Clinical trial results:
TriMaster: Randomised Double-Blind Crossover study of a DPP4 inhibitor, SGLT2 inhibitor and thiazolidinedione as third line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on dual therapy with metformin and a sulphonylurea

Summary

EudraCT number	2015-002790-38
Trial protocol	GB
Global end of trial date	14 December 2021

Results information

Result version number	v1 (current)
This version publication date	17 December 2022
First version publication date	17 December 2022
Summary attachment (see zip file)	TriMaster Patient Stratification Paper - final author accepted version (TriMaster_PatientStratificationFinalPaper_Submitted.pdf)

Trial information

Trial identification

Sponsor protocol code	1603221

Additional study identifiers

ISRCTN number	ISRCTN12039221
ClinicalTrials.gov id (NCT number)	NCT02653209
WHO universal trial number (UTN)	-
Other trial identifiers	REC: 16/SC/0147, IRAS: 183044

Notes:

Sponsors

Sponsor organisation name	Royal Devon University Healthcare NHS Foundation Trust
Sponsor organisation address	Barrack Road, Exeter, United Kingdom, EX2 DW
Public contact	Chief Investigator, University of Exeter Medical School, 0044 1392408260, a.t.hattersley@exeter.ac.uk
Scientific contact	Chief Investigator, University of Exeter Medical School, 0044 1392408260, a.t.hattersley@exeter.ac.uk

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	25 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2021
Global end of trial reached?	Yes
Global end of trial date	14 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to test 2 hypotheses of how well or poorly different subgroups of patients respond to particular drugs based on particular clinical characteristics such as their weight or blood test results.

Hypothesis 1:
Patients with insulin resistance (characterised by a raised BMI >30 kg/m2), compared to non-obese patients (BMI ≤30) will:
a) respond well to pioglitazone
b) respond less well to sitagliptin

Hypothesis 2:
Patients with modestly reduced renal function, compared to those with normal renal function will:
a) respond poorly to canagliflozin
b) respond well to sitagliptin

Therefore the study's primary research question:
a) Do obese patients (BMI >30kgm-2), compared to non-obese patients, achieve a lower HbA1c when given pioglitazone rather than sitagliptin?

b) Do patients with an eGFR <90 mls/min/1.73m2 achieve a lower HbA1c, compared to patients with an eGFR>90 mls/min/1.73m2, when givena sitagliptin rather than canagliflozin.

Protection of trial subjects:

This study used established existing medications within their licensed indications to determine predictors of treatment response. SmPC updates related to drug safety were reviewed on a monthly basis by the CI/host centre via the https://www.medicines.org.uk/emc website. All required urgent safety measures were communicated to all PIs and research teams via email and the study database. Where necessary, participant information sheets were updated with new drug information.

All study data was stored in link-anonymised format by unique participant ID in locked offices within research facilities. Where medical notes were required to confirm eligibility these were stored in line with NHS data protection guidelines. Electronic data was held on password protected computers, and databases hosted on University of Exeter secure severs requiring unique log-in access for each individual involved in research.

Blood samples and meal tests were undertaken by fully qualified clinical staff.

Participants were provided with contact information for local research staff, in case of side effects including hypoglycaemia and/or adverse events. This information was restated before each new drug period.

An emergency unblinding service was provided by NIHR Exeter Clinical Research Facility, where following a detailed protocol staff were able to unblind study medication 24/7 for the duration of the study.

Background therapy:

Metformin alone, or metformin and a sulphonylurea

Evidence for comparator:

The three drugs used in the study were those oral-therapy classes recommended by the UK's NICE as standard care for those patients with type 2 diabetes who required a second or third intensification of drug treatment to maintain glucose levels. At the time of study design and set up these were thiazolidindione (pioglitazone), DPP4-i (sitagliptin) and SGLT2-i (canagliflozin).

Actual start date of recruitment	22 November 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: 525
Worldwide total number of subjects	525
EEA total number of subjects	0

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)	303
From 65 to 84 years	222
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

742 patients were screened for eligibility between 22 November 2016 and 24 January 2020, at 24 UK centres. Of these, 210 patients did not meet eligibility criteria, and seven withdrew before being randomized. 525 participants were randomized to one of the six sequences of drug allocations.

Pre-assignment

Screening details:

742 patients were identified in primary care/ research cohorts and screened for eligibility. Those eligible were invited to participate, provided with information sheets and attended a screening appointment. Written informed consent was given before screening data, including samples collected to confirm eligibility. Those eligible were randomised.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Randomisation was carried out at the baseline visit as described in the study protocol and statistical analysis plan. The three therapies were allocated in random order according to six possible treatment orders: ABC, ACB, BAC, BCA, CAB, CBA. Drugs were blinded by over-encapsulation

Arms

Arm title	All subjects

Arm description:

All subjects - ABC, ACB, BAC, BCA, CAB, CBA

Arm type	Active comparator
Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (30mg) once daily

Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Number of subjects in period 1	All subjects
Started	525
Completed	503
Not completed	22
Ineligible	2
Consent withdrawn by subject	10
Adverse event, non-fatal	4
Lost to follow-up	4
Protocol deviation	2

Period 2

Period 2 title	Period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The three therapies were allocated in random order according to six possible treatment orders: ABC, ACB, BAC, BCA, CAB, CBA. Drugs were blinded by over-encapsulation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pioglitazone

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (30mg) once daily

Arm title	Sitagliptin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Arm title	Canagliflozin

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Number of subjects in period 2	Pioglitazone	Sitagliptin	Canagliflozin
Started	168	168	167
Completed	165	162	163
Not completed	3	6	4
Consent withdrawn by subject	1	5	1
Physician decision	-	1	-
Adverse event, non-fatal	2	-	1
Lost to follow-up	-	-	1
Protocol deviation	-	-	1

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The three therapies were allocated in random order according to six possible treatment orders: ABC, ACB, BAC, BCA, CAB, CBA. Drugs were blinded by over-encapsulation

Arms

Are arms mutually exclusive?	Yes
Arm title	Pioglitazone

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (30mg) once daily

Arm title	Sitagliptin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Arm title	Canagliflozin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

1x capsule (100mg) once daily

Number of subjects in period 3	Pioglitazone	Sitagliptin	Canagliflozin
Started	164	160	166
Completed	152	154	163
Not completed	12	6	3
Adverse event, serious fatal	2	1	-
Consent withdrawn by subject	3	4	2
Physician decision	1	1	-
Adverse event, non-fatal	5	-	-
Protocol deviation	1	-	1

Period 4

Period 4 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The three therapies were allocated in random order according to six possible treatment orders: ABC, ACB, BAC, BCA, CAB, CBA. Drugs were blinded by over-encapsulation

Arms	
Are arms mutually exclusive?	Yes
Arm title	Pioglitazone
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use
Dosage and administration details: 1x capsule (30mg) once daily	
Arm title	Sitagliptin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use
Dosage and administration details: 1x capsule (100mg) once daily	
Arm title	Canagliflozin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Canagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use
Dosage and administration details: 1x capsule (100mg) once daily	

Number of subjects in period 4	Pioglitazone	Sitagliptin	Canagliflozin
Started	155	161	153
Completed	152	158	148
Not completed	3	3	5
Consent withdrawn by subject	1	-	2
Adverse event, non-fatal	2	1	2
Diagnosis of T1DM	-	1	-
Lost to follow-up	-	-	1
Protocol deviation	-	1	-

Period 5	
Period 5 title	Period 4 - final visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blinding to the allocation order remained until study end but there were no study drugs in period 4.

Arms	
Arm title	All subjects

Arm description:

All subjects, ABC, ACB, BAC, BCA, CAB, CBA

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 5	All subjects
Started	458
Completed	457
Not completed	1
Did not provide data	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline = 525	

Reporting group values	Baseline	Total	
Number of subjects	525	525	
Age categorical Units: Subjects			
Adults (18-64 years)	303	303	
From 65-84 years	222	222	
Age continuous Units: years			
arithmetic mean	61.9		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	142	142	
Male	383	383	

Subject analysis sets	
Subject analysis set title	BMI >30 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata >30 Sitagliptin	
Subject analysis set title	BMI >30 - Pioglitazone
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata >30 Pioglitazone	
Subject analysis set title	BMI <30 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata <30 Sitagliptin	
Subject analysis set title	BMI <30 - Pioglitazone
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata <30 Pioglitazone	
Subject analysis set title	eGFR <90 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 2 - eGFR strata <90 - Sitagliptin	
Subject analysis set title	eGFR >90 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 2 - eGFR strata >90 - Sitagliptin	
Subject analysis set title	eGFR <90 - Canagliflozin

Subject analysis set type	Per protocol
Subject analysis set description:	
Hypothesis 2 - eGFR strata <90 - Canagliflozin	
Subject analysis set title	eGFR >90 - Canagliflozin
Subject analysis set type	Per protocol
Subject analysis set description:	
Hypothesis 2 - eGFR strata >90 - Canagliflozin	

Reporting group values	BMI >30 - Sitagliptin	BMI >30 - Pioglitazone	BMI <30 - Sitagliptin
Number of subjects	215	215	141
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean standard deviation	 61.5 ± 9.2	 61.5 ± 9.2	 64.2 ± 8.7
Gender categorical Units: Subjects			
Female Male	58 157	58 157	37 104

Reporting group values	BMI <30 - Pioglitazone	eGFR <90 - Sitagliptin	eGFR >90 - Sitagliptin
Number of subjects	141	163	179
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean standard deviation	 64.2 ± 8.7	 67.2 ± 7.4	 57.8 ± 8.7
Gender categorical Units: Subjects			
Female Male	37 104	36 127	54 179

Reporting group values	eGFR <90 - Canagliflozin	eGFR >90 - Canagliflozin	
Number of subjects	163	179	
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean standard deviation	 67.2 ± 7.4	 57.8 ± 8.7	

Gender categorical Units: Subjects			
Female	36	54	
Male	127	179	

End points

End points reporting groups

Reporting group title	All subjects
Reporting group description: All subjects - ABC, ACB, BAC, BCA, CAB, CBA	
Reporting group title	Pioglitazone
Reporting group description: -	
Reporting group title	Sitagliptin
Reporting group description: -	
Reporting group title	Canagliflozin
Reporting group description: -	
Reporting group title	Pioglitazone
Reporting group description: -	
Reporting group title	Sitagliptin
Reporting group description: -	
Reporting group title	Canagliflozin
Reporting group description: -	
Reporting group title	Pioglitazone
Reporting group description: -	
Reporting group title	Sitagliptin
Reporting group description: -	
Reporting group title	Canagliflozin
Reporting group description: -	
Reporting group title	All subjects
Reporting group description: All subjects, ABC, ACB, BAC, BCA, CAB, CBA	
Subject analysis set title	BMI >30 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata >30 Sitagliptin	
Subject analysis set title	BMI >30 - Pioglitazone
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata >30 Pioglitazone	
Subject analysis set title	BMI <30 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata <30 Sitagliptin	
Subject analysis set title	BMI <30 - Pioglitazone
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 1 - BMI strata <30 Pioglitazone	
Subject analysis set title	eGFR <90 - Sitagliptin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 2 - eGFR strata <90 - Sitagliptin	
Subject analysis set title	eGFR >90 - Sitagliptin
Subject analysis set type	Per protocol

Subject analysis set description: Hypothesis 2 - eGFR strata >90 - Sitagliptin	
Subject analysis set title	eGFR <90 - Canagliflozin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 2 - eGFR strata <90 - Canagliflozin	
Subject analysis set title	eGFR >90 - Canagliflozin
Subject analysis set type	Per protocol
Subject analysis set description: Hypothesis 2 - eGFR strata >90 - Canagliflozin	

Primary: HbA1c value achieved after each treatment period

End point title	HbA1c value achieved after each treatment period
End point description:	
End point type	Primary
End point timeframe: 16 weeks on treatment (12-18weeks)	

End point values	BMI >30 - Sitagliptin	BMI >30 - Pioglitazone	BMI <30 - Sitagliptin	BMI <30 - Pioglitazone
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	100	100	100
Units: mmol/mol				
arithmetic mean (standard deviation)	60.5 (± 11.5)	59.0 (± 11.5)	58.3 (± 8.6)	59.7 (± 10.4)

End point values	eGFR <90 - Sitagliptin	eGFR >90 - Sitagliptin	eGFR <90 - Canagliflozin	eGFR >90 - Canagliflozin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	100	100	100
Units: mmol/mol				
arithmetic mean (standard deviation)	59.0 (± 9.6)	60.6 (± 11.7)	60.7 (± 8.7)	59.6 (± 9.4)

Statistical analyses

Statistical analysis title	Hypothesis 1
Comparison groups	BMI >30 - Sitagliptin v BMI >30 - Pioglitazone v BMI <30 - Sitagliptin v BMI <30 - Pioglitazone
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	4.85
Variability estimate	Standard deviation

Statistical analysis title	Hypothesis 2
Comparison groups	eGFR <90 - Sitagliptin v eGFR >90 - Sitagliptin v eGFR <90 - Canagliflozin v eGFR >90 - Canagliflozin
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	4.61
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from consent to study end, including of-treatment period between visits 4 and 5.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 503 (8.15%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowel cancer			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip surgery			
subjects affected / exposed	2 / 503 (0.40%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Physiotherapy				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Knee arthroplasty				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatectomy				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal operation				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Alcohol use				
subjects affected / exposed	2 / 503 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory tract infection				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

COPD				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	2 / 503 (0.40%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Nervous breakdown				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Cardiac ventriculogram				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Eye injury				
subjects affected / exposed	4 / 503 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute chest syndrome				

subjects affected / exposed	41 / 503 (8.15%)			
occurrences causally related to treatment / all	0 / 45			
deaths causally related to treatment / all	0 / 3			
Atrial fibrillation				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	3 / 503 (0.60%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina unstable				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Vertigo				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 503 (0.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bleeding			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Flank pain			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tenosynovitis			
subjects affected / exposed	1 / 503 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	406 / 503 (80.72%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign and malignant combined			
subjects affected / exposed	3 / 503 (0.60%)		
occurrences (all)	3		
Vascular disorders			
Vascular disorders combined			
subjects affected / exposed	22 / 503 (4.37%)		
occurrences (all)	24		
Surgical and medical procedures			
Surgical and medical procedures combined			
subjects affected / exposed	22 / 503 (4.37%)		
occurrences (all)	32		
General disorders and administration site conditions			
General disorders and administration site conditions combined			
subjects affected / exposed	123 / 503 (24.45%)		
occurrences (all)	165		
Immune system disorders			
Immune system disorders combined			

subjects affected / exposed	3 / 503 (0.60%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Reproductive system and breast disorders combined			
subjects affected / exposed	124 / 503 (24.65%)		
occurrences (all)	176		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders combined			
subjects affected / exposed	90 / 503 (17.89%)		
occurrences (all)	112		
Psychiatric disorders			
Psychiatric disorders combined			
subjects affected / exposed	26 / 503 (5.17%)		
occurrences (all)	31		
Investigations			
Investigations combined			
subjects affected / exposed	24 / 503 (4.77%)		
occurrences (all)	31		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural combined			
subjects affected / exposed	26 / 503 (5.17%)		
occurrences (all)	34		
Cardiac disorders			
Cardiac disorders combined			
subjects affected / exposed	16 / 503 (3.18%)		
occurrences (all)	20		
Nervous system disorders			
Nervous system disorders combined			
subjects affected / exposed	118 / 503 (23.46%)		
occurrences (all)	163		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	14 / 503 (2.78%)		
occurrences (all)	14		
Ear and labyrinth disorders			

Ear and labyrinth disorders combined subjects affected / exposed occurrences (all)	12 / 503 (2.39%) 12		
Eye disorders Eye disorders combined subjects affected / exposed occurrences (all)	34 / 503 (6.76%) 35		
Gastrointestinal disorders Gastrointestinal disorders combined subjects affected / exposed occurrences (all)	200 / 503 (39.76%) 373		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all)	1 / 503 (0.20%) 1		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders combined subjects affected / exposed occurrences (all)	95 / 503 (18.89%) 131		
Renal and urinary disorders Renal and urinary disorders combined subjects affected / exposed occurrences (all)	149 / 503 (29.62%) 201		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 503 (0.20%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders combined subjects affected / exposed occurrences (all)	131 / 503 (26.04%) 174		
Infections and infestations Infections combined subjects affected / exposed occurrences (all)	14 / 503 (2.78%) 14		
Metabolism and nutrition disorders			

Metabolism and nutrition disorders combined			
subjects affected / exposed	187 / 503 (37.18%)		
occurrences (all)	351		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2016	Amendment to randomisation process to allocate individual bottles rather than 'packs' of 3 bottles to allow for shorter expiry dates, and clarification of safety reporting procedures
25 May 2017	Amendment to exclusion criteria to allow patients who have previously tried the study drugs to be included, as long as this has not been in the previous 3 months. The original criteria was unnecessarily strict and did not reflect real-world prescribing habits. The amendment also removed the blanket exclusion for patients in concurrent clinical trials, providing sufficient washout period between IMPs.
07 September 2017	Amendment to eligibility criteria to include patients taking metformin-only, or metformin and a sulfonylurea. This was adjusted due to the change in guidelines and prescribing trends leading to decline in use of sulfonylureas. At the time of study design sulfonylureas were the most commonly prescribed second line therapy in the UK. Subsequent decline in their use in favour of DPP4-inhibitors and SGLT2 inhibitors 22, resulted in the inclusion of patients currently treated with either metformin and sulfonylureas or metformin only. We will perform a sensitivity analysis to determine if the difference in study "epoch" (before/after this amendment) has any impact on the main study outcomes. Altered exclusion criteria also added 'limb ischaemia' due to updated safety information for Canagliflozin, and an upper limit of HbA1c >110mmol/mol.
06 July 2018	Amendment to sample size due to over-cautious sample calculations (alpha changed to 0.05), extension to recruitment period due to delays in regulatory approvals at study set-up and slow early recruitment, and additional secondary analysis included on the advice of the Data Monitoring Committee.
13 June 2019	Amendment to study analysis plan. Following advice from the Trial Steering Committee statistician, the protocol was amended to analyse only those completing at least 12 weeks on therapy, as this will determine whether the strata result in differences in response (we cannot adequately measure glycaemic response by HbA1c if the patient has been on the drug for less than 12 weeks). A separate analysis will be performed to determine whether the strata influence tolerability by assessing whether the proportion completing at least 12 weeks on therapy differs by drug and strata.
30 April 2020	Amendment to ensure ongoing participant safety and study integrity during Covid-19 pandemic. Urgent safety measures included (i) extension of visit windows to 14-18 weeks to allow greater flexibility for participants who are unwell/isolating, (ii) provision for remote visits with sample collection outside the usual research setting, (iii) ensuring participants remained on study therapy when only a remote visit is possible, by allowing an additional 'continuation' bottle of the same IMP to be issued, or when no other option, transfer to the next IMP without collection of blood samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33371044