EU Clinical Trials Register

Clinical trial results:
REducing with MetfOrmin Vascular Adverse Lesions in T1DM (The REMOVAL study)

Summary

EudraCT number	2011-000300-18
Trial protocol	GB NL DK
Global end of trial date	17 February 2017

Results information

Result version number	v1 (current)
This version publication date	21 June 2019
First version publication date	21 June 2019

Trial information

Trial identification

Sponsor protocol code	GN10DI406

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01483560
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Dalnair Street, Glasgow, United Kingdom, G3 8SW
Public contact	Dr Maureen Travers, NHS Greater Glasgow and Clyde Research and Development , 0044 01412321813, R&DIMP@ggc.scot.nhs.uk
Scientific contact	Dr Maureen Travers, NHS Greater Glasgow and Clyde Research and Development , 0044 01412321813, john.petrie@glasgow.ac.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	126 University Place, Glasgow, United Kingdom, G12 8TA
Public contact	Prof John Petrie, University of Glasgow, 0044 01413303325, john.petrie@glasgow.ac.uk
Scientific contact	Prof John Petrie, University of Glasgow, 0044 01413303325, john.petrie@glasgow.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	11 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2017
Global end of trial reached?	Yes
Global end of trial date	17 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of REMOVAL is to test whether metformin tablets added in with insulin treatment in type 1 diabetes can prevent the early blood vessel complications which lead to heart attacks and strokes.

Protection of trial subjects:

Participants were provided with the best care possible throughout the follow-up period. They were encouraged and supported to work towards and maintain
target glycaemic control (HbA1c < 7.0%/ 53 mmol/mol) independent of the treatment to which they were randomized (i.e. metformin or placebo). This was achieved by: (i) increased attention to lifestyle measures; (ii) supported adjustment of insulin doses; and (iii) intensifying insulin regimens and doses where necessary.
Before inclusion in the study, all participants were screened by a physician to ensure that the entry criteria were met. During the study, participants were seen in their local diabetes clinic regularly at 3-6 monthly intervals. At these visits, measures related to patient safety were monitored and action taken if clinically relevant as per the Study Protocol. Telephone calls to participants were made and documented by study personnel four times during the initial three months and thereafter half-yearly (alternating with the study visits) in order to monitor and record adverse events and advise on dosing of insulin and titration of study medication. All participants had a contact number for local clinical personnel on a study card in case of medical needs outside the planned study visits or telephone contacts. All adverse effects were reported using established standard operating procedures meeting international regulatory requirements. A Data and Safety Monitoring Board met six monthly to review unblinded details of adverse events and had the sanction of recommending study termination to the Steering Committee if appropriate. In addition, a Glycaemia Committee met six monthly to review summarized details of glycaemic
control (HbA1c) and rates of major and minor hypoglycaemia. It sent detailed reports (masked to treatment allocation) on participants' HbA1c and rates of hypoglycaemia to each site every 6 months along with benchmarking data from other sites in their region.

Background therapy:

During the run-in period CVD risk factor management was optimised in accordance with local guidelines at sites and insulin regimens were reviewed with the aim of optimising glycaemic control (target HbA1c 7·0% [53 mmol/mol]) with additional clinic visits if necessary. Adjustments in insulin doses towards target HbA1c were made at the discretion of site staff rather than being specified by the protocol. Participants continued to have access to usual local arrangements for diet, lifestyle and weight management throughout the trial; ongoing management of glycaemia, blood pressure and lipids was under the care of the site principal investigator and usual care team. Participants with ongoing treatment with oral steroids, pramlintide or GLP-1 agonist therapy were specifically excluded.

Evidence for comparator: -

Actual start date of recruitment	01 October 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	20 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 254
Country: Number of subjects enrolled	Australia: 75
Country: Number of subjects enrolled	Canada: 113
Country: Number of subjects enrolled	Netherlands: 38
Country: Number of subjects enrolled	Denmark: 13
Worldwide total number of subjects	493
EEA total number of subjects	305

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)	493
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

501 participants screened
493 participants enrolled
428 participants randomised
36 participants withdrew prior to randomisation
61 participants withdrew post randomisation (35 metformin, 26 placebo)

Pre-assignment

Screening details:

4 week Run-In period

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500mg tablets
Either 1 or 2 tablets, once or twice a day.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 or 2 tablets, once or twice a day.

Number of subjects in period 1[1]	Metformin	Placebo
Started	219	209
Completed	193	194
Not completed	26	15
Consent withdrawn by subject	26	15

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 493 subjects were enrolled into the trial.

65 were found to be ineligible during the Run-In period.

Reasons such as: Did not meet inclusion/exclusion criteria, withdrew prior to randomisation, unwilling to attend visits etc.

This left 428 subjects to be randomised to either arm.

Baseline characteristics

Reporting groups

Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Reporting group values	Metformin	Placebo	Total
Number of subjects	219	209	428
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	219	209	428
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	90	85	175
Male	129	124	253

Subject analysis sets

Subject analysis set title	Mean Carotid
Subject analysis set type	Per protocol

Subject analysis set description:

Progression of averaged mean far wall common carotid artery intima media thickness IMT (mean cIMT) measured using B mode ultrasonography with a 7 0 MHz or higher broadband linear array transducer and concurrent recording of 3-lead ECG. Longitudinal images of the common carotid artery will be obtained at anterior, lateral and posterior angles at baseline, 12, 24 and 36 months using Meijer's arc to standardize the transducer angle.

Reporting group values	Mean Carotid		
Number of subjects	387		
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)	387		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Mean Carotid
Subject analysis set type	Per protocol

Subject analysis set description:

Progression of averaged mean far wall common carotid artery intima media thickness IMT (mean cIMT) measured using B mode ultrasonography with a 7 0 MHz or higher broadband linear array transducer and concurrent recording of 3-lead ECG. Longitudinal images of the common carotid artery will be obtained at anterior, lateral and posterior angles at baseline, 12, 24 and 36 months using Meijer's arc to standardize the transducer angle.

Primary: Mean Carotid IMT

End point title	Mean Carotid IMT
End point description:	
End point type	Primary
End point timeframe:	

Baseline, 12, 24 and 36 months

End point values	Metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: Slope				
number (not applicable)	0.006	0.01		

Statistical analyses

Statistical analysis title	Averaged Mean far wall cIMT
Comparison groups	Metformin v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1664 [1]
Method	Mixed models analysis

Notes:

[1] - The primary cIMT endpoint treatment effect was not statistically significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent form up to 30 days after the subject completed or discontinued the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Metformin

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Metformin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 219 (15.53%)	31 / 209 (14.83%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer			
subjects affected / exposed	6 / 219 (2.74%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiac disorders			
Coronary related events			
subjects affected / exposed	3 / 219 (1.37%)	6 / 209 (2.87%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Cerebrovascular, ischemic events			
subjects affected / exposed	5 / 219 (2.28%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections			

subjects affected / exposed	7 / 219 (3.20%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic and nutrition related			
subjects affected / exposed	8 / 219 (3.65%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Metformin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 219 (43.84%)	97 / 209 (46.41%)	
Eye disorders			
Laser, cataract, Vitrectomy			
subjects affected / exposed	28 / 219 (12.79%)	76 / 209 (36.36%)	
occurrences (all)	28	76	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2012	Protocol Change - principal change in inclusion criteria and adverse event reporting An update to the Merck Licence and IMP Dossier.
09 September 2015	The main update to the protocol was procedures to allow abbreviated follow up of the last 50 participants recruited. In order to achieve adequate power for the primary endpoint and minimize the need for time extensions from the funder, the Steering Group took the decision when 90% of the target number of participants had been enrolled to continue to recruit but to abbreviate the duration of follow up for the remaining participants (n=50). By this method, exposure to randomized treatment will still be 98.8% of that originally planned. Point of clarification regarding ongoing carotid IMT Quality Control: Protocol v2.0 stated that each centre would perform six monthly carotid IMT scans on five healthy volunteers from the start of the study and every six months until completion of the study to assess for any measurement drift. Results of Quality Control (QC) would then be fed back to centres on a regular basis with follow up retraining/ certification as necessary. However it is increasingly difficult to retain the same healthy volunteers for repeated measurements. The possibility of repeat scans on patients had been included in version 2.3 of the PIS (in Oct 2012) in case this became a problem, and therefore patients had consented to the option of additional scans at visits 1, 8, 12 qnd 16 (i.e. annual visits) for QC purposes. On a pragmatic basis therefore an alternative Quality Assurance plan has been agreed so that a subgroup of actual study participants are invited to undergo repeat scans at each annual visit to assess reproducibility Protocol v3.0 includes an update to reflect this arrangement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported