Clinical trial results:
A Prospective Randomized Double Blind Multicenter Phase III Study Comparing two Methods of Cardioplegia in Aortic Valve Surgery Custodiol-N versus Custodiol

Summary

EudraCT number	2012-003776-40
Trial protocol	DE
Global end of trial date	06 December 2019

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022
Summary attachment (see zip file)	CSRCustodiol-N_AVS (20200121SYNOPSIS.pdf)

Trial information

Trial identification

Sponsor protocol code	CL-N-CSM-AV-III/05/12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02098772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Franz Köhler Chemie GmbH
Sponsor organisation address	Werner-von – Siemens-Str. 14-28, Bensheim, Germany, 64625
Public contact	Dr. Roman Petrov, Dr. Franz Köhler Chemie GmbH, +49 625110830, r.petrov@koehler-chemie.de
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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	04 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2019
Global end of trial reached?	Yes
Global end of trial date	06 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this investigation is to compare the cardioprotective effects and safety of two cardioplegic solutions, Custodiol and Custodiol-N in patients undergoing aortic valve surgery +/- bypass surgery.

Protection of trial subjects:

Patients were monitored for adverse events. Safety laboratory examinations were performed according to protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2014
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	Germany: 530
Worldwide total number of subjects	530
EEA total number of subjects	530

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)	169
From 65 to 84 years	359
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

To obtain a sample for analysis per protocol of 394 patients a total of 530 patients with aortic valve disease was scheduled to be enrolled. One patient included did not receive treatment at all, one other patient received not the treatment randomised to.

Pre-assignment

Screening details:

The study population was selected from patients of either sex who were to undergo surgery for aortic valve replacement (with or without coronary bypass surgery).

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Custodiol

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Custodiol
Investigational medicinal product code	B05CX10
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

During aortic valve surgery, after cross clamping of the aorta on cardiopulmonary bypass, the Custodiol® or Custodiol-N solution, was infused into the root of the aorta at a temperature of 4 - 6°C.

Arm title	Custodiol-N

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Custodiol-N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

During aortic valve surgery, after cross clamping of the aorta on cardiopulmonary bypass, the Custodiol® or Custodiol-N solution, was infused into the root of the aorta at a temperature of 4 - 6°C.

Number of subjects in period 1	Custodiol	Custodiol-N
Started	265	265
Completed	265	263
Not completed	0	2
Adverse event, serious fatal	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
This reporting group equals the full analysis data set	

Reporting group values	Treatment	Total	
Number of subjects	530	530	
Age categorical Units: Subjects			
Adults (18-64 years)	168	168	
From 65-84 years	360	360	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	181	181	
Male	349	349	

End points

End points reporting groups

Reporting group title	Custodiol
Reporting group description: -	
Reporting group title	Custodiol-N
Reporting group description: -	
Subject analysis set title	Custodiol per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol analysis set: 205 patients for the Custodiol® group and 206 for the Custodiol-N group.	
Subject analysis set title	Custodiol-N per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol analysis set: 205 patients for the Custodiol® group and 206 for the Custodiol-N group.	

Primary: Peak CK-MB value

End point title	Peak CK-MB value
End point description:	
End point type	Primary
End point timeframe:	
CK-MB peak value from 4 to 24 hours (measurements 4, 8, 12, 16, 20, 24 hours ± 30 min) after release of the aortic cross clamp.	

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: Units				
arithmetic mean (standard deviation)	65.1 (± 110.7)	58.1 (± 38.2)		

Statistical analyses

Statistical analysis title	CK-MB peak value (full analysis set)
Statistical analysis description:	
Primary analysis was performed taking the logarithm of 4h-24h-peak CK-MB values as primary endpoint. The null hypothesis was: “No effect of Custodiol-N over Custodiol® with respect to CKMB peak value”.	

Comparison groups	Custodiol v Custodiol-N
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.4815
Method	likelyhood ratio test (5% level)

Notes:

[1] - Likelihood ratio test +at the 5 per cent level of the treatment group parameter in a linear model. Missing log (CK-MB) values were handled by multiple imputation before deriving peak values.

Primary: Peak CK-MB (per protocol set)

End point title	Peak CK-MB (per protocol set)

End point description:

End point type	Primary

End point timeframe:

Within 24 h from opening of aortic cross clamp

End point values	Custodiol per protocol analysis set	Custodiol-N per protocol analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	206		
Units: U/L				
arithmetic mean (standard deviation)	59.6 (± 42.7)	58.4 (± 38.6)		

Statistical analyses

Statistical analysis title	CK-MB 24h peak value (per protocol data set)
Comparison groups	Custodiol-N per protocol analysis set v Custodiol per protocol analysis set
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9122
Method	likelihood ratio test (5% level)

Secondary: Adrenaline requirement on SICU within 24 hours (cumulative dose)

End point title	Adrenaline requirement on SICU within 24 hours (cumulative dose)

End point description:

Values provided for full analysis set

End point type	Secondary

End point timeframe:

Within 24 h after opening of aortic cross clamp

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	262		
Units: µg/kg body mass				
arithmetic mean (standard deviation)	3.88 (± 35.57)	9.04 (± 78.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dobutamine requirement on SICU within 24 hours (cumulative dose)

End point title	Dobutamine requirement on SICU within 24 hours (cumulative dose)

End point description:

Data for full analysis set provided.

End point type	Secondary

End point timeframe:

Within 24 h following oopening of aortic cross clamp.

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	262		
Units: µg/kg body mass				
arithmetic mean (standard deviation)	3.88 (± 35.57)	9.04 (± 78.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Noradrenaline requirement on SICU within 24 hours (cumulative dose)

End point title	Noradrenaline requirement on SICU within 24 hours (cumulative dose)

End point description:

Values for full analysis set provided. Data in the Custodiol-N group were distorted by one single patient for whom a dose of 317 mg per kg body weight were documented.

End point type	Secondary

End point timeframe:

Within 24 h after opening of aortic cross clamp.

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	260		
Units: µg/kg body mass				
arithmetic mean (standard deviation)	75.81 (± 380.37)	842.46 (± 9811.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5-day peak value of Troponin-T

End point title	5-day peak value of Troponin-T

End point description:

Due to a confusion of the unit there was one single peak value of 841000 pg/mL in the Custodiol-N group, after removing this single value, the mean value for the remaining group was 1271.3 pg/mL.

End point type	Secondary

End point timeframe:

4, 8, 12, 16, 20, 24 hours ± 30 min and on the days 2, 3, 4 and 5 after release of the aortic cross clamp

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: pg/mL				
arithmetic mean (standard deviation)	1227.4 (± 1262.7)	4465.4 (± 51796.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: CK-MB area under the curve

End point title	CK-MB area under the curve

End point description:

End point type	Secondary

End point timeframe:

Between 4 and 24 hours after removal of the aortic cross-clamp

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: area under curve				
arithmetic mean (standard deviation)	1009.5 (± 1199.6)	924.08 (± 593.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Troponin T area under the curve

End point title	Troponin T area under the curve

End point description:

End point type	Secondary

End point timeframe:

Between 4 and 24 hours after removal of the aortic cross-clamp

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: area under the curve				
arithmetic mean (standard deviation)	16020 (± 14870)	64972 (± 796589)		

Statistical analyses

No statistical analyses for this end point

Secondary: Need of defibrillation

End point title	Need of defibrillation

End point description:

End point type	Secondary

End point timeframe:

Up to day 5 after opening of aortic cross clamp.

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	261		
Units: patients needing defibrillations				
0 defibrillations needed	256	252		
1 defibrillation needed	7	7		
2 defibrillations needed	1	1		
3 defibrillations needed	0	1		
4 defibrillations needed	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement for intraaortic ball pump treatment (IABP)

End point title	Requirement for intraaortic ball pump treatment (IABP)

End point description:

End point type	Secondary

End point timeframe:

Within 5 days from surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: patients needing IABP	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure

End point title	Blood pressure

End point description:

End point type	Secondary

End point timeframe:

Within 5 days from surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: mmHg				
arithmetic mean (standard deviation)				
systolic	135.8 (± 18.8)	136.5 (± 19.4)		
diastolic	77.0 (± 11.3)	77.2 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of surgical intensive care unit (SICU) stay

End point title	Length of surgical intensive care unit (SICU) stay

End point description:

End point type	Secondary

End point timeframe:

Following surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	262		
Units: days				
arithmetic mean (standard deviation)	2.6 (± 3.8)	2.4 (± 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of mechanical ventilation (intubation to extubation)

End point title	Duration of mechanical ventilation (intubation to extubation)

End point description:

The duration 24 h and 4 min was displayed as 24.67h; 27 h 55 min as 27.92h.

End point type	Secondary

End point timeframe:

Following surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	261		
Units: hours				
arithmetic mean (standard deviation)	24.67 (± 31.7)	27.92 (± 54.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of cardiac arrhythmias

End point title	Occurrence of cardiac arrhythmias

End point description:

End point type	Secondary

End point timeframe:

Within 5 days after surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: arrhythmias				
no arrhythmia	168	159		
1 episode of arhythmia	72	73		
2 episodes	17	20		
3 episodes	4	4		
4 episodes	2	5		
5 episodes	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Repeated patient transfer to intensive care unit

End point title	Repeated patient transfer to intensive care unit

End point description:

End point type	Secondary

End point timeframe:

Within 6 days after surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: number of patients	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

Within 30 days from surgery

End point values	Custodiol	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	263		
Units: number of fatalities	4	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days from surgery

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Custodiol saftey data set

Reporting group description:

One patient randomised to Custodiol-N received Custodiol instead and was excluded from efficacy analysis. However, for safety analysis, this patient was analysed in the Custodiol-group

Reporting group title	Custodiol-N safety data set

Reporting group description: -

Serious adverse events	Custodiol saftey data set	Custodiol-N safety data set	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 266 (12.78%)	28 / 263 (10.65%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	2	1	
Investigations			
Investigations			
subjects affected / exposed	1 / 266 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	4 / 266 (1.50%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 266 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac disorders			
subjects affected / exposed	9 / 266 (3.38%)	12 / 263 (4.56%)	
occurrences causally related to treatment / all	1 / 10	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders	Additional description: One fatality in the Cutodiol-N group was documented as cerebral infarction.		
subjects affected / exposed	3 / 266 (1.13%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 266 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 266 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 266 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 266 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	3 / 266 (1.13%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Custodiol saftey data set	Custodiol-N safety data set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 266 (90.60%)	248 / 263 (94.30%)	
Investigations			
Investigations			
subjects affected / exposed	79 / 266 (29.70%)	83 / 263 (31.56%)	
occurrences (all)	162	151	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	70 / 266 (26.32%)	67 / 263 (25.48%)	
occurrences (all)	88	85	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	56 / 266 (21.05%)	41 / 263 (15.59%)	
occurrences (all)	63	43	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	114 / 266 (42.86%)	136 / 263 (51.71%)	
occurrences (all)	168	194	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	91 / 266 (34.21%)	91 / 263 (34.60%)	
occurrences (all)	124	128	
General disorders and administration site conditions			
General disorders and administrations site conditions			
subjects affected / exposed	42 / 266 (15.79%)	41 / 263 (15.59%)	
occurrences (all)	51	47	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	45 / 266 (16.92%)	41 / 263 (15.59%)	
occurrences (all)	62	54	
Respiratory, thoracic and mediastinal disorders			

Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	190 / 266 (71.43%)	183 / 263 (69.58%)	
occurrences (all)	325	321	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	70 / 266 (26.32%)	61 / 263 (23.19%)	
occurrences (all)	78	67	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	18 / 266 (6.77%)	17 / 263 (6.46%)	
occurrences (all)	18	17	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	22 / 266 (8.27%)	13 / 263 (4.94%)	
occurrences (all)	22	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2014	New formulation of IMP
13 May 2015	Specification trial medication, new risk assessment
21 April 2016	Changes in protocol (resulted in version 22.03.2016) following updated IB (version 04-2016)
09 January 2017	Increase number of patients
16 November 2017	change of time for perfusion of the heart

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported