



Clinical trial results:

Pilot Trial: The effects of intravenous heme arginate on HO-1 expression and oxidative stress in the human heart

Summary

EudraCT number	2013-000887-27
Trial protocol	AT
Global end of trial date	13 June 2017

Results information

Result version number	v1 (current)
This version publication date	04 April 2020
First version publication date	04 April 2020

Trial information

Trial identification

Sponsor protocol code	2.0
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02314780
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Prof. Dr. Martin Andreas, Medical University of Vienna, +43 14040069660, martin.andreas@meduniwien.ac.at
Scientific contact	Prof. Dr. Martin Andreas, Medical University of Vienna, +43 14040069660, martin.andreas@meduniwien.ac.at

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	29 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2017
Global end of trial reached?	Yes
Global end of trial date	13 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the effects of heme arginate administration in two different doses on myocardial HO-1 induction.

Protection of trial subjects:

The trial was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki and in agreement with the Austrian laws and regulation. The Ethics Committee of the Medical University of Vienna approved the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 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	Austria: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	8
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who were scheduled for elective surgical aortic valve replacement were assessed for eligibility after hospitalization. A sample size of 24 subjects was calculated. The ethical board approved up to 36 subjects with an interim analysis of the first 24 subjects. The trial was stopped after the interim analysis because of significant results.

Pre-assignment

Screening details:

A total of 31 patients signed the informed consent to participate in the trial. Of them, 27 subjects were randomized.

Pre-assignment period milestones

Number of subjects started	31
Number of subjects completed	27

Pre-assignment subject non-completion reasons

Reason: Number of subjects	organizational reasons: 3
Reason: Number of subjects	other reason: 1

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, Carer

Blinding implementation details:

A non-transparent infusion kit was used for the administration of the investigational medicinal products in order to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Normosang (high dose)

Arm description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 3 mg/kg diluted to 110 ml with 0,9% sodium chloride.

Arm type	Experimental
Investigational medicinal product name	Normosang
Investigational medicinal product code	1-27260
Other name	heme arginate
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

24 hours prior to the planned surgical aortic valve replacement, heme arginate at a dose of 3 mg/kg diluted to 110ml with 0,9% sodium chloride was administered at a single intravenous infusion using an infusion pump. To avoid any local irritation from drug infusion, 250ml 0,9% sodium chloride solution was administered thereafter.

Arm title	Normosang (low dose)
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Arm description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 1 mg/kg diluted to 110 ml with 0,9% sodium chloride.

Arm type	Experimental
Investigational medicinal product name	Normosang
Investigational medicinal product code	1-27260
Other name	heme arginate
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

24 hours prior to the planned surgical aortic valve replacement, heme arginate at a dose of 1 mg/kg diluted to 110ml with 0,9% sodium chloride was administered at a single intravenous infusion using an infusion pump. To avoid any local irritation from drug infusion, 250ml 0,9% sodium chloride solution was administered thereafter.

Arm title	Placebo
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Arm description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of an equivalent volume of 0,9% sodium chloride solution.

Arm type	Placebo
Investigational medicinal product name	0,9% Sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

24 hours prior to the planned surgical aortic valve replacement, an equivalent volume of sodium chloride solution was administered at a single intravenous infusion using an infusion pump.

Number of subjects in period 1^[1]	Normosang (high dose)	Normosang (low dose)	Placebo
Started	9	10	8
Completed	9	7	8
Not completed	0	3	0
no operation 24 hours after drug administration	-	3	-

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: 31 subjects were enrolled in the trial. Of them, 4 patients (3 patients for organizational reasons and 1 patient for other reasons) were excluded from the trial prior to randomization and drug administration.

Baseline characteristics

Reporting groups

Reporting group title	Normosang (high dose)
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 3 mg/kg diluted to 110 ml with 0,9% sodium chloride.	
Reporting group title	Normosang (low dose)
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 1 mg/kg diluted to 110 ml with 0,9% sodium chloride.	
Reporting group title	Placebo
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of an equivalent volume of 0,9% sodium chloride solution.	

Reporting group values	Normosang (high dose)	Normosang (low dose)	Placebo
Number of subjects	9	10	8
Age categorical Units: Subjects			
Adults (18-64 years)	2	1	3
From 65-84 years	7	9	5
Gender categorical Units: Subjects			
Male	3	5	3
Female	6	5	5

Reporting group values	Total		
Number of subjects	27		
Age categorical Units: Subjects			
Adults (18-64 years)	6		
From 65-84 years	21		
Gender categorical Units: Subjects			
Male	11		
Female	16		

End points

End points reporting groups

Reporting group title	Normosang (high dose)
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 3 mg/kg diluted to 110 ml with 0,9% sodium chloride.	
Reporting group title	Normosang (low dose)
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 1 mg/kg diluted to 110 ml with 0,9% sodium chloride.	
Reporting group title	Placebo
Reporting group description: 24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of an equivalent volume of 0,9% sodium chloride solution.	

Primary: Myocardial HO-1 mRNA levels (atrial tissue)

End point title	Myocardial HO-1 mRNA levels (atrial tissue)
End point description: The right atrial appendage was clamped and cut for cannulation before cardiopulmonary bypass. The tissue samples were snap-frozen in the operating theater after sampling.	
End point type	Primary
End point timeframe: intraoperative	

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: arbitrary unit				
arithmetic mean (standard deviation)	392.7 (± 195.7)	229.8 (± 173.1)	10.8 (± 8.8)	

Statistical analyses

Statistical analysis title	HO-1 mRNA concentrations (appendage)
Comparison groups	Normosang (low dose) v Placebo v Normosang (high dose)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	ANOVA

Primary: Myocardial HO-1 mRNA levels (ventricular tissue before aortic cross-clamping)

End point title	Myocardial HO-1 mRNA levels (ventricular tissue before aortic cross-clamping)
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End point description:

A small biopsy was taken from the right ventricular free wall directly before aortic cross-clamping. The tissue samples were snap-frozen in the operating theater after sampling.

End point type	Primary
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End point timeframe:

intraoperative

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: arbitrary units				
arithmetic mean (standard deviation)	203.6 (± 148.7)	88.6 (± 49.1)	7.9 (± 5.0)	

Statistical analyses

Statistical analysis title	HO-1 mRNA level (ventricle pre)
Comparison groups	Normosang (high dose) v Normosang (low dose) v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANOVA

Primary: Myocardial HO-1 mRNA levels (ventricular tissue after aortic cross-clamping)

End point title	Myocardial HO-1 mRNA levels (ventricular tissue after aortic cross-clamping)
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End point description:

A small biopsy was taken from the right ventricular free wall after aortic clamp release before weaning from cardiopulmonary bypass. The tissue samples were snap-frozen in the operating theater after sampling.

End point type	Primary
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End point timeframe:

intraoperative

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: arbitrary units				
arithmetic mean (standard deviation)	219.4 (\pm 162.8)	108.1 (\pm 73.2)	8.3 (\pm 5.4)	

Statistical analyses

Statistical analysis title	HO-1 mRNA (ventricle post)
Comparison groups	Normosang (high dose) v Normosang (low dose) v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	ANOVA

Primary: Myocardial HO-1 protein concentrations (atrial tissue)

End point title	Myocardial HO-1 protein concentrations (atrial tissue)
End point description:	The right atrial appendage was clamped and cut for cannulation before cardiopulmonary bypass. The tissue samples were snap-frozen in the operating theater after sampling.
End point type	Primary
End point timeframe:	intraoperative

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: pixels under the curve				
arithmetic mean (standard deviation)	29022 (\pm 8583)	28585 (\pm 10692)	8401 (\pm 3889)	

Statistical analyses

Statistical analysis title	HO-1 protein concentration (appendage)
Comparison groups	Normosang (high dose) v Normosang (low dose) v Placebo

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANOVA

Primary: Myocardial HO-1 protein concentrations (ventricular tissue before aortic cross-clamping)

End point title	Myocardial HO-1 protein concentrations (ventricular tissue before aortic cross-clamping)
End point description: A small biopsy was taken from the right ventricular free wall directly before aortic cross-clamping. The tissue samples were snap-frozen in the operating theater after sampling.	
End point type	Primary
End point timeframe: intraoperative	

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: pixels under the curve				
arithmetic mean (standard deviation)	13752 (\pm 8069)	10534 (\pm 4686)	6842 (\pm 4343)	

Statistical analyses

Statistical analysis title	HO-1 protein concentrations (ventricle pre)
Comparison groups	Normosang (high dose) v Normosang (low dose) v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.138
Method	ANOVA

Primary: Myocardial HO-1 protein concentrations (ventricular tissue after aortic cross-clamping)

End point title	Myocardial HO-1 protein concentrations (ventricular tissue after aortic cross-clamping)
End point description: A small biopsy was taken from the right ventricular free wall after aortic clamp release before weaning from cardiopulmonary bypass. The tissue samples were snap-frozen in the operating theater after sampling.	
End point type	Primary

End point timeframe:
intraoperative

End point values	Normosang (high dose)	Normosang (low dose)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	7	8	
Units: pixels under the curve				
arithmetic mean (standard deviation)	17062 (± 18164)	11277 (± 3918)	12037 (± 10962)	

Statistical analyses

Statistical analysis title	HO-1 protein concentrations (ventricle post)
Comparison groups	Normosang (high dose) v Normosang (low dose) v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.696
Method	ANOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events occurring within 96 hours after the administration of Normosang/sodium chloride solution were reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Normosang (high dose)
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Reporting group description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 3 mg/kg diluted to 110 ml with 0,9% sodium chloride.

Reporting group title	Normosang (low dose)
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Reporting group description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of heme arginate at a dose of 1 mg/kg diluted to 110 ml with 0,9% sodium chloride.

Reporting group title	Placebo
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Reporting group description:

24 hours prior to the planned surgical aortic valve replacement, subjects received a single intravenous infusion of 100 ml 0,9% sodium chloride solution.

Serious adverse events	Normosang (high dose)	Normosang (low dose)	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	0 / 10 (0.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery compression			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			

subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Normosang (high dose)	Normosang (low dose)	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	5 / 10 (50.00%)	4 / 8 (50.00%)
Investigations			
Blood culture positive			
subjects affected / exposed	0 / 9 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 9 (11.11%)	3 / 10 (30.00%)	3 / 8 (37.50%)
occurrences (all)	1	3	3
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

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

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

Biopsy samples were small and protein concentration could not be measured in every sample. The sample size is small for a 3-arm randomized controlled trial.
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30354231>