Clinical trial results:
Effect of ACE-Inhibition on Microvascular Function in Women with Assessed Microvascular Dysfunction and No Obstructive Coronary Artery Disease.

Summary

EudraCT number	2014-004490-17
Trial protocol	DK
Global end of trial date	20 February 2017

Results information

Result version number	v1 (current)
This version publication date	13 May 2021
First version publication date	13 May 2021

Trial information

Trial identification

Sponsor protocol code	72

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02525081
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bispebjerg University Hospital
Sponsor organisation address	Bispebjerg Bakke 23, Copenhagen, Denmark, 2400
Public contact	https://clinicaltrials.gov, Bispebjerg University Hospital, Eva.Irene.Bossano.Prescott@regionh.dk
Scientific contact	https://clinicaltrials.gov, Bispebjerg University Hospital, Eva.Irene.Bossano.Prescott@regionh.dk
Sponsor organisation name	Bispebjerg University Hospital
Sponsor organisation address	Bispebjerg Bakke 23, Copenhagen NV, Denmark, 2400
Public contact	Professor Eva Prescott, Department of Cardiology, Bispebjerg University Hospital, 0045 22572614, Eva.Irene.Bossano.Prescott@regionh.dk
Scientific contact	Professor Eva Prescott, Department of Cardiology, Bispebjerg University Hospital, 0045 22572614, Eva.Irene.Bossano.Prescott@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	20 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2017
Global end of trial reached?	Yes
Global end of trial date	20 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to explore effects of long term treatment with ACE-inhibitor on the microvasculature assessed by coronary flow reserve by transthoracic echocardiography in normotensive patients with microvascular dysfunction (CFR<2.2) and Angina Pectoris but no coronary artery disease

Protection of trial subjects:

Patients who where bother by potential side effects and did not want to continue in the study were able to withdraw from the study.
If patients could not complete main examination (stress echocardiography with adenosine infusion) due to discomfort we stopped the infusion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2015
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: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	42

From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from July 2015 to December 2015

Pre-assignment

Screening details:

A total of 201 patients from the iPOWER cohort met inclusion and exclusion criteria. Further, 138 patients were excluded as per protocol. We included 63 patients. A total of 55 patients completed the study (ACE inhibitor group, 28, and placebo, 27).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramipril

Arm description:

Interventional

Arm type	Experimental
Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Between 2.5 to 10 mg per day (up titrated according to systolic blood pressure)

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Between 2.5 to 10 mg per day (up titrated according to blood pressure)

Number of subjects in period 1	Ramipril	Placebo
Started	32	31
Completed	28	27
Not completed	4	4
Consent withdrawn by subject	2	4
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Ramipril
Reporting group description: Interventional	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Ramipril	Placebo	Total
Number of subjects	32	31	63
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	58.6	57.3	
standard deviation	± 11.6	± 12.5	-
Gender categorical Units: Subjects			
Female	32	31	63
Male	0	0	0
Systolic blood pressure Units: mmHg			
arithmetic mean	124.1	127.4	
standard deviation	± 11	± 11	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	70.2	67.2	
standard deviation	± 7.7	± 7.8	-
Heart rate Units: beats/min			
arithmetic mean	65.9	66.2	
standard deviation	± 11.3	± 10.1	-

Subject analysis sets	
Subject analysis set title	Baseline characteristic
Subject analysis set type	Intention-to-treat

Subject analysis set description:
unpaired t-test has been performed to evaluate division of baseline characteristic between groups

Reporting group values	Baseline characteristic		
Number of subjects	63		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	57.9		
standard deviation	± 11.9		
Gender categorical Units: Subjects			
Female	63		
Male	0		
Systolic blood pressure Units: mmHg			
arithmetic mean	125.7		
standard deviation	± 11		
Diastolic blood pressure Units: mmHg			
arithmetic mean	68.7		
standard deviation	± 7.9		
Heart rate Units: beats/min			
arithmetic mean	68.7		
standard deviation	± 7.9		

End points

End points reporting groups

Reporting group title	Ramipril
Reporting group description:	
Interventional	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Baseline characteristic
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
unpaired t-test has been performed to evaluate division of baseline characteristic between groups	

Primary: Change in coronary flow velocity reserve

End point title	Change in coronary flow velocity reserve
End point description:	
Coronary flow velocity reserve is measured by dipyridamole induced stress transthoracic Doppler echocardiography, which assess coronary microvascular function	
End point type	Primary
End point timeframe:	
4-6 months	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: ratio				
arithmetic mean (confidence interval 95%)	0.34 (0.11 to 0.56)	0.26 (0.03 to 0.48)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model
Statistical analysis description:	
An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis	
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[1] - No difference detected between interventional groups

Secondary: Change in GLS at rest

End point title	Change in GLS at rest
End point description: GLS: Global longitudinal strain	
End point type	Secondary
End point timeframe: 4-6 months	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: percentage				
arithmetic mean (confidence interval 95%)	-0.24 (-1.07 to 0.59)	-0.03 (-0.85 to 0.79)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model
Statistical analysis description: An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis	
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed models analysis

Secondary: Change in GLS at hyperemia

End point title	Change in GLS at hyperemia
End point description:	
End point type	Secondary
End point timeframe: 4-6 months	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: percentage				
arithmetic mean (confidence interval 95%)	-0.17 (-1.06 to 0.72)	-0.03 (-0.91 to 0.86)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[2] - No difference detected between interventional groups

Secondary: Change in the GLS reserve

End point title	Change in the GLS reserve

End point description:

GLS: GLobal longtudinal strain

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: percentage				
arithmetic mean (confidence interval 95%)	-0.03 (-1.04 to 0.99)	-0.07 (-1.07 to 0.93)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[3] - No difference detected between interventional groups

Secondary: Change in left ventricular ejection fraction

End point title	Change in left ventricular ejection fraction

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: percentage				
arithmetic mean (confidence interval 95%)	0.56 (-1.47 to 2.59)	0.93 (-1.14 to 3)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[4] - No difference detected between interventional groups

Secondary: Change in left ventricular mass index

End point title	Change in left ventricular mass index

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: g/m2				
arithmetic mean (confidence interval 95%)	0.76 (-5.01 to 6.53)	0.76 (-5.11 to 6.64)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[5] - No difference detected between interventional groups

Secondary: Change in left atrial volume index

End point title	Change in left atrial volume index

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	31		
Units: mL/m2				
arithmetic mean (confidence interval 95%)	1.49 (-0.8 to 3.79)	1.44 (-0.89 to 3.78)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[6] - No difference detected between interventional groups

Secondary: Change in deceleration time

End point title	Change in deceleration time

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: ms				
arithmetic mean (confidence interval 95%)	-18.19 (-31.83 to -4.55)	-9.53 (-22.97 to 3.9)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[7] - No difference detected between interventional groups

Secondary: Change in E/A ratio

End point title	Change in E/A ratio

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: ratio				
arithmetic mean (confidence interval 95%)	-0.04 (-0.1 to 0.02)	-0.01 (-0.07 to 0.05)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[8] -
No difference detected between interventional groups

Secondary: Change in e'

End point title	Change in e'

End point description:

End point type	Secondary
End point timeframe:	
4-6 months	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: cm/s				
arithmetic mean (confidence interval 95%)	-0.09 (-0.63 to 0.46)	0.14 (-0.41 to 0.7)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model
Statistical analysis description:	
An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis	
Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Notes:	
[9] - No difference detected between interventional groups	

Secondary: Change in E/e'

End point title	Change in E/e'
End point description:	

End point type	Secondary
End point timeframe:	
4-6 months	

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: ratio				
arithmetic mean (confidence interval 95%)	-0.22 (-0.75 to 0.32)	-0.15 (-0.68 to 0.38)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Secondary: Change in flow mediated dilation

End point title	Change in flow mediated dilation

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percentage				
arithmetic mean (confidence interval 95%)	0.4 (-1.81 to 2.61)	0.77 (-1.5 to 3.03)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Placebo v Ramipril

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[10] - No difference detected between interventional groups

Secondary: Change in nitroglycerine mediated dilation

End point title	Change in nitroglycerine mediated dilation

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: percentage				
arithmetic mean (confidence interval 95%)	-2.21 (-5.94 to 1.52)	-2.21 (-6.01 to 1.59)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Secondary: Change in resting arterial diameter

End point title	Change in resting arterial diameter

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mm				
arithmetic mean (confidence interval 95%)	-0.2 (-0.35 to -0.06)	-0.07 (-0.23 to 0.08)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[11] - No difference detected between interventional groups

Secondary: Change in arterial diameter at peak hyperaemia

End point title	Change in arterial diameter at peak hyperaemia

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: mm				
arithmetic mean (confidence interval 95%)	-0.2 (-0.36 to -0.03)	-0.06 (-0.24 to 0.11)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[12] - No difference detected between interventional groups

Secondary: Change in shear rate area under the curve to peak

End point title	Change in shear rate area under the curve to peak

End point description:

End point type	Secondary

End point timeframe:

4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: s-1/s				
arithmetic mean (confidence interval 95%)	5049 (-58 to 10157)	235 (-5100 to 5569)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:

An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Ramipril v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:
[13] - No difference detected between interventional groups

Secondary: Change in physical limitation

End point title	Change in physical limitation

End point description:

End point type	Secondary

End point timeframe:
4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: score				
arithmetic mean (confidence interval 95%)	-0.36 (-5.99 to 5.28)	3.74 (-1.85 to 9.33)		

Statistical analyses

Statistical analysis title	Unstructured linear mixed model

Statistical analysis description:
An unstructured linear mixed model (PROC MIXED in SAS) was used to perform baseline-adjusted analysis

Comparison groups	Placebo v Ramipril
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:
[14] - No difference detected between interventional groups

Secondary: Change in angina stability

End point title	Change in angina stability

End point description:

End point type	Secondary

End point timeframe:
4-6 months

End point values	Ramipril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: score				
arithmetic mean (confidence interval 95%)	15.39 (5.20 to 25.58)	27.33 (17.37 to 37.29)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 29th of July 2015 to the 28th of April 2016.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	No dictionary
Dictionary version	0

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

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: A standard dictionary was not used for collection of adverse events and therefore the reporting does not fit into this reporting system.
Overall, the proportion of participants experiencing an event categorized as either an adverse event, adverse reaction (common side effects) or serious adverse event was not significantly different between treatment groups: 20% vs. 18% (p = 0.74), 22% vs. 28% (p = 0.33) and 5% vs. 5% (p = 0.80), respectively.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported