



Clinical trial results:

Inhibition of aldosterone to diminish diffuse myocardial fibrosis in atrial fibrillation

Summary

EudraCT number	2013-000797-30
Trial protocol	DK
Global end of trial date	26 March 2017

Results information

Result version number	v1 (current)
This version publication date	14 March 2021
First version publication date	14 March 2021
Summary attachment (see zip file)	Methods and results summary (Summary EUDRACT.docx)

Trial information

Trial identification

Sponsor protocol code	SPI-IIT-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02764619
WHO universal trial number (UTN)	-
Other trial identifiers	Amendment 3, protocol 3.0: SPI-IIT-002

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital, Svendborg
Sponsor organisation address	Baageoes Alle 15, Svendborg, Denmark, 5700
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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	03 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2017
Global end of trial reached?	Yes
Global end of trial date	26 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether or not therapy with a mineralocorticoid receptor antagonist (MRA), in this case spironolactone, added to optimal medical treatment in normotensive or hypertensive patients with paroxysmal or persistent atrial fibrillation diminishes diffuse myocardial fibrosis in left atria and ventricle, atrial remodeling and thus improve left atrial function as compared with conventional treatment.

Protection of trial subjects:

Reports of adverse events (AE) were collected throughout the study period, classified and graded according to seriousness, intensity, outcome, and causality with study medication. Adverse events of special interest were gynecomastia, hyperkalemia, and worsening of renal function compared to baseline. Breast tissue pain or discomfort ≥ 1 month, or visually apparent gynecomastia were regarded as a serious AE, and the subject was withdrawn from the study. The severity of hyperkalemia was defined according to the European Resuscitation Council guidelines into mild (5.5–5.9 mmol/L), moderate (6.0–6.4 mmol/L), and severe (>6.5 mmol/L). The worsening of renal function was defined according to the Kidney Disease Improving Global Outcomes Guidelines. A relative increase in serum creatinine or estimated glomerular filtration rate (calculated by MDRD) $<25\%$ from baseline and serum potassium <6.0 mmol/L was considered acceptable. In case of a moderate increase of serum creatinine 25–29% from baseline or moderate hyperkalemia 6.0–6.4 mmol/L, potassium supplements, concomitant treatment with ACEI/ARB, or temporarily study medication was removed. The subject was withdrawn from the study if the serum creatinine or eGFR increased by $\geq 30\%$ compared to baseline, or the serum creatinine increased ≥ 200 micromoles/L, or in case of serious hyperkalemia (≥ 6.5 mmol/L).

Background therapy:

Optimal medical therapy for concomitant medical conditions such as hypertension, diabetes mellitus, thyroid diseases, and atrial fibrillation was encouraged. Optimal therapy for atrial fibrillation included beta-blockers, verapamil, diltiazem, digoxin, and anticoagulant therapy, where appropriate.

Evidence for comparator: -

Actual start date of recruitment	01 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 125
Worldwide total number of subjects	125
EEA total number of subjects	125

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)	50
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single center study conducted at Odense University Hospital, Svendborg Hospital, Denmark from November 2013 through February 2017. All eligible inpatients and outpatients with paroxysmal or persistent atrial fibrillation were recruited from the Department of Cardiology, Odense University Hospital, Svendborg.

Pre-assignment

Screening details:

Demographic, clinical and laboratory data were collected at baseline (pre-treatment). Clinical data included measurements of blood pressure, height, weight, and 12-lead ECG. Office blood pressure was recorded three times after 10 minutes of supine rest. Lab parameters: potassium, sodium, creatinine, BUN, eGR, hemoglobin, hematocrite.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study subjects were randomly assigned (1:1 ratio) to receive either spironolactone 25 mg (Spirix® 25 mg) or placebo once daily, using a permuted block design with variable block size (between 1 and 4) stratified by type of AF (paroxysmal and persistent AF). Blinding was done by Odense University Hospital, Pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Spironolactone

Arm description:

Intervention arm

Arm type	Active comparator
Investigational medicinal product name	Spironolactone oo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A tablet containing 25 mg, administered once daily

Arm title	Placebo
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Arm description:

Control arm, placebo

Arm type	Placebo
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Spironolactone	Placebo
Started	63	62
Completed	63	62

Baseline characteristics

Reporting groups

Reporting group title	Spironolactone
Reporting group description:	
Intervention arm	
Reporting group title	Placebo
Reporting group description:	
Control arm, placebo	

Reporting group values	Spironolactone	Placebo	Total
Number of subjects	63	62	125
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			
Mean age in years			
Units: years			
arithmetic mean	63.8	64.1	
standard deviation	± 7.5	± 8.8	-
Gender categorical			
Units: Subjects			
Female	21	24	45
Male	42	38	80

End points

End points reporting groups

Reporting group title	Spironolactone
Reporting group description:	
Intervention arm	
Reporting group title	Placebo
Reporting group description:	
Control arm, placebo	

Primary: Laft atrial post-contrast T1 time

End point title	Laft atrial post-contrast T1 time
End point description:	
Post-contrast T1 times were measured on left atrial wall and the myocardium of left ventricle	
End point type	Primary
End point timeframe:	
12 months	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[1]	52 ^[2]		
Units: milliseconds				
arithmetic mean (confidence interval 95%)	6.1 (0.2 to 12.2)	0.7 (-4.4 to 5.9)		

Notes:

[1] - Data from CMR study are presented

[2] - Data from CMR study are presented

Statistical analyses

Statistical analysis title	Mixed linear model with maximized likelihood
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Primary: Peak strain values from left atrium

End point title	Peak strain values from left atrium ^[3]
End point description:	
Co-primary endpoints	

End point type	Primary
End point timeframe:	
12 months	
Notes:	
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Same method as aforementioned, mixed linear method	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[4]	52 ^[5]		
Units: percent				
arithmetic mean (confidence interval 95%)	-1.9 (-15.3 to 11.2)	-13.9 (-22.9 to -3.7)		

Notes:

[4] - Data are presented from CMR study

[5] - Data are presented from CMR study

Statistical analyses

No statistical analyses for this end point

Primary: Peak strain value from left ventricle

End point title	Peak strain value from left ventricle ^[6]
End point description:	
Co-primary endpoint	
End point type	Primary
End point timeframe:	
12 months	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Same method as before, linear mixed model

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[7]	52 ^[8]		
Units: percent				
arithmetic mean (confidence interval 95%)	0.05 (-0.9 to 1.03)	-0.3 (-1.2 to 0.6)		

Notes:

[7] - cmr data , gls

[8] - cmr data, gls

Statistical analyses

No statistical analyses for this end point

Primary: Left ventricular post-contrast T1 time

End point title	Left ventricular post-contrast T1 time ^[9]
End point description:	
Co-primary end-point	
End point type	Primary

End point timeframe:

12 months

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Same method as aforementioned, mixed linear method

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[10]	52 ^[11]		
Units: milliseconds				
arithmetic mean (confidence interval 95%)	10.3 (-3.2 to 23.9)	-7.5 (-19.2 to 4.1)		

Notes:

[10] - cmr data, post-contrast T1 time

[11] - cmr data, post- contrast T1 time on LV

Statistical analyses

No statistical analyses for this end point

Secondary: LAVI

End point title	LAVI
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End point description:

End point type	Secondary
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End point timeframe:

12 months

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[12]	52 ^[13]		
Units: millilitre(s)/square m				
arithmetic mean (confidence interval 95%)	-3.8 (-9.2 to 1.8)	4.7 (-1.9 to 11.9)		

Notes:

[12] - cmr data, LAVI

[13] - cmr data, lavi

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrences of atrial fibrillation

End point title	Recurrences of atrial fibrillation
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End point description:

1. Free from recurrence of atrial fibrillation
2. Total number recurrences of atrial fibrillation
3. Total number recurrences of atrial fibrillation after 90 days blanking period
4. Total number DC cardioversions

End point type	Secondary
End point timeframe:	
12 months	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: count	33	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Gynecomastia

End point title	Gynecomastia
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: count	8	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

All subjects in the trial were followed for 12 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	3
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Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Same method as aforementioned, mixed linear method

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2015	<p>1.The primary targeted sample size is decreased from 150 to 130 eligible participants.</p> <p>2. Primary end-points are altered based on statistical calculations and assumptions following newest literature. The primary end-points regarding burden of atrial fibrillation (AF burden) and biomarkers measured in blood are replaced as secondary endpoints. With a sample size of 130 participants the trial will have reasonable statistical power (>80 %, $p<0.05$) to detect an effect on primary end-points regarding measurements on cardiovascular magnetic resonance (CMR) and transthoracic echocardiography.</p> <p>3.Endpoints regarding cardiovascular magnetic resonance (CMR) and transthoracic echocardiography (TTE) are left unchanged.</p> <p>4.Eligibility of study participants:</p> <ul style="list-style-type: none">• Detection of one AF-episode of either paroxysmal or persistent AF on 12-lead ECG or Holter monitoring with AF-episode lasting ≥ 30 seconds within the last 12 months prior to the screening visit.• Eligible subjects are recruited regardless of symptoms of AF estimated by EHRA classification I-IV.• Patients with CHA2DS2-VASc score ≥ 1 will be encouraged to start anticoagulant treatment, but will not be excluded if there are reasonable reasons not to, i.e. risk of bleeding. Patients can choose between standard anticoagulation therapies, i.e. warfarin or non vitamin-K oral anticoagulants (NOAC) such as dabigatran, apixaban and rivaroxaban. <p>5.Secondary end-point regarding patient diaries is removed and will not be used in statistical analysis or interpretation of data in this trial. Previously collected patient diaries will be properly destructed.</p> <p>6. By 01.12.2015 the screening area will be extended to the whole Funen. This will comprise inpatients from the Departments of Cardiology at Odense University Hospital and Svendborg Hospital and outpatients from the Outpatients Clinic of Cardiology at Odense University Hospital, Nyborg Hospital and Svendborg Hospital.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 November 2015	Substantial amendment	-

Notes:

Limitations and caveats

None reported