Clinical trial results:
Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria

Summary

EudraCT number	2012-000452-34
Trial protocol	DK IT GB NL ES CZ GR BE
Global end of trial date	27 November 2018

Results information

Result version number	v1 (current)
This version publication date	23 October 2020
First version publication date	23 October 2020
Summary attachment (see zip file)	priority (priority lancet DE 2020.pdf) priority supl (PRIORITY suppl fig and tables Lancet DE Rev2_clean.docx)

Trial information

Trial identification

Sponsor protocol code	3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02040441
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	steno diabetes center copenhagen
Sponsor organisation address	niels steensens vej 2, gentofte, Denmark, 2820
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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	06 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2018
Global end of trial reached?	Yes
Global end of trial date	27 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm that urinary proteomics can predict development of microalbuminuria (as a surrogate marker for the development of overt nephropathy) in a cohort of 2000 type 2 diabetic patients with normal urinary albumin excretion.
the intervention part was in the subset with high proteomic risk, expected to be approx 250 participants out of the total population, randomised to placebo or spironolactone

Protection of trial subjects:

DMC was monitoring conduct of trial, minimal dose expected to work used, and number of visits reduced to a minimum

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 13
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Denmark: 64
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 41
Worldwide total number of subjects	209
EEA total number of subjects	196

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)	120
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between March 25, 2014, and Sept 30, 2018, we enrolled and followed-up 1775 participants (observational
cohort), 1559 (88%) of 1775 participants had a low-risk urinary proteomic pattern and 216 (12%) had a high-risk pattern of whom 209 were included in the trial cohort and assigned to spironolactone (n=102) or placebo (n=107).

Pre-assignment

Screening details:

we recruited people aged 18–75 years with type 2 diabetes, preserved kidney function, and normoalbuminuria from 15 specialist centres in ten European countries (Belgium, Czech Republic, Denmark, Germany, Greece, Italy, the Netherlands, North Macedonia, Spain, and the UK

Period 1

Period 1 title	intervention (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

Blinding implementation details:

interactive web-response system
to either spironolactone 25 mg once daily or
matching placebo, following a computer-generated
randomisation scheme. Treatment allocation was doubleblind,
with participants and investigators masked to
allocation. The medications for each treatment group were
identical in appearance and were supplied in identical
bottles, labelled appropriately to maintain masking within
the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	spironoloactone

Arm description:

25 mg spironolactone daily

Arm type	Active comparator
Investigational medicinal product name	spironolactone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg orally daily in single tablet or matching placebo

Arm title	placebo

Arm description:

matching placebo

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
1 tablet

Number of subjects in period 1	spironoloactone	placebo
Started	102	107
Completed	102	107

Baseline characteristics

Reporting groups	
Reporting group title	spironoloactone
Reporting group description: 25 mg spironolactone daily	
Reporting group title	placebo
Reporting group description: matching placebo	

Reporting group values	spironoloactone	placebo	Total
Number of subjects	102	107	209
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	63	63	
standard deviation	± 6	± 7	-
Gender categorical Units: Subjects			
Female	33	29	62
Male	69	78	147

End points

End points reporting groups

Reporting group title	spironoloactone
Reporting group description: 25 mg spironolactone daily	
Reporting group title	placebo
Reporting group description: matching placebo	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat trial cohort consisted of all participants with a valid proteomic score with a high-risk pattern who were randomly assigned to receive study medication.	

Primary: microalbuminuria

End point title	microalbuminuria
End point description: number of subjects progressing from normoalbuminuria to microalbuminuria (U-albumin creatinine ration>30 mg/g creatinine and at least 30% increase from baseline)	
End point type	Primary
End point timeframe: 4 years	

End point values	spironoloactone	placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	107	209	
Units: cases with microalbuminuria				
microalb	26	35	51	

Statistical analyses

Statistical analysis title	logrank test
Statistical analysis description: surcival analysis	
Comparison groups	spironoloactone v placebo
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.34

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
up to 4 years	
Adverse event reporting additional description:	
selected safety outcomes of special interest in the trial cohort were hyperkalaemia (plasma or serum level of potassium >0·4 mmol/L above local upper reference), gynaecomastia, and hypotension.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	spironolactone group
Reporting group description:	
active treated randomised to spironolactone	
Reporting group title	placebo
Reporting group description:	
placebo treated	

Serious adverse events	spironolactone group	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 102 (6.86%)	14 / 107 (13.08%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	6 / 102 (5.88%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
nervous system disorder			
subjects affected / exposed	0 / 102 (0.00%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			

subjects affected / exposed	1 / 102 (0.98%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	spironolactone group	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 102 (47.06%)	64 / 107 (59.81%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
neoplasm			
subjects affected / exposed	5 / 102 (4.90%)	4 / 107 (3.74%)	
occurrences (all)	5	4	
Vascular disorders			
vascular disorder			
subjects affected / exposed	11 / 102 (10.78%)	6 / 107 (5.61%)	
occurrences (all)	11	6	
Surgical and medical procedures			
surgical procedure			
subjects affected / exposed	3 / 102 (2.94%)	6 / 107 (5.61%)	
occurrences (all)	3	6	
General disorders and administration site conditions			
admin site disorder			
subjects affected / exposed	8 / 102 (7.84%)	14 / 107 (13.08%)	
occurrences (all)	8	14	
Reproductive system and breast disorders			
Reproductive system disorder prophylaxis			
subjects affected / exposed	3 / 102 (2.94%)	4 / 107 (3.74%)	
occurrences (all)	11	7	
Respiratory, thoracic and mediastinal disorders			
respiratory disorder			
subjects affected / exposed	12 / 102 (11.76%)	4 / 107 (3.74%)	
occurrences (all)	12	4	
Investigations			

investigations			
subjects affected / exposed	29 / 102 (28.43%)	13 / 107 (12.15%)	
occurrences (all)	29	13	
Injury, poisoning and procedural complications			
injury			
subjects affected / exposed	10 / 102 (9.80%)	13 / 107 (12.15%)	
occurrences (all)	10	13	
Congenital, familial and genetic disorders			
congenital			
subjects affected / exposed	1 / 102 (0.98%)	0 / 107 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	4 / 102 (3.92%)	3 / 107 (2.80%)	
occurrences (all)	4	3	
Nervous system disorders			
nervous system disorder			
subjects affected / exposed	18 / 102 (17.65%)	22 / 107 (20.56%)	
occurrences (all)	18	22	
Blood and lymphatic system disorders			
blood and lymph system disorders			
subjects affected / exposed	7 / 102 (6.86%)	2 / 107 (1.87%)	
occurrences (all)	7	2	
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	2 / 102 (1.96%)	2 / 107 (1.87%)	
occurrences (all)	2	2	
Eye disorders			
eye disorders			
subjects affected / exposed	5 / 102 (4.90%)	8 / 107 (7.48%)	
occurrences (all)	10	18	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	12 / 102 (11.76%)	8 / 107 (7.48%)	
occurrences (all)	26	17	
Skin and subcutaneous tissue disorders			

skin disorder			
subjects affected / exposed	11 / 102 (10.78%)	15 / 107 (14.02%)	
occurrences (all)	11	15	
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	3 / 102 (2.94%)	7 / 107 (6.54%)	
occurrences (all)	5	17	
Endocrine disorders			
endocrine disorders			
subjects affected / exposed	3 / 102 (2.94%)	2 / 107 (1.87%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
musculosceltal disorder			
subjects affected / exposed	18 / 102 (17.65%)	19 / 107 (17.76%)	
occurrences (all)	18	29	
Infections and infestations			
infections			
subjects affected / exposed	22 / 102 (21.57%)	24 / 107 (22.43%)	
occurrences (all)	46	66	
Metabolism and nutrition disorders			
metabolism			
subjects affected / exposed	44 / 102 (43.14%)	23 / 107 (21.50%)	
occurrences (all)	44	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2015	Changes made Adaptation of the approximately number of patient screening from 7000 to 2700 and number of patient planned to included is changed from 3280 to 2000. In addition the treatment/ observational period are changed from 3 years for all included to a period between 2 to 4.4 years dependent on the time of inclusion. Justification Please see justification for revised samples size changes made to section 15.1 and justification of extension of the period for the first included patient, under justification for changes made in section 9.1.1 and 9.1.2. Section 6.6 Changes made Changed screening window from (Week -8 to -4) to (week -12 to -4) and run-in-period from (week -7 to -3) to (week -11 to -2). The periodic study visits is revised in accordance with the different follow-up period described in the revised section 9.1.1 and 9.1.2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32135136