Study Drug (IMP)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.3
upper limit	51.2

Secondary: Change in SBP from baseline to follow-up	
End point title	Change in SBP from baseline to follow-up
End point description: Change in systolic blood pressure (SBP) from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmHg				
arithmetic mean (standard deviation)	-10.23 (± 10.4)	-4.3 (± 9.3)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Comparator (other glucose lowering therapy) v Study Drug (IMP)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	4.5

Secondary: Change in DBP from baseline to follow-up

End point title	Change in DBP from baseline to follow-up
End point description:	
Change in diastolic blood pressure (DBP) from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe:	
Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmHg				
arithmetic mean (standard deviation)	-6.8 (± 5.6)	-6.5 (± 6.6)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Comparator (other glucose lowering therapy) v Study Drug (IMP)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	6.3

Secondary: Change in total cholesterol from baseline to follow-up	
End point title	Change in total cholesterol from baseline to follow-up
End point description: Change in total cholesterol from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.03 (± 0.4)	-0.3 (± 0.4)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8

Secondary: Change in HDL-C from baseline to follow-up

End point title	Change in HDL-C from baseline to follow-up
End point description:	
Change in HDL cholesterol from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe:	
Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.02 (± 0.1)	-0.03 (± 0.1)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Secondary: Change in LDL-C from baseline to follow-up	
End point title	Change in LDL-C from baseline to follow-up
End point description: Change in LDL cholesterol from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/L				
arithmetic mean (standard deviation)	0.1 (± 0.3)	-0.2 (± 0.4)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.8

Secondary: Change in triglycerides from baseline to follow-up	
End point title	Change in triglycerides from baseline to follow-up
End point description: Change in triglycerides level from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.2 (± 0.5)	-0.2 (± 0.5)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.5

Secondary: Change in treatment satisfaction from baseline to follow-up	
End point title	Change in treatment satisfaction from baseline to follow-up
End point description: Change in DTSQ score for treatment satisfaction from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: DTSQ score				
arithmetic mean (standard deviation)	3.3 (± 4.4)	3.9 (± 6.6)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	5.4

Secondary: Change in disease burden from baseline to follow-up	
End point title	Change in disease burden from baseline to follow-up
End point description: Change in DTSQ score for disease burden from baseline to 3-4 weeks post-Ramadan.	
End point type	Secondary
End point timeframe: Between baseline and 3-4 weeks post-Ramadan.	

End point values	Study Drug (IMP)	Comparator (other glucose lowering therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: DTSQ score				
arithmetic mean (standard deviation)	-1.4 (± 4.2)	-0.8 (± 4.5)		

Statistical analyses

Statistical analysis title	Mean difference (Study drug - Comparator)
Comparison groups	Study Drug (IMP) v Comparator (other glucose lowering therapy)

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	4.1

Secondary: Overall activity level

End point title	Overall activity level

End point description:

End point type	Secondary

End point timeframe:

From pre-Ramadan to during-Ramadan, from pre-Ramadan to post-Ramadan, and from during-Ramadan to post-Ramadan.

End point values	PA sub-study pre-Ramadan	PA sub-study during Ramadan	PA sub-study post-Ramadan	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: mg				
arithmetic mean (standard deviation)	29.0 (± 8.0)	26.9 (± 6.3)	31.4 (± 8.4)	

Statistical analyses

Statistical analysis title	Change in overall activity (pre-during Ramadan)

Statistical analysis description:

NOTE: the number below (N=32) is auto-generated and inaccurate. There were N=10 people in this analysis (10 people with data both pre- and during-Ramadan), assessing the change in overall activity level from pre-Ramadan to during-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.14
upper limit	1.77

Statistical analysis title	Change in overall activity (pre-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=30) is auto-generated and inaccurate. There were N=8 people in this analysis (8 people with data both pre- and post-Ramadan), assessing the change in overall activity level from pre-Ramadan to post-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study post-Ramadan
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	3.79

Statistical analysis title	Change in overall activity (during-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=20) is auto-generated and inaccurate. There were N=7 people in this analysis (7 people with data both during- and post-Ramadan), assessing the change in overall activity level from during-Ramadan to post-Ramadan.

Comparison groups	PA sub-study post-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	4.18

Secondary: Total MVPA

End point title	Total MVPA

End point description:

End point type	Secondary

End point timeframe:

From pre-Ramadan to during-Ramadan, from pre-Ramadan to post-Ramadan, and from during-Ramadan to post-Ramadan.

End point values	PA sub-study pre-Ramadan	PA sub-study during Ramadan	PA sub-study post-Ramadan	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: min/day				
arithmetic mean (standard deviation)	110.5 (± 53.6)	103.4 (± 40.0)	123.2 (± 47.9)	

Statistical analyses

Statistical analysis title	Change in total MVPA (pre-during Ramadan)

Statistical analysis description:

NOTE: the number below (N=32) is auto-generated and inaccurate. There were N=10 people in this analysis (10 people with data both pre- and during-Ramadan), assessing the change in total MVPA from pre-Ramadan to during-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.44
upper limit	14.26

Statistical analysis title	Change in total MVPA (pre-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=30) is auto-generated and inaccurate. There were N=8 people in this analysis (8 people with data both pre- and post-Ramadan), assessing the change in total MVPA from pre-Ramadan to post-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study post-Ramadan

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.38
upper limit	13.94

Statistical analysis title	Change in total MVPA (during-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=20) is auto-generated and inaccurate. There were N=7 people in this analysis (7 people with data both during- and post-Ramadan), assessing the change in total MVPA from during-Ramadan to post-Ramadan.

Comparison groups	PA sub-study during Ramadan v PA sub-study post-Ramadan
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.01
upper limit	21.57

Secondary: MVPA in 1-min bouts

End point title	MVPA in 1-min bouts

End point description:

End point type	Secondary

End point timeframe:

From pre-Ramadan to during-Ramadan, from pre-Ramadan to post-Ramadan, and from during-Ramadan to post-Ramadan.

End point values	PA sub-study pre-Ramadan	PA sub-study during Ramadan	PA sub-study post-Ramadan	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: min/day				
arithmetic mean (standard deviation)	39.6 (± 27.4)	42.3 (± 31.5)	48.3 (± 34.1)	

Statistical analyses

Statistical analysis title	Change in MVPA in 1-min bouts (pre-during Ramadan)

Statistical analysis description:

NOTE: the number below (N=32) is auto-generated and inaccurate. There were N=10 people in this analysis (10 people with data both pre- and during-Ramadan), assessing the change in MVPA in 1-min bouts from pre-Ramadan to during-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.93
upper limit	18.5

Statistical analysis title	Change in MVPA in 1-min bouts (pre-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=30) is auto-generated and inaccurate. There were N=8 people in this analysis (8 people with data both pre- and post-Ramadan), assessing the change in MVPA in 1-min bouts from pre-Ramadan to post-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study post-Ramadan
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.27
upper limit	12.25

Statistical analysis title	Change in MVPA in 1min bouts (during-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=20) is auto-generated and inaccurate. There were N=7 people in this analysis (7 people with data both during- and post-Ramadan), assessing the change in MVPA in 1-min bouts from during-Ramadan to post-Ramadan.

Comparison groups	PA sub-study post-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.21
upper limit	10.64

Secondary: MVPA in 5-min bouts

End point title	MVPA in 5-min bouts

End point description:

End point type	Secondary

End point timeframe:

From pre-Ramadan to during-Ramadan, from pre-Ramadan to post-Ramadan, and from during-Ramadan to post-Ramadan.

End point values	PA sub-study pre-Ramadan	PA sub-study during Ramadan	PA sub-study post-Ramadan	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: min/day				
arithmetic mean (standard deviation)	18.3 (± 20.0)	24.2 (± 30.4)	22.6 (± 23.7)	

Statistical analyses

Statistical analysis title	Change in MVPA in 5-min bouts (pre-during Ramadan)

Statistical analysis description:

NOTE: the number below (N=32) is auto-generated and inaccurate. There were N=10 people in this analysis (10 people with data both pre- and during-Ramadan), assessing the change in MVPA in 5-min bouts from pre-Ramadan to during-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study during Ramadan

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.49
upper limit	22.01

Statistical analysis title	Change in MVPA in 5-min bouts (pre-post Ramadan)
Statistical analysis description:	
NOTE: the number below (N=30) is auto-generated and inaccurate. There were N=8 people in this analysis (8 people with data both pre- and post-Ramadan), assessing the change in MVPA in 5-min bouts from pre-Ramadan to post-Ramadan.	
Comparison groups	PA sub-study pre-Ramadan v PA sub-study post-Ramadan
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.15
upper limit	8.3

Statistical analysis title	Change in MVPA in 5min bouts (during-post Ramadan)
Statistical analysis description:	
NOTE: the number below (N=20) is auto-generated and inaccurate. There were N=7 people in this analysis (7 people with data both during- and post-Ramadan), assessing the change in MVPA in 5-min bouts from during-Ramadan to post-Ramadan.	
Comparison groups	PA sub-study post-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.82
upper limit	7.22

Secondary: MVPA in 10-min bouts

End point title	MVPA in 10-min bouts

End point description:

End point type	Secondary

End point timeframe:

From pre-Ramadan to during-Ramadan, from pre-Ramadan to post-Ramadan, and from during-Ramadan to post-Ramadan.

End point values	PA sub-study pre-Ramadan	PA sub-study during Ramadan	PA sub-study post-Ramadan	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	11	9	
Units: min/day				
arithmetic mean (standard deviation)	8.8 (± 11.5)	13.4 (± 19.7)	11.5 (± 15.5)	

Statistical analyses

Statistical analysis title	Change in MVPA in 10min bouts (pre-during Ramadan)

Statistical analysis description:

NOTE: the number below (N=32) is auto-generated and inaccurate. There were N=10 people in this analysis (10 people with data both pre- and during-Ramadan), assessing the change in MVPA in 10-min bouts from pre-Ramadan to during-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.98
upper limit	17.98

Statistical analysis title	Change in MVPA in 10min bouts (pre-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=30) is auto-generated and inaccurate. There were N=8 people in this analysis (8 people with data both pre- and post-Ramadan), assessing the change in MVPA in 10-min bouts from pre-Ramadan to post-Ramadan.

Comparison groups	PA sub-study pre-Ramadan v PA sub-study post-Ramadan
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.28
upper limit	9.1

Statistical analysis title	Change in MVPA in 10min bouts(during-post Ramadan)

Statistical analysis description:

NOTE: the number below (N=20) is auto-generated and inaccurate. There were N=7 people in this analysis (7 people with data both during- and post-Ramadan), assessing the change in MVPA in 10-min bouts from during-Ramadan to post-Ramadan.

Comparison groups	PA sub-study post-Ramadan v PA sub-study during Ramadan
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	2.27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Consent to last dose of drug.

Adverse event reporting additional description:

At each visit, the investigator documented adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of relation to study treatment. All SAEs and non-serious AEs classified as severe or possibly/probably related were followed up until resolution.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Canagliflozin (Invokana™)

Reporting group description:

Canagliflozin (Invokana™) 100mg or 300mg, orally, once daily.

Reporting group title	Comparator (other glucose lowering agents)

Reporting group description:

Standard second-line therapy (a sulphonylurea or pioglitazone or repaglinide or DPP-4 inhibitor) in line with NICE guidelines as the preferred second-line therapy after metformin.

Serious adverse events	Canagliflozin (Invokana™)	Comparator (other glucose lowering agents)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Canagliflozin (Invokana™)	Comparator (other glucose lowering agents)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	8 / 13 (61.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Localised inflammation	Additional description: Localised inflammation to Flash Glucose Monitoring Sensor		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Muscular chest pain			
subjects affected / exposed	2 / 12 (16.67%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Scalp Cyst			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Tiredness			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Immune system disorders			
Hay fever			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Benign breast cyst			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Penile Itching	Additional description: Itching at end of penis		
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Nose bleed			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Libido decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Lateral myocardial infarction	Additional description: The participant had a routine ECG as part of his study visit. His ECG was abnormal and a previous lateral myocardial infarction was suspected. The participant was not unwell at the time of the ECG and was not hospitalized.		
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Pins and Needles in foot			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Shakiness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorders			
Gritty eyes			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Cracked Lips			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Dry mouth			

subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Heartburn			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Itchy skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	3 / 12 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Urge incontinence			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Micturition urgency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Urinary frequency			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Ankle Swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Back pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Knee pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Subluxation left shoulder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Chest infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cold			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tinea	Additional description: Left foot		
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	5 / 12 (41.67%)	3 / 13 (23.08%)	
occurrences (all)	5	3	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2016	Following the receipt of a Direct Healthcare Professional Communication report (dated 21st March 2016) regarding the risk of diabetic ketoacidosis (DKA) during treatment with SGLT2-inhibitors including Canagliflozin, the study team updated the protocol to include additional exclusion criteria, revised the treatment management sub-section, and revised the expected serious adverse events/reactions sub-section. Further, the study team revised timelines throughout the protocol to indicate a study extension of 3-4 months (recruitment phase extended to April 2017 but follow-up period reduced from 12 months to 3 months) to enable the LPLV in September 2017.
14 November 2016	Exclusion criteria revised to include 1) Any contraindication to the IMP 2) individuals on loop diuretics. The study team added an ALT blood test at baseline to assess eligibility (12. Impaired liver function (ALT ≥ 2.5 times upper limit of normal)). Further, the study team included some treatment management information about lower limbs and AKI in the treatment section of the protocol (following the recent safety updates) and included AKI in the expected SAE/SAR section of the protocol (in line with updated SmPC).
27 June 2017	The study team extended the study timelines to enable an extended recruitment period (proposed recruitment end date: April 2018) to aid the study team to recruit participants to time and target. Further, the inclusion/exclusion criteria were revised to aid recruitment following a high screen failure rate in the previous recruitment phase. HbA1c ranges were widened, the requirement to fast for 10 consecutive days was removed, and participants taking DPP-4 inhibitors were included. The study team revised the wording within the protocol (randomisation & code breaking, study design and statistical methods) about stratification to include DPP-4 inhibitors. Specifically, randomisation was carried out using block design and stratified by site (Leicester and Birmingham) and entry therapy (monotherapy, dual therapy not including DPP-4 inhibitor, and dual therapy including DPP-4 inhibitor). Participants with monotherapy at entry were randomised 1:1 to metformin + Canagliflozin (Invokana™) or to metformin + a sulphonylurea or repaglinide or pioglitazone; whilst participants with dual therapy at entry were randomised 1:1 to metformin + Canagliflozin (Invokana™) or to existing dual therapy combination. Finally the study team included some additional information for Repaglinide under the treatment section of the protocol following the SmPC review. In an interaction study with healthy volunteers, co-administration of clopidogrel (300 mg loading dose), a CYP2C8 inhibitor, increased repaglinide exposure (AUC0–∞) 5.1-fold and continued administration (75 mg daily dose) increased repaglinide exposure (AUC0–∞) 3.9-fold. A small, significant decrease in blood glucose values was observed. Since the safety profile of the co-treatment had not been established in these patients, the concomitant use of clopidogrel and repaglinide were avoided.
19 February 2018	Notification to the MHRA from the Chief Investigator about the decision to terminate recruitment of participants into the trial. This decision was made solely due to practical issues/challenges with recruitment. All patients enrolled into the study at that time and receiving treatment were followed-up until September 2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 February 2018	Despite the study team's success with a previous Ramadan study and ongoing engagement with our local communities, the 'Can Do Ramadan' study team faced many challenges with recruitment (including changes to local prescribing practice) and the study did not achieve its recruitment target, culminating in its early closure having only recruited 21.5% of the recruitment target. After much deliberation, the Chief Investigator and Senior Management team took the decision to stop actively recruiting to the 'Can Do Ramadan' study but to continue to follow-up the actively participating participants (up until September 2018), resulting in descriptive analysis of the main study data.	-

Notes:

Limitations and caveats

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

Despite the study team's success with a previous Ramadan study and engagement with local communities, the team faced many challenges with recruitment and the study did not achieve its recruitment target, culminating in its early closure.

Notes: