Clinical trial results:
Lymphatic dysfunction as a cause of calcium channel blocker oedema in post-menopausal women

Summary

EudraCT number	2015-001761-11
Trial protocol	DK
Global end of trial date	11 October 2017

Results information

Result version number	v1 (current)
This version publication date	26 October 2019
First version publication date	26 October 2019

Trial information

Trial identification

Sponsor protocol code	300488

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul Jensens Boulevard, Aarhus N, Denmark,
Public contact	T-forskning, Aarhus University Hosp, The Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital., 0045 50720716, shey@clin.au.dk
Scientific contact	T-forskning, Aarhus University Hosp, The Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital., 0045 50720716, shey@clin.au.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	11 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2017
Global end of trial reached?	Yes
Global end of trial date	11 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim with this study is to investigate the mechanism behind the oedema development often associated with treatment of cardiovascular disease with calcium channel blockers. The current belief is that a preferential arterial over venous dilation leads to increased fluid filtration. We will test this concept by measuring capillary filtration, which surprisingly has never been done before. The current belief will furthermore be challenged by also measuring the lymphatic removal of interstitial fluid during treatment with calcium channel blockers. Lymph vessels could potentially be an off-target effect of the drugs and augment oedema formation. This might explain why some patients treated with these drugs develop oedemas.

Protection of trial subjects:

Participants where contacted a week after completion of trial to ensure there well-being. GCP-unit monitered the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	13
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study subjects were included from June 2016 to April 2017 in four blocks of four subjects and assigned a unique number (1–16). The trial was completed in October 2017. Aarhus University Hospital Pharmacy performed randomization and blinding.
The were recruited by flyers and post varies of social platforms.

Pre-assignment

Screening details:

The inclusion criteria were postmenopausal women. Exclusion criteria were arterial hypotension, orthostatic hypotension, angina pectoris, previous acute myocardial infarction, previous gastrointestinal bleeding, peripheral edema at inclusion in the trial, currently under treatment with any type of CCB, angiotensin converting enzyme inhibitor.

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, Data analyst

Blinding implementation details:

Aarhus University Hospital Pharmacy performed randomization and blinding.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo treatment for 12 weeks before crossing over to treatment

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

Dosage and administration details:

During the first 8 weeks, the dose was 5mg (1 capsule) amlodipine or placebo per day. During the last 4 weeks, the dose was increased to 10 mg (2 capsules) (Fig. 1). Amlodipine Actavis and placebo pills were packed in identical empty hard gelatine capsules (CAPSUGEL) to blind the subjects and investigator.

Arm title	Amlodipine treatment

Arm description:

12 weeks og amlodipine treatment before crossing over to placebo

Arm type	Experimental

Investigational medicinal product name	Amlodipine actavis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

During the first 8
weeks, the dose was 5mg (1 capsule) amlodipine or placebo per day. During the last 4 weeks, the dose was increased to 10 mg (2 capsules) (Fig. 1). Amlodipine Actavis and placebo pills were packed in identical empty hard gelatine capsules (CAPSUGEL) to blind the subjects and investigator.

Number of subjects in period 1	Placebo	Amlodipine treatment
Started	16	16
Completed	16	16

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
16	

Reporting group values	Overall Trial	Total	
Number of subjects	16	16	
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)	13	13	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	16	16	
Male	0	0	

Subject analysis sets	
Subject analysis set title	NIRF measurements
Subject analysis set type	Full analysis

Subject analysis set description:

NIRF imaging was analyzed as already explained. Data storage was done in Microsoft Excel, whereas GraphPad Prism and Stata/SE 15.1 were used for all statistical analyses and graphical presentation of the data. All data were tested for normality and presented as mean – standard deviation (SD) and for significance with paired and unpaired Student's t-test (data with

Reporting group values	NIRF measurements		
Number of subjects	16		
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)	13		
From 65-84 years	3		
85 years and over	0		
Gender categorical Units: Subjects			
Female	16		
Male	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo treatment for 12 weeks before crossing over to treatment	
Reporting group title	Amlodipine treatment
Reporting group description:	
12 weeks og amlodipine treatment before crossing over to placebo	
Subject analysis set title	NIRF measurements
Subject analysis set type	Full analysis
Subject analysis set description:	
NIRF imaging was analyzed as already explained. Data storage was done in Microsoft Excel, whereas GraphPad Prism and Stata/SE 15.1 were used for all statistical analyses and graphical presentation of the data. All data were tested for normality and presented as mean – standard deviation (SD) and for significance with paired and unpaired Student's t-test (data with	

Primary: Pumping Pressure

End point title	Pumping Pressure
End point description:	
End point type	Primary
End point timeframe:	
Full trial	

End point values	Placebo	Amlodipine treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mmHg				
arithmetic mean (standard deviation)	54.7 (± 9.4)	53.9 (± 13.9)		

Statistical analyses

Statistical analysis title	Students T-test
Comparison groups	Placebo v Amlodipine treatment
Number of subjects included in analysis	32
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

7 participants developed edema during treatment. But was not excluded, but the measurements were completed before ending treatment. This was a part of the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

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: 7 participant developed edema during treatment, which was expected as a part of the trial. These patients remained included in the study and completed examination

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