SYNOPSIS

Sponsor Dr. Franz Köhler Chemie GmbH Werner-von-Siemens-Str. 14 - 28 D-64625 Bensheim, Germany Phone: +49 – 6251- 1083-0 Fax: +49 - 6251 - 1083-146		*(For National Authority use only)*
Name of finished product Custodiol-N		
Names of active ingredients Sodium chloride, potassium chloride, magnesium chloride hexahydrate, calcium chloride dihydrate, histidine, N-acetylhistidine monohydrate, tryptophan, aspartic acid, glycine, alanine, arginine, α-Ketoglutaric acid, deferoxamine mesilate, LK 614 (3,4-dimethoxy-N-methylbenz-hydroxame acid)		

Title of study:

A Prospective Randomized Double Blind Multicentre Phase III Study Comparing two Methods of Cardioplegia in Aortic Valve Surgery: Custodiol-N versus Custodiol®

Indication

Cardioplegia in patients undergoing aortic valve surgery with or without coronary bypass surgery

Coordinating investigator (Leiter der klinischen Prüfung) and main study centre

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Investigational medicinal product

Custodiol-N

Comparator medicinal product

Custodiol®

Dosing schedule and mode of administration:

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.

Duration of study for each patient

The duration of trial participation took up to 54 days overall.

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Study objectives

The objective of this investigation was to compare the cardio-protective effects and safety of two cardioplegic solutions, Custodiol® and Custodiol-N in patients undergoing aortic valve surgery with or without coronary bypass surgery.

Study population

Inclusion criteria:

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).

(1) Patients ≥ 30 and ≤85 years of age
(2) Male or female with aortic valve disease
(3) Able to understand character and individual consequences of the clinical trial and to provide written informed consent to participate in the study
(4) Women of childbearing potential (i.e., those who have not undergone a hysterectomy or who have not been post-menopausal for at least 12 consecutive months) had to test negative for pregnancy prior to bypass surgery.

Exclusion criteria:

(1) History of recent (< 6 weeks) Q-wave myocardial infarction

(2) Left ventricular ejection fraction < 25% (as assessed by any one of the following: contrast ventriculography, multigated acquisition scanning [MUGA], or 2-D ECHO)

(3) Patients on intra-aortic balloon devices or with history of previous coronary artery bypass surgery

(4) Pregnant or lactating patients

(5) Patients who had participated in any other interventional studies within 30 days previous to enrolment

(6) Patients in cardiogenic shock (defined as a systolic BP < 90 mmHg for over one hour despite inotropic and chronotropic support)

(7) Patients with severe chronic obstructive lung disease (FEV1 < 50%)

(8) Previous cardiac valvular disease (clinically relevant)

(9) GFR <60 ml/min

(10) Planned Ross-procedure, Mitral valve surgery, Aortic valve reconstruction, double valve surgery, other concomitant operations excluding coronary artery bypass surgery or closing a patent foramen ovale

(11) Evidence of severe organic (e.g. cirrhosis of the liver) or psychiatric disease by history or physical examination

(12) History of alcohol abuse, illicit drug use, significant mental illness, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of study enrolment.

Number of subjects planned and analysed

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.

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Methods

prospective, double blind, multicentre, randomized, Phase III comparison study intended to demonstrate superiority in surgical outcome of Custodiol-N compared with Custodiol® as determined by CK-MB peak value between 4 -24 hours after opening of the aortic cross-clamp (primary endpoint), catecholamine requirement (cumulative dose) and cardiac Troponin T, occurrence of comorbid events postoperatively (e.g., myocardial infarction)

Criteria for evaluation

The effect intended by the IMP was a safe cardioplegia. Therefore, all criteria for evaluation were safety criteria:
Primary Endpoint:
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.
Secondary Endpoints:
• Catecholamine requirement on SICU within 24 hours (cumulative dose)
• CK-MB (peak) on the days 2, 3, 4 and 5 after removal of aortic cross clamp
• Cardiac Troponin T 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
• CK-MB area under the curve between 4 and 24 hours after removal of the aortic cross-clamp
• Troponin T area under the curve between 4 and 24 hours after removal of the aortic cross-clamp
• Defibrillation
• Requirement for IABP
• Blood pressure
• Length of SICU stay
• Duration of mechanical ventilation (intubation to extubation)
• Occurrence, severity, type, and duration of cardiac arrhythmias
• Laboratory parameters
• Repeated patient transfer to SICU
• Mortality any time during post-op through Day 30
• Safety (documentation and reporting of AE and SAE)

Statistical methods

• 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”.
• Likelihood ratio test +at the 5 per cent level of the treatment group parameter in a linear model with age included as an additional covariate
• Missing log (CK-MB) values were handled by multiple imputation before deriving peak values.
• Detailed analyses were specified in a Statistical Analysis Plan.

Results: Study population and compliance with treatment

The full analysis set (FAS) comprised 265 patients for the Custodiol® group and 263 for the Custodiol-N group, the per protocol analysis set 205 patients for the Custodiol® group and 206 for the Custodiol-N group.

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Results: Primary endpoint

In average, the CK-MB readings analysed in the full analysis set were for the time points 4/8/12/16/20/24 hours ± 30 min after release of the aortic cross clamp for patients of the Custodiol® group 46.42/49.01/51.81/51.21/52.79/50.11 U/L, and for the Custodiol-N group 44.91/47.22/47.76/47.04/44.41/42.31 U/L.
The mean values for the same time points were for the per protocol analysis set:
46.49/49.46/49.63/48.86/46.08/44.46 U/L for the Custodiol® group, and
44.97/47.75/48.69/47.54/45.80/43.14 U/L for the Custodiol-N group.

When calculated for the entire period of 24 h after clamp opening and the FAS, the peak value was 65.1 U/L (± 110.7 standard deviation= SD) for the Custodiol® group and 58.1 ± 38.2 U/L for the Custodiol-N group. The 95% confidence interval (CI) for an effect estimate Custodiol-N versus Custodiol® was [0.893; 1.055] (p= 0.4815) for the full analysis set (FAS) and [0.905; 1.075] (p= 0.7896) for the per protocol analysis set. The 24 h peak value for the per protocol analysis set was for the Custodiol® group 59.6 ± 42.7 U/L, for the Custodiol-N group it was calculated as 58.4 ± 38.6 U/L.

Results: Secondary endpoints (including Safety)

• Catecholamine requirement on SICU within 24 hours (cumulative dose). For adrenalin the values were 3.88 (±35.57) µg/kg body weight documented for the Custodiol® and 9.04 ± 78.24 µg/kg body weight for Custodiol-N. For dobutamine the figures were 105.68 ±602.48 µg/kg body weight for Custodiol® and 134.82 ±795.52 µg/kg body weight for Custodiol-N. For noradrenaline intake, a parameter estimate from the 0.9 quantile was calculated, showing 95% confidence limits of [-36.157; 57.676]. CK-MB (peak) on the days 2, 3, 4 and 5 after removal of aortic cross clamp: The 95% CI of an effect estimate Custodiol-N versus Custodiol® was [0.882; 1.041] (p=0.3078) for the FAS.

• Cardiac Troponin T 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: The 5-day peak value of Troponin-T was 4464.2 pg/mL in the Custodiol-N group compared to 1230.3 pg/mL in the Custodiol® group. However, 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.

95% CI of an effect estimate Custodiol-N versus Custodiol® was [0.899; 1.205] (p=0.5941) for the FAS and [0.902; 1.208] (p=0.5628) for the per protocol (PP) analysis set.

• CK-MB area under the curve between 4 and 24 hours after removal of the aortic cross-clamp: The mean value was 1009.5 (±1199.6) for the Custodiol® group and 924.35 (±594.21) for the Custodiol-N group for the FAS.

For the PP data set the mean AUC was 961.56 (±665.03) for the Custodiol® group and 934.66 (±607.42) for the Custodiol-N group.

The 95% CI of an effect estimate Custodiol-N versus Custodiol® was [0.882; 1.041] (p=0.5641) for the FAS and [0.895; 1.063] (p=0.5641) for the per protocol analysis set [0.895; 1.063] (p=0.5641).

• Troponin T area under the curve between 4 and 24 hours after removal of the aortic cross-clamp: The 95% CI of an effect estimate Custodiol-N versus Custodiol® was [0.868; 1.158] (p=0.9687) for the FAS and [0.883; 1.171] (p=0.8197) for the per protocol analysis set.

• Defibrillation: For the Custodiol® group there were 256/7/1/1 patients who needed 0/1/2/4 defibrillations up to day 5, for the Custodiol-N group there were 252/7/3/1 patients who needed 0/1/2/3 defibrillations up to day 5.

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(*continued:* Results: Secondary endpoints (including Safety))

• Requirement for intraaortic ball pump treatment (IABP). Within 5 days from surgery IABP was documented for 1 patient of the Custodiol® group and 2 patients of the Custodiol-N group.

• Blood pressure: In mean the values for blood pressure (systolic/diastolic) were 135.8/77.0 mmHg (±18.8 systolic/ ±11.3 diastolic) for Custodiol® and 136.5/77.2 (±19.4 systolic/ ±10.9 diastolic) mmHg for Custodiol-N

• Length of surgical intensive care unit (SICU) stay: In average, the duration at SICU was 2.6 ± 3.8 days in the Custodiol® group and 2.4 ± 4.2 days in the Custodiol-N group.

• Duration of mechanical ventilation (intubation to extubation): In average, the time of ventilation was 24 h 4 minutes (±31:42) for the Custodiol® group and 27 h 55 min (± 54:31) for the Custodiol-N group.

• Occurrence, severity, type, and duration of cardiac arrhythmias after surgery (FAS): No arrhythmia at all was documented for 168 patients of the Custodiol® group and 159 of the Custodiol-N group. One episode of arrhythmia occurred in 72/73 patients of the Custodiol®/Custodiol-N group, 2 episodes in 17/20, 3 episodes in 4/4, 4 episodes in 2/5, 5 episodes in 2/2 patients of the Custodiol®/Custodiol-N group.

• Laboratory parameters: After considering interfering effects such as the incorrect input of units, none of the measured laboratory values (haematocrit, haemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, white blood cells, Thrombocytes, International normalized ratio (INR), Activated partial thromboplastin time (aPTT), Cardiac Troponin-T (cTn-T), Creatinine kinase (total CK), Creatinine kinase-MB (CK-MB) 4, 8, 12, 16, 20, 24 hours and once a day on the days 2, 3, 4 and 5 after removal of cross clamp, C-reactive protein (CRP), albumin, alkaline phosphatase, blood urea nitrogen (BUN), Calcium, Carbon Dioxide, Chloride, Creatinine, Direct bilirubin, Total bilirubin, Gamma glutamyl transferase, glucose, lactate dehydrogenase, phosphate, potassium, serum glutamic-oxaloacetic transaminase (SGOT/AST), serum glutamic-pyruvic transaminase /SGPT/ALT), total protein, sodium, total cholesterol) showed a difference between the groups.

• Repeated patient transfer to SICU: Of the Custodiol® group 2 patients were readmitted to SICU within 5 days after surgery, compared to 10 patients of the Custodiol-N group.

• Mortality any time during post-op through Day 30: Within 30 days of the trial, 4 deaths were documented for the Custodiol® group and 3 for the Custodiol-N group.

• Safety (documentation and reporting of AE and SAE): Altogether 2389 adverse events were observed in the entire trial. They were similarly distributed over both treatment groups (1230 AEs Custodiol® vs. 1159 AEs Custodiol-N). More than 90% of all patients who enrolled the trial experienced at least one adverse event (90.6% and 94.3% in the Custodiol® and Custodiol-N group, respectively).

Conclusions

In conclusion it can be stated that the use of Custodiol-N under the conditions of this trial was not inferior to Custodiol®. The safety analysis showed comparable results for both drugs.

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