Clinical Study Report Synopsis

in accordance with section 13 GCP-V

Version 01, 02.11.2022

Study title: ADVANCE-CSX Pilot - Antioxidant Treatment with Vitamin C in Cardiac Surgery Patients - a Clinical Pilot Study

Sponsor's Protocol Code Number: 19-098

EudraCT Number: 2019-001086-32

National Competent Authority reference: 4043744

Initial National Authority Approval: 02.01.2020

Name of Sponsor: RWTH Aachen, represented by the principal, represented by the Dean of the Medical Faculty Univ.-Prof. Dr. rer. nat. Stefan Uhlig Pauwelsstraße 30, 52074 Aachen Tel.: 0241 / 80 80092, Fax. 0241 / 80 3390092 Email: ctc-a-spoqs@ukaachen.de
Name of Finished Product(s): Vitamin C 1000 Injektionslösung
Name of Active Substance(s): Ascorbic acid
Study Title: ADVANCE-CSX Pilot - Antioxidant Treatment with Vitamin C in Cardiac Surgery Patients - a Clinical Pilot Study
Study design: Single-center, prospective, double blinded, randomized controlled clinical pilot trial
Final Protocol version: Version 1.1 dated 11.12.2019
Amendments: none
Final Patient Informed Consent version: Version 1.1 dated 11.12.2019
Investigator(s): Prof. Dr. med. Christian Stoppe
Site(s): Department of Intensive Care Medicine, University Hospital RWTH Aachen Pauwelsstraße 30, 52074 Aachen

Publication (reference): none

Study period: not applicable, as no sites were initiated or subjects enrolled

Date of first subject enrolment: not applicable, as no sites were initiated or subjects enrolled

Date of last subject completed: not applicable, as no sites were initiated or subjects enrolled

Temporary halt: 04/21/2020 postponed recruitment start due to COVID-19 pandemic

Early Termination: 10/06/2022

Due to administrative problems on the sponsor's side, start of recruitment was not feasible for a long period. The resulting increase in financial and regulatory requirements led to the decision to terminate the trial early.

Phase of Development: III

Objectives and criteria for evaluation:

Objective(s): In this mono-center randomized controlled clinical pilot trial in the University Hospital RWTH Aachen the objectives were to gather experience about feasibility, pharmacokinetics and efficacy of vitamin C administration, as well as to increase the evidence about the most appropriate vitamin C administration strategy in cardiac surgery patients. The oxidation-reduction-potential (ORP) as a feasible, readily accessible tool to measure the efficacy of an antioxidant, shall be evaluated. First evidence of vitamin C administration on blood vitamin C levels, oxidative stress and inflammation shall be gathered and first impressions about the clinical significance of a vitamin C treatment in cardiac surgery patients gained.

The secondary outcomes shall assess the influence of vitamin C on inflammation and organ dysfunction. Patient outcomes, such as ICU- and hospital length of stay, hemodynamic and ventilator parameters and mortality will be evaluated as well.

Primary endpoints:

- Analysis of a blood sample with the RedoxSYS Diagnostic SystemTM (Aytu BioScience, Inc., USA)
- Analysis of a blood sample for its vitamin C content

Secondary endpoints:

- ICU length of stay
- Hospital length of stay
- ICU readmission rate
- Hospital readmission rate
- Lab work: IL-6, CRP, PCT, leukocytes
- SOFA Score (daily records)
- Ventilation data (hours and mode of ventilation)

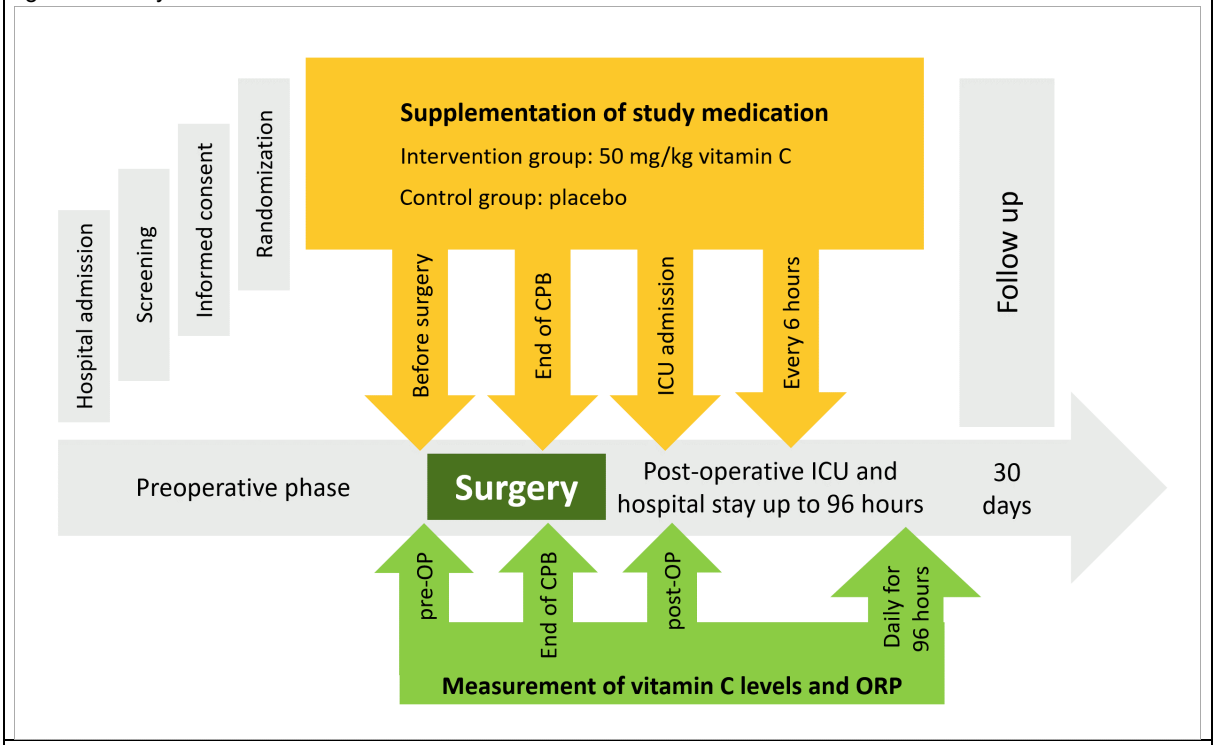
- Hemodynamic parameters (heart rate, blood pressure, vasopressors)
- Duration and dosage of sedation
- Richmond Agitation Scale (RAS)
- Confusion Assessment Method for the ICU (CAM-ICU)
- Laboratory analyses as per hospital standard: blood count, electrolytes, and markers of organ dysfunctions (creatinine, liver enzymes, hemoglobin, infection parameters)
- Need for ventilation, vasopressors, renal replacement therapy
- Surgical reevaluation, hemorrhage, thromboembolic events, cardiovascular events, infection and sepsis

Methodology:

This is a single-center, prospective, double blinded, randomized controlled clinical pilot trial evaluating the influence of vitamin C administration on vitamin C blood levels, oxidative stress, inflammation and organ dysfunction in cardiac surgery patients after informed consent.

As shown in Figure 1, the patients will be randomized to receive 50 mg/kg of vitamin C –or placebo– intravenously after induction of anesthesia before surgery, at the end of cardiopulmonary bypass, at admission to the ICU and 4 times daily during ICU stay (max. 96 hours) after surgery. The blood levels of vitamin C and the ORP values will be assessed before surgery, after cardiopulmonary bypass, at ICU admission and daily for 96 hours before the respective vitamin C supplementation.

Figure 1: Study Flowchart



Number of subjects:

Planned: 30

Analysed: 0

After approval of the trial, the trial site was not initiated and no trial participants have been recruited or enrolled in the trial.

Diagnosis and main criteria for inclusion and exclusion:

Study population: Adult cardiac surgery patients

Inclusion criteria:

- Adult cardiac surgery patients
- Given informed consent
- High risk cardiac surgery, defined by the presence of one or more of the following:
  - a) Planned combined valve/CABG or multiple valve surgeries, or combined cardiac/aortic surgical procedures
  - b) Any cardiac surgery with a high perioperative risk profile, defined as a predicted operative mortality of ≥ 5% (EuroSCORE II).

Exclusion criteria:

- Pregnant or lactating patients
- Clinical kidney failure or recurring formation of kidney stones
- Glucose-6-phosphatase dehydrogenase deficiency,
- Hemochromatosis or disease requiring frequent blood transfusions
- Patients already receiving an intense nutrition support (home parenteral or enteral nutrition) in addition to normal nutrition on hospital admission
- Known allergy to study nutrients
- Death expected within 96 hours after admission due to severity of disease
- Enrolment in an industry sponsored randomized trial within the last 30 days

Test product(s):

Name of finished product(s): Vitamin C 1000 Injektionslösung

Marketing authorization number(s): 6425372.00.01

Name of active substance(s): Ascorbic acid

Dose(s):

- 50 mg/kg of vitamin C intravenously after induction of anaesthesia before surgery, at the end of cardiopulmonary bypass, at admission to the intensive care unit (ICU)
- 4 times daily (200 mg/kg/d) until ICU discharge (maximum for 96 hours) after surgery

Mode of administration: intravenously

Batch number(s): no participants were enrolled, therefore no product was administered

Duration of treatment: induction of anaesthesia before surgery until ICU discharge (maximum for 96 hours) after surgery

Reference therapy:

Product name(s): Placebo (sodium-chloride 0.9% solution)

Dose:

- Once intravenously after induction of anaesthesia before surgery, at the end of cardiopulmonary bypass, at admission to the intensive care unit (ICU)
- 4 times daily until ICU discharge (maximum for 96 hours) after surgery

Mode of administration: intravenously

Batch number(s): no participants were enrolled, therefore no product was administered

Statistical methods:
Descriptive statistics will be presented regarding the pilot study feasibility outcomes. Safety variables will be described by arm. Due to the limited sample size and the potential of rolling the pilot study into the definitive study, clinical efficacy outcomes will be reported overall but not by arm. There are no planned interim analyses for these pilot trials.

Treatment Compliance:
As the trial participants will exclusively be treated while their ICU stay, no additional measures for compliance were implemented.

Efficacy and Safety variables:
We will follow patients prospectively while in the hospital, documenting nutrition and outcome related data. We will record baseline parameters, data to judge organ dysfunction and data on ventilation and hemodynamics, we all as record any additional trace element/multivitamin supplementation given. We will perform laboratory analyses to measure ORP and blood vitamin c levels and collect data obtained from routine laboratory analyses during the ICU and hospital-stay. We will evaluate adverse and serious adverse reactions. Regarding data on infection state, we will record culture results and antibiotics used and pertinent clinical data to enable the adjudication of infectious complications. Following discharge from the hospital, the charts will be reviewed by two investigators to evaluate and categorize all infectious complications. Based on the International Sepsis Forum guidelines, we have developed standard definitions of definite, probably, and possible infectious complications most commonly associated with critical illness. All study patients will be followed for 30 days after discharge or death, whichever comes first.
The following tables (Table 1-3) summarize the outcome parameters, as well as the used tools, recorded parameters and the collection timing.

Table 1: Primary outcomes: Safety and Feasibility

Outcome parameter	Instru-ment	Description
Safety	Chart review	Occurrence adverse effects with special focus on • Formation of kidney stones, urninary infections and renal failure • Hemolysis • Hyperglycemia

Effectivity and separation		To determine if separation between the intervention- and control-group regarding ORP and the vitamin C serum levels can be achieved through the administration of vitamin C
Compliance		To determine what proportion of the patients received all prescribed interventions (target: >90 % of patients receiving all interventions)
Contamination		Avoidance of administration of vitamin C control group (target: <5%)

Table 2: Primary biochemical outcomes

Outcome parameter	Instrument	Collection timing
Serum ORP	Analysis of a blood sample with the RedoxSYS Diagnostic SystemTM (Aytu BioScience, Inc., USA)	Before surgery, after cardiopulmonary bypass, at ICU admission, daily for 96 hours
Serum Vitamin C	Analysis of a blood sample for its vitamin C content	

Table 3: Secondary outcome parameters

Secondary Outcome Parameter		Instrument	Collection Timing
Mortality		Chart review	Hospital discharge 30- day follow-up
Length of stay	ICU length of stay		Hospital discharge
	Hospital length of stay		
Readmission	ICU readmission rate		Hospital discharge 30- day follow-up
	Hospital readmission rate		
Inflammatory reaction	Lab work: IL-6, CRP, PCT, leukocytes	Laboratory analyses of blood samples	Daily during ICU stay until 96 hours after surgery
Acute Organ Dysfunction	SOFA Score (daily records)	Chart review	Daily during ICU stay As per clinical routine
	Ventilation data (hours and mode of ventilation)		
	Hemodynamic parameters (heart rate, blood pressure, vasopressors)		
	Duration and dosage of sedation		
	Richmond Agitation Scale (RAS)		
	Confusion Assessment Method for the ICU (CAM-ICU)		
	Laboratory analyses as per hospital standard: blood count, electrolytes, and markers of organ dysfunctions (creatinine, liver enzymes, hemoglobin, infection parameters)		
Persistent Organ Dysfunction	Need for ventilation, vasopressors, renal replacement therapy		Hospital discharge, 30-day follow up

Complications	Surgical reevaluation, hemorrhage, thromboembolic events, cardiovascular events, infection and sepsis		Hospital discharge 30-day follow-up

Data Quality Assurance:

Standardization procedures will be implemented to ensure accurate, consistent, complete and reliable data, including methods to ensure standardization within assessors (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, and validation methods).

Risk Evaluation/Protocol Deviations: There were no trial sites initiated and no participants enrolled in the trial. Therefore, no risk evaluation was necessary and no protocol deviations took place.

Safety Evaluation:

Patients will be monitored daily for adverse events (AEs) and unexpected events (UEs) during the entire hospital stay. All AEs and UEs will be recorded. Patients will be monitored daily for unexpected serious adverse events until death or discharge from ICU.

Adverse Events: 0

Safety results: As no participants were enrolled in the trial, no adverse events occurred.

Summary of results: n.a., as no participants were enrolled in the trial

Subject disposition: n.a., as no participants were enrolled in the trial

Demographics: n.a., as no participants were enrolled in the trial

Efficacy results: n.a., as no participants were enrolled in the trial

Conclusion: n.a., as no participants were enrolled in the trial

The undersigned authors agree to the content of this clinical study report by giving their signatures. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.

Sponsor

RWTH Aachen, represented by the principal, represented by the Dean of the Medical Faculty

Univ.-Prof. Dr. rer. nat. Stefan Uhlig

Place, Date:

Signature:

Principal Investigator

Prof. Dr. med. Christian Stoppe

Place, Date:

Signature:

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Place, Date:

Signature: