Clinical trial results:
Pilot randomised controlled trial of SITAgliptin for Depressive Symptoms in type 2 diabetes

Summary

EudraCT number	2015-004527-32
Trial protocol	GB
Global end of trial date	08 August 2019

Results information

Result version number	v1 (current)
This version publication date	30 August 2020
First version publication date	30 August 2020

Trial information

Trial identification

Sponsor protocol code	SITADS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Prof Khalida Ismail , King's College London, 0044 02078483545, khalida.2.ismail@kcl.ac.uk
Scientific contact	Prof Khalida Ismail , King's College London, 0044 02078483545, khalida.2.ismail@kcl.ac.uk
Sponsor organisation name	King's College Hospital NHS Foundation Trust
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Public contact	Prof Khalida Ismail, King's College London, 0044 02078483545, khalida.2.ismail@kcl.ac.uk
Scientific contact	Prof Khalida Ismail, King's College London, 0044 02078483545, khalida.2.ismail@kcl.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	08 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2019
Global end of trial reached?	Yes
Global end of trial date	08 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether sitagliptin improves depressive symptoms improve in patients with type 2 diabetes.
To investigate whether sitagliptin improves blood glucose control and reduces systemic inflammation in patients with type 2 diabetes.

Protection of trial subjects:

Patients are free to withdraw consent for study treatment and/or consent to participate in the study at any time and without the prejudice to further treatment. Patients who withdraw from study treatment, but are willing to continue to participate in the follow-up visits, should be followed according to the procedures outlined in the protocol.

Background therapy:

Eligible participants will already be prescribed a minimum of one first-line anti-diabetes agent (metformin or sulphonylurea) for at least 3 months. This ensures that this trial accords with NICE Guidelines on the treatment of T2D. Adherence with current diabetes treatment will be assessed using the Brief Adherence Rating Scale. At baseline, consenting participants will not be prescribed any concomitant anti-depressant treatment or incretin-based diabetes therapy. During the trial, however, commencement of additional glucose-lowering therapy (including insulin) will be permitted if prescribed by GP or diabetes specialist. The only exception is the commencement of other incretin-based therapy, which will not be permitted due to potential interaction with sitagliptin. Commencement of other treatment for depression (pharmacological or psychotherapeutic) by GP or specialist mental health services will also be permitted during the trial and measured as an outcome.

Evidence for comparator: -

Actual start date of recruitment	10 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	40
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment duration January 2018 to January 2019.
Potential participants were identified from the registers of participating GP surgeries in the London boroughs of Southwark, Lewisham, Lambeth and Bromley.

Pre-assignment

Screening details:

General Practices searched for patients with a diagnosis of type 2 diabetes for at least 6 months, aged 18-75 and with last recorded HbA1c 53-86 mmol/mol. Patients were then contacted by the GP and invited to meet the study team for a screening visit. All patients provided signed and dated informed consent before enrollment.

Pre-assignment period milestones

Number of subjects started	153[1]
Number of subjects completed	44

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen fail: 109

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Pre-assignment period includes scree failures who were not enrolled

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sitagliptin

Arm description:

Sitagliptin 100mg oral (PO) once per day (OD)

Arm type	Experimental
Investigational medicinal product name	sitagliptin
Investigational medicinal product code	
Other name	Januvia
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100mg per day for up to 12 weeks

Arm title	Placebo

Arm description:

placebo PO OD

Arm type	Placebo

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

Dosage and administration details:

PO OD

Number of subjects in period 1	Sitagliptin	Placebo
Started	22	22
Completed	16	20
Not completed	6	2
Consent withdrawn by subject	5	2
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description: Sitagliptin 100mg oral (PO) once per day (OD)	
Reporting group title	Placebo
Reporting group description: placebo PO OD	

Reporting group values	Sitagliptin	Placebo	Total
Number of subjects	22	22	44
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	59.9	57.7	
standard deviation	± 9.6	± 6.8	-
Gender categorical Units: Subjects			
Female	10	10	20
Male	12	12	24
Current medication regime Units: Subjects			
Metformin/gliclazide monotherapy	15	13	28
Dual therapy	7	9	16
Any previous macrovascular complication			
Defined as any previous heart attack, stroke, coronary artery bypass graft, carotid revascularisation or peripheral arterial revascularisation			
Units: Subjects			
Yes	4	3	7
No	18	19	37
Retinopathy present Units: Subjects			
Yes	6	5	11
No	16	17	33

Diabetes Duration			
Units: Years			
arithmetic mean	6.45	7.41	
standard deviation	± 4.4	± 4.9	-
Fasting glucose			
Units: mg/L			
arithmetic mean	8.8	8.1	
standard deviation	± 3.5	± 2.5	-
HOMA-IR			
Homeostasis Model Assessment of Insulin Resistance			
Units: percent			
arithmetic mean	6.63	5.34	
full range (min-max)	1.78 to 23.54	3.07 to 8.29	-
HbA1c			
Units: mmol/mol			
arithmetic mean	62.2	60.2	
standard deviation	± 7.0	± 6.3	-
Hypoglycaemia symptoms score			
Units: Score			
arithmetic mean	36.1	31.0	
standard deviation	± 9.4	± 12.8	-
BMI			
body mass index			
Units: kg/m2			
arithmetic mean	31.7	31.8	
standard deviation	± 5.9	± 4.2	-
Total cholesterol			
Units: mmol/L			
arithmetic mean	4.39	4.35	
standard deviation	± 0.8	± 1.1	-
Baseline hs-CRP			
Units: mg/L			
arithmetic mean	4.75	2.40	
full range (min-max)	0.98 to 7.23	1.05 to 5.95	-
Systolic BP			
blood pressure			
Units: mmHg			
arithmetic mean	131.6	127.1	
standard deviation	± 14.8	± 14.8	-
Diastolic BP			
blood pressure			
Units: mmHg			
arithmetic mean	79.3	76.2	
standard deviation	± 11.2	± 9.7	-
PHQ-9 score			
Patient Health Questionnaire for baseline depressive symptoms (0-27)			
Units: Score			
arithmetic mean	15.5	13.8	
standard deviation	± 4.3	± 4.6	-
QIDS-SR-16 score			
16-item Quick Inventory of Depressive Symptomatology (0-27)			
Units: Score			

arithmetic mean	13.7	12.4	
standard deviation	± 4.4	± 4.8	-

End points

End points reporting groups	
Reporting group title	Sitagliptin
Reporting group description: Sitagliptin 100mg oral (PO) once per day (OD)	
Reporting group title	Placebo
Reporting group description: placebo PO OD	

Primary: Change in depressive symptoms	
End point title	Change in depressive symptoms
End point description: Primary: change in depressive symptoms after 12 weeks as measured by the Patient Health Questionnaire-9 (PHQ-9) and Quick Inventory of Depressive Symptomatology (QIDS-SR-16).	
End point type	Primary
End point timeframe: Baseline to 12 weeks	

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: score				
arithmetic mean (confidence interval 95%)				
QIDS-SR-16	10.25 (7.63 to 12.87)	9.10 (6.91 to 11.29)		
PHQ-9	9.94 (6.85 to 13.03)	9.05 (5.97 to 12.13)		

Attachments (see zip file)	Changes in QIDS-SR-16 score during study/Changes in QIDS- Changes in PHQ-9 score during study/Changes in PHQ-9 score

Statistical analyses

Statistical analysis title	Difference between groups QIDS-SR-16
Statistical analysis description: The primary treatment analyses will compare the difference in depressive symptoms after 12 weeks between the two groups after adjusting for baseline outcome scores (“ANCOVA” approach.) A linear mixed model using STATA’s xtmixed command will be used for estimation.	
Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	6
Variability estimate	Standard deviation
Dispersion value	0.71

Statistical analysis title	Difference between groups PHQ-9 Score

Statistical analysis description:

The primary treatment analyses will compare the difference in depressive symptoms after 12 weeks between the two groups after adjusting for baseline outcome scores ("ANCOVA" approach.) A linear mixed model using STATA's xtmixed command will be used for estimation.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	4.98
Variability estimate	Standard deviation
Dispersion value	0.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to 24 weeks

Adverse event reporting additional description:

Every 4 weeks, participants will be asked to report any adverse events to the investigators.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Sitagliptin

Reporting group description:

Sitagliptin 100mg oral (PO) once per day (OD)

Reporting group title	Placebo

Reporting group description:

placebo PO OD

Serious adverse events	Sitagliptin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
transient ischemic attack	Additional description: hospitalisation due to possible transient ischemic attack		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
unilateral deafness	Additional description: an incident of unilateral deafness (which attributed by an ear-nose-throat specialist to a diuretic medication [furosemide]),		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
osteoarthritis	Additional description: of right hip		
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sitagliptin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)	11 / 22 (50.00%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Dyspepsia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 22 (9.09%)	6 / 22 (27.27%)	
occurrences (all)	2	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	6 / 22 (27.27%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2017	Protocol v2.0 Update to endpoint timings
25 July 2017	Protocol v3.0 Imp dosing updated to 2 x 50mg capsules Change to code break mechanism Inclusion/Exclusion criteria clarification
27 June 2019	Protocol v4.1, recruitment stopped at 44 rather than 60 patients

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported