Clinical trial results:
Kidney Fat in Type 2 Diabetes & Diabetic Kidney Disease and the Effects of Ezetimibe: A Cross-Sectional Study and Randomized, Placebo-Controlled Trial

Summary

EudraCT number	2020-001155-40
Trial protocol	DK
Global end of trial date	12 May 2022

Results information

Result version number	v1 (current)
This version publication date	21 August 2023
First version publication date	21 August 2023

Trial information

Trial identification

Sponsor protocol code	16032020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT16032020
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Borgmester Ib Juuls Vej 83, Herlev, Denmark, 2730
Public contact	Professor Peter Rossing, Complications Research, Steno Diabetes Center Copenhagen, 0045 3091 3383, peter.rossing@regionh.dk
Scientific contact	Professor Peter Rossing, Complications Research, Steno Diabetes Center Copenhagen, 30913383 3091 3383, peter.rossing@regionh.dk

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 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2022
Global end of trial reached?	Yes
Global end of trial date	12 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether ezetimibe reduces albuminuria and kidney parenchymal fat content in individuals with type 2 diabetes and non-severe chronic kidney disease in a randomized, double-blinded, placebo-controlled intervention study in around 60 individuals.
Also to compare, in a cross-sectional study, the kidney parenchymal fat content between controls (planned n=30), individuals with type 2 diabetes and no chronic kidney disease (planned n=30) and individuals with type 2 diabetes and non-severe chronic kidney disease.
Results only reported here for intervention study.

Protection of trial subjects:

Study conducted in compliance with the Good Clinical Practice standard, Declaration of Helsinki and Danish Data Protection Act. Potocol was approved by the Capital Region’s Scientific Ethics Committee (jr.nr. H-20021349) and the Danish Medicines Agency (jr.nr. 2020033463). External monitoring was conducted by the Good Clinical Practice-unit affiliated with the University of Copenhagen. All participants gave written informed consent. Appropriate safety laboratory analyses and screening and precautions for MRI scans were carried out.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2020
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	Denmark: 115
Worldwide total number of subjects	115
EEA total number of subjects	115

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)	48
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with T2D were recruited by letter of invitation to relevant candidates attending Steno Diabetes Center Copenhagen

Pre-assignment

Screening details:

Main eligibility criteria were: T2D (WHO-criteria), persistent urine albumin creatine ratio (UACR) ≥ 30mg/g, estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m2, age 40-80 years and absence of contraindication to MRI. CKD primarily ascribed to other causes than diabetes was an exclusion criterium.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ezetimibe

Arm description:

Ezetimibe group

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

Dosage and administration details:

10 mg once daily for 16 weeks

Arm title	Placebo

Arm description:

Placebo group

Arm type	Placebo
Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily for 16 weeks

Number of subjects in period 1[1]	Ezetimibe	Placebo
Started	25	24
Completed	25	24

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: We aimed to screen and enroll 120 subjects for this "DiaKiDZ" study encompassing both an intervention study and a cross-sectional study. Only 60 were to be enrolled for the intervention study. Only results from intervention study (where 57 subjects ended up being enrolled) are reported here.

Baseline characteristics

Reporting groups	
Reporting group title	Intervention period

Reporting group description: -

Reporting group values	Intervention period	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	17	17	
From 65-84 years	32	32	
85 years and over	0	0	
Age continuous			
Age			
Units: years			
arithmetic mean	67		
standard deviation	± 7	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	41	41	
Sodium-glucose cotransporter-2 inhibitor Units: Subjects			
Yes	34	34	
No	15	15	
Glucagon-like peptide-1 receptor agonist Units: Subjects			
Yes	33	33	
No	16	16	
BMI			
Body mass index			
Units: kg/m2			
arithmetic mean	31		
standard deviation	± 4	-	
Waist circmference			
Waist circumference			
Units: cm			
arithmetic mean	114		
standard deviation	± 110	-	

Diabetes duration Units: years median inter-quartile range (Q1-Q3)	 19 12 to 26	 -	
Urine albumin creatinine ratio Units: mg/g geometric mean inter-quartile range (Q1-Q3)	 95 41 to 297	 -	
Estimated glomerular filtration rate Units: ml/min/1.73m2 arithmetic mean standard deviation	 76 ± 22	 -	
HbA1c, IFCC Units: mmol/mol arithmetic mean standard deviation	 57 ± 10	 -	
Total cholesterol Units: mmol/l arithmetic mean standard deviation	 3.6 ± 0.7	 -	
plasma triglyceride Units: mmol/l median inter-quartile range (Q1-Q3)	 1.76 1.13 to 2.90	 -	

End points

End points reporting groups	
Reporting group title	Ezetimibe
Reporting group description: Ezetimibe group	
Reporting group title	Placebo
Reporting group description: Placebo group	

Primary: Change in urine albumine creatinine ratio	
End point title	Change in urine albumine creatinine ratio
End point description: End-of-treatment urine albumin creatinine ratio	
End point type	Primary
End point timeframe: 16 weeks	

End point values	Ezetimibe	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: mg/g				
geometric mean (inter-quartile range (Q1-Q3))	140 (49 to 213)	67 (34 to 148)		

Statistical analyses

Statistical analysis title	Relative change in urine albumine creatinine ratio
Statistical analysis description: Effect (β) of ezetimibe relative to placebo on urine albumine creatinine ratio	
Comparison groups	Ezetimibe v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.83
Method	Regression, Linear
Parameter estimate	Least squares mean
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.31

Notes:

[1] - Change (β) in urine albumin creatinine ratio with ezetimibe relative to placebo.
β: regression coefficient (back-transformed) from a multiple linear regression model with (log-transformed) end-of-treatment urine albumin creatinine ratio as dependent variable and treatment group (ezetimibe or placebo) and (log-transformed) baseline urine albumin creatinine ratio as independent variables.

Secondary: Change in kidney parenchyma fat content

End point title	Change in kidney parenchyma fat content
End point description:	
End-of-treatment kidney parenchyma fat content	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	Ezetimibe	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	19		
Units: percent				
geometric mean (inter-quartile range (Q1-Q3))	0.6 (0.4 to 1.2)	1.0 (0.4 to 2.0)		

Statistical analyses

Statistical analysis title	Relative change in kidney parenchyma fat content
Statistical analysis description:	
Effect of ezetimibe relative to placebo on kidney parenchyma fat content	
Comparison groups	Ezetimibe v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.12
Method	Regression, Linear
Parameter estimate	Least squares mean
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.14

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Enrolment to end-of-treatment (approx. 19 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26

Reporting groups	
Reporting group title	Ezetimibe group
Reporting group description: -	
Reporting group title	Placebo group
Reporting group description: -	

Serious adverse events	Ezetimibe group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Subdural haematoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ezetimibe group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)	11 / 24 (45.83%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Change in stool or flatulence			
subjects affected / exposed	6 / 25 (24.00%)	6 / 24 (25.00%)	
occurrences (all)	6	6	
Dyspepsia or reflux			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2021	Addition in Protocol of "MR estimate (by Dixon's method) of kidney parenchymal fat fraction" to secondary endpoints in both cross-sectional and intervention part of study. In cross-secional part of study, previous other secondary endpoints have been delegated to tertiary endpoints. Addition in Protocol of "Images are also obtained to estimate fat fraction in the kidney parenchyma by Dixon's method." in the description of the Kidney MR examination. In this description the duration of the MR examination has also been changed from 20-30 minutes to 40-60 minutes and the duration of fasting before the examination has been shortened to 4 hours (from 6 hours). Change in Participation Information of duration of study visit with MR examination to 60 minutes and addition of 4 hours fasting from food and 2 hours fasting from liquid before examination. Change in Protocol and Participant Information in inclusion criteria to "Age ≥ 40 and ≤ 80 years" from "Age ≥ 40 and ≤ 75 years" Removal of following inclusion criterion for intervention group: "LDL above 1,5mmol/L at screening" End of study postponed to 31/12/2021 from 30-06-2021

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/37278273