## 1 TITLE PAGE

**FULL VERSION FOR REGULATORY SUBMISSION**

# Ciclosporin to Protect Renal function In Cardiac Surgery

# CiPRICS

## A Phase II, Double-Blind, Randomized, Placebo-Controlled Study

Test Product: Single dose of CicloMulsion® (5 mg/mL), 2.5 mg/kg as intravenous injection

Protocol Number: 2014.001

EudraCT Number: 2014-004610-29

Final Report: 12-May-2017

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| Sponsor and Sponsor's Responsible: | Henrik Bjursten, Sweden |
| Principal Investigator: | Henrik Bjursten, Sweden |
| Study Initiation Date: | 07-Apr-2015 |
| Study Completion Date: | 30-Jun-2016 |
| Date of the Last Post-hoc Follow-up Data: | 06-Oct-2016 |

**Confidential**

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

## 2 SYNOPSIS

The synopsis of this clinical study report is located in a separate document.

## 3 TABLE OF CONTENTS

**LIST OF TABLES**

**LIST OF FIGURES**

## 4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | Adverse event |
| AIC | Akaike information criterion |
| AKI | Acute kidney injury |
| ALAT | Alanine aminotransferase |
| ALP | Alkaline phosphatase |
| ANCOVA | Analysis of covariation |
| ANOVA | Analysis of variance |
| ASA | Acetyl salicylic acid |
| ASAT | Aspartate aminotransferase |
| AUC | Area under the curve |
| B | Blood |
| CABG | Coronary artery bypass grafting |
| CI | Confidence interval |
| CK | Creatine kinase |
| CKD-EPI | Chronic Kidney Disease - Improved Prediction Equations (method to estimate GFR) |
| CK-MB | Creatine kinase isoenzyme MB |
| CL | Clearance |
| COPD | Chronic obstructive pulmonary disease |
| CRF | Case report form |
| CRP | C-reactive protein |
| CyC | Cystatin C |
| DSUR | Development Safety Update Report |
| ECC | Extracorporeal circulation |
| ECG | Electrocardiography |
| eGFR | Estimated glomerular filtration rate |
| Est | Estimate |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GT | Gamma-glutamyltransferase |
| Hb | Haemoglobin |
| i.v. | Intravenous |

| | |
|---|---|
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| ICU | Intensive care unit |
| IEC | Independent ethics committee |
| IGFBP7 | Insulin-like growth factor-binding protein 7 |
| IMP | Investigational medicinal product |
| ITT | Intention to treat |
| LD | Lactate dehydrogenase |
| LLOQ | Lower limit of quantification |
| LN | Natural logarithm |
| LVEF | Left ventricular ejection fraction |
| MDRD | Modified Diet in Renal Disease (method to estimate GFR, based on creatinine) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified intent-to-treat |
| MPA | Medical Products Agency |
| mPTP | Mitochondrial permeability transition pore |
| NCA | Non-compartmental analysis |
| NSAID | Non-steroidal anti-inflammatory drugs |
| P | Plasma |
| PP | Per protocol |
| PT | Preferred term |
| RIFLE | Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease |
| S | Serum |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SE | Standard error |
| SOC | System organ class |
| SUSAR | Suspected unexpected serious adverse reaction |
| THIVA | Thoracic intensive care unit |
| TIMP-2 | Tissue inhibitor of metalloproteinases-2 |
| TnT | Troponin T |
| U | Urine |

# 5 ETHICS

## 5.1 Independent Ethics Committee (IEC)

The investigator obtained approval of the study protocol/protocol amendments, the patient information and the informed consent from both the Regional Ethical Review Board and the health authorities before enrolment of any patient in the study.

If significant changes were made to the study protocol after approval, an addition to the protocol ("Amendment") was to be written and sent to the IEC and the Swedish Medical Product Agency (MPA) for approval before such changes were implemented. A significant change was defined as a change that influences the participating person's safety or their physical or psychological welfare and/or influences the trial's scientific value or is of importance in any other way.

A list of all IECs consulted is given in Appendix 16.1.3.

## 5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, applicable regulatory requirements, the principles of International Council for Harmonisation (ICH) good clinical practice (GCP) and the Declaration of Helsinki.

## 5.3 Patient Information and Consent

It was the responsibility of the investigator to provide each patient with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study. All patients were given the opportunity to ask questions about the study and were given sufficient time to decide whether or not to participate in the study. The prospective patient had the right at any time to withdraw from the study.

According to ICH GCP guideline and the Helsinki Declaration, a study patient has to give written consent to participate in the clinical trial, before he/she can be included in the study. The principal investigator and those who were delegated the task provided both oral and written information to patients who fulfilled the inclusion criteria and may be subject for the study. The information should be as objective and transparent as possible. This information was given to the patient the day before surgery. A copy of the patient information and of the signed consent were given to the patient.

Written information for the patient and a sample patient consent form is available in the Trial Master File.

## 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

| | |
|---|---|
| Sponsor and Principal Investigator: | Henrik Bjursten, Sweden<br>(This study was investigator-initiated.) |
| Monitor: | FoU-centrum Skåne (Clinical Studies Sweden – Forum South)<br>Skåne University Hospital<br>Lund, Sweden. |
| Independent interim safety analysis group | An independent interim safety analysis group was responsible for the analysis and assessment of data at the two pre-planned interim safety analyses. |

## 7 INTRODUCTION

Acute kidney injury (AKI) is a common complication after cardiac surgery and incidences of 5-40% have been reported depending on definition (1-4). Several studies have shown that a decreased renal function after cardiac surgery is associated with decreased long-term survival (2-4).

Acetylcysteine, sodium bicarbonate and erythropoietin have been suggested as effective prophylaxis, but larger studies have not shown any efficacy (5-8). To date no effective prophylactic treatment has been identified.

The exact mechanism for inducing AKI in cardiac surgery is not known and may be multifactorial. The kidney is highly vulnerable for hypoxic injury. Approximately 20% of the total cardiac output is received by the kidneys and 90% of this blood flow is distributed to the renal cortex, where only about 18% of the oxygen content is extracted. At the same time, the medullary region receives only 10% of the total renal blood flow but has a far greater oxygen extraction, about 79% (9). Cardiac surgery with extracorporeal circulation (ECC) is associated with episodes of the combination of low cardiac output and hypovolemia, which may result in renal ischemia-reperfusion injury, especially in the poorly oxygenated and metabolic active outer medulla (10). Thus, renal ischemia-reperfusion injury is claimed to play a role in the resulting AKI.

Ciclosporin has been used since the early 1980's as an immunosuppressant in kidney and other solid organ transplantation. In addition to its well-known immunosuppressive properties, ciclosporin is a potent inhibitor of mitochondrial permeability transition, and several animal studies have indicated that ciclosporin can limit ischaemia-reperfusion injury under experimental conditions (11-14) and in various organs (13, 15, 16) including the kidney (17-20). The major suggested mechanism for this involves mitochondrial permeability transition pores (mPTP). The inner mitochondrial membrane is normally impermeable to most solutes, enabling efficient ATP production through oxidative phosphorylation. Elevated $Ca^{2+}$ levels and oxidative stress triggered by reperfusion after ischaemia result in opening of mPTP. Opening of mPTP during reperfusion has been suggested to amplify or accelerate cell death, causing reperfusion-induced necrosis (21-27). Upon mPTP opening, energy production is halted and molecules smaller than approximately 1500 Da equilibrates over the membrane. The osmotic force of matrix proteins results in matrix swelling, which leads to rupture of the outer membrane and release of pro-apoptotic factors such as cytochrome c into the cytosol, further pushing the cell towards death (23, 28, 29). The precise molecular composition of the mPTP is unknown, however, a key component is the peptidyl-prolyl cis-trans isomerase cyclophilin D. It has been demonstrated that cyclophilin D gene-ablated mice were protected against renal ischaemic injury (30) and that a normal rat kidney cell line with knock-down of the cyclophilin D gene was protected against hypoxia-induced necrotic death (31). The opening of the mPTP can be inhibited pharmacologically by ciclosporin (32) and a cyclophilin D-activated mPTP has been demonstrated also in human mitochondria (33, 34).

The current study was the first clinical study investigating the possible renoprotective effect of ciclosporin after ischemia-reperfusion in humans. Previous clinical studies have investigated the effects of ciclosporin against injury after ischemia and reperfusion in the heart and trauma to the brain. Administration of ciclosporin in conjunction with percutaneous coronary intervention, heart surgery or traumatic brain injury in humans has not revealed any ciclosporin-induced safety concerns (35-40).

The current study assessed the safety and efficacy of ciclosporin to prevent AKI following heart surgery in patients with a high risk of developing AKI.

# 8 STUDY OBJECTIVES AND ENDPOINTS

## 8.1 Objectives

The primary objective was to study the efficacy of ciclosporin, with brand name CicloMulsion®, given preoperatively in coronary artery bypass grafting (CABG) study patients to reduce the degree of AKI after CABG surgery. A number of biological markers for kidney function were to be evaluated.

Secondary objectives were related to the study drug's potential effect on brain and heart. These were to be evaluated by specific biomarkers. Also, safety parameters including incidence and nature of adverse events (AEs) during the study period (Days 0–30) and safety biochemistry during Days 0–4 were to be followed.

## 8.2 Endpoints

Primary endpoint:
Relative plasma cystatin C (P-CyC) change from Day -1 to Day 3.

Secondary efficacy endpoints:

- P-CyC, P-CyC $AUC_{Day\text{-}1\text{–}4}$ (area under the concentration-time curve for P-CyC on Days-1 to Day 4), P-CyC eGFR (estimated glomerular filtration rate), P-creatinine, MDRD eGFR, creatine kinase isoenzyme MB (P-CK MB), P-Troponin T (P-TnT) and S-S100 B on Day -1 throughout Day 4.
- U-tissue inhibitor of metalloproteinases-2 (U-TIMP-2) and U-insulin-like growth factor-binding protein 7 (U-IGFBP7) on Day 0.
- Evaluation of e.g. ECC time on efficacy variables.
- B-ciclosporin on Days 0–1.
- Incidence of AKI according to RIFLE criteria (RIFLE = Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease) based on P-creatinine and/or eGFR (41).

Secondary safety endpoints:

- Safety aspects as AE and serious AEs (SAEs) were to be followed during the whole study period.
- Safety biochemistry: plasma concentrations of $K^+$, $Mg^{2+}$, urea, myoglobin, creatine kinase (CK), bilirubin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltransferase (GT), lactate dehydrogenase (LD), C-reactive protein (CRP) and leukocytes.
- Body temperature and blood pressure were followed on Days -1-4.
- Leg wound infection scored according to accepted scoring system (see Study Protocol Appendix B).

See also Section 9.7.1.3 and the Statistical Analysis Plan (SAP) in Appendix 16.1.9 for further details regarding the endpoints.

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

The clinical study was a double-blind, placebo-controlled randomised single-centre study of ciclosporin for renal protection. Screening and inclusion of patients were performed pre-operatively. Eligible patients were blindly allocated into one of the two treatment groups in a 1:1 ratio, to receive a single intravenous (i.v.) bolus injection of 0.5 mL/kg CicloMulsion® (ciclosporin) or a single i.v. bolus injection of equivalent volume of placebo, i.e. 0.5 mL/kg (Figure 1). In addition, the randomisation was stratified into two pre-defined subgroups; patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$.

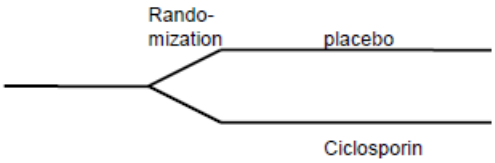


**Figure 1: Parallel group design**

Blood samples for baseline values were collected preoperatively. The investigational medicinal product (IMP), i.e. active study drug or placebo, was given as a single i.v. dose after anaesthesia induction. The patient followed the normal routine regarding further treatment. After surgery, renal function parameters and biomarkers were followed on Days 0-4, see Section 9.5.1 for further details.

Safety monitoring of AEs and SAEs began at the start of administration of IMP. The study duration was 1 month from enrolment (30 days postoperatively). The patients were contacted by phone at the end of the study to be asked about AEs, SAEs and signs of infection. All ongoing AEs, SAEs and suspected unexpected serious adverse reactions (SUSARs) had to be followed up until resolution, until the condition had stabilised according to the investigator, or up to 6 months, see Section 9.5.1.3 for further details.

Two interim safety analyses were planned and conducted; the first after completion of 50 patients and the second after completion of 100 patients, see Section 11.2.3 for further details.

## 9.2 Discussion of Study Design, Including the Choice of Control Group

This study was designed as a double-blind, randomised placebo-controlled study to minimise the observer's and experimenter's bias on study drugs effects.

Placebo, rather than another active drug, was chosen as no other renoprotective drug is available for this indication, and thus, placebo corresponds to standard routine care.

## 9.3 Selection of Study Population

Overall, it was planned to include approximately 150-170 patients to obtain a total of 150 evaluable patients planned for CABG. Patients were not eligible if they had uncontrolled

hypertension, were pregnant or fertile women, had received ciclosporin treatment within 4 weeks, had an eGFR of <15 or >90 mL/min/1.73 $m^2$ or dialysis, known ongoing malignancy, off-pump surgery, intake of medicines with known interaction with ciclosporin, or hypersensitivity to ciclosporin or any of the excipients of the lipid emulsion.

### 9.3.1 Inclusion Criteria

All of the following inclusion criteria had to be fulfilled for inclusion:
1. The patient was scheduled for non-emergent (decision to operate more than one hour before start of surgery) CABG surgery.
2. Preoperative CyC eGFR or creatinine (MDRD) eGFR was 15-90 mL/min/1.73 $m^2$. eGFR was calculated using both MDRD and CyC. The lowest eGFR value was used for the inclusion criterion assessment.
3. The patient gave his/her written consent to participate.

### 9.3.2 Exclusion Criteria

All of the following exclusion criteria had to be answered by a "No" for inclusion:
1. The patient had uncontrolled hypertension (defined as: uncontrolled [treated or untreated] hypertension [>180/110 mmHg]).
2. Hypersensitivity to the active drug or vehicle, including egg-, soya- or peanut protein.
3. The patient was pregnant or a fertile woman (defined as menstruation within the last 12 months).
4. The patient had been treated with ciclosporin within 4 weeks prior to the surgery.
5. The patient had a known ongoing malignancy (defined as: according to the investigator, e.g. ongoing treatment).
6. The patient had ongoing immunosuppressive treatment.
7. The patient had severe hepatic dysfunction (defined as: according to the investigator, e.g. diagnosed cirrhosis).
8. The patient was treated with dialysis.
9. The patient had pre-operatively ongoing and/or increasing clinical infection with CRP levels of >50 mg/L. Clinical signs of infection may or may not be present. Increase in CRP due to signs of cardiac origin (42), according to the investigator, was not to be considered as an exclusion criterion.
10. The patient had a severe ongoing viral infection, including HIV, hepatitis C, current or history of hepatitis B.
11. For non-allowed and restricted ongoing and concomitant medications, see Section 9.4.6.2.
12. The patient was planned for off-pump CABG surgery.
13. The patient was included in other ongoing clinical trial.
14. For any other reason, the patient was unsuitable to participate in the study, according to the investigator.

### 9.3.3 Removal of Patients from Therapy or Assessment

The study patient could withdraw from the study at any time for any reason without prejudice to future treatment. In addition, the study patient could be withdrawn at the investigator's discretion at any time if regarded in the study patient's best interest.
Pre-defined withdrawal criteria were:

- Change of surgical procedure to other than solitary CABG with ECC.
- Serious violation of the study protocol, as judged by the investigator.

All study patients that discontinued the study were to continue to receive routine care. All study patients that discontinued the study were to be asked for the reason (if possible) and the presence of any AE.

### 9.3.4 Stopping or Suspending the Study

There were no protocol-defined circumstances under which the study would be stopped or suspended. However, if there were reasons for cancelling the study, the principal investigator could do that at any time. If so, the principal investigator was to immediately inform all involved in the study and report to the Swedish MPA.

## 9.4 Treatment

### 9.4.1 Treatments Administered

#### 9.4.1.1 Investigational Medicinal Products (IMPs)

The IMP was CicloMulsion® (5 mg/mL, 100 mL glass vials) or its placebo (100 mL glass vials), supplied as an emulsion for i.v. injection.

The matching placebo consisted of all components of the CicloMulsion® emulsion except ciclosporin: refined soybean oil, medium-chain triglycerides, egg lecithin, glycerol, oleic acid, sodium hydroxide and water for injection.

CicloMulsion® and its placebo were ready-to-use lipid emulsions, i.e. did not need any step of preparation or dilution. A separate Drug Handling Manual was provided.

CicloMulsion® or placebo was administered as a single i.v. bolus dose injection, 0.5 mL/kg body weight. This corresponds to a dose of 2.5 mg/kg ciclosporin if the study patient was randomised to active study drug, i.e. CicloMulsion®. The study drug/placebo was given in a central venous catheter as an injection during 10 minutes, without concomitant administration of other drugs in this line. The line was flushed with 0.9% NaCl after administration of the study drug. Further details were provided in the Drug Handling Manual.

CicloMulsion® or placebo was administered after anaesthetic induction when the patient was in a stable circulatory state and before the study patient was connected to the ECC.

#### 9.4.1.2 Non-Investigational Products

Preoperative medication was administrated according to clinical routines. Prior to surgery, the patients received a premedication with oral diazepam.

Anaesthesia induction was according to standardised procedure with fentanyl, midazolam and propofol. The preferred dose of propofol was approximately 6 mg/kg/h during steady state. Both propofol and anesthetic gas may have anti-inflammatory, and thus, renoprotective effects (43). Anesthetic gas was prohibited in this study. Maintenance of anaesthesia was performed with propofol infusion and fentanyl as needed according to the anaesthesiologist in charge. A Ringer-acetate solution was infused continuously from induction until initiation of ECC, and restarted after termination of ECC. All dosing was according to the responsible anaesthesiologist. Muscle relaxation was initiated with suxamethonium or rocuronium and

maintained with rocuronium. ECC was performed according to the perfusionist and surgeon in charge.

All other procedures including blood transfusions were according to normal routine care protocol and assessment of the physicians in charge of the patient.

### 9.4.2 Identity of IMPs

CicloMulsion® and its matching placebo were supplied by NeuroVive Pharmaceutical AB, Lund, Sweden and manufactured by Fresenius-Kabi Corporation, Graz, Austria.

Batch number CicloMulsion®: 16HG0185
Batch number placebo: PP1442041

The IMP was to be stored at controlled room temperature (minimum 2°C, not above 25°C, not to be frozen). Detailed storage conditions were printed on the labels of the individual containers of the IMP together with the expiry date as appropriate.

Use after expiry date: Not applicable since no IMP was used after the expiry date (30-Jun-2016).

### 9.4.3 Avoidance of Bias

#### 9.4.3.1 Method of Assigning Patients to Treatment Groups

Eligible patients were allocated into one of the two treatment groups at a 1:1 ratio, to receive a single i.v. bolus injection of 2.5 mg/kg (0.5 mL/kg) CicloMulsion® (ciclosporin), or a single i.v. bolus injection of equivalent volume of placebo (0.5 mL/kg). In addition, the randomisation was stratified into two pre-defined subgroups: patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$. Approximately 50 patients from the group with an eGFR of 15-59 mL/min/1.73 $m^2$ were to be included. Also within each eGFR group, study drug and placebo were stratified in a 1:1 ratio.

For randomisation to ciclosporin or placebo, a blinded randomisation list, pre-generated by a statistician not included in the study group, was used to assign a unique sequential Treatment Number to each bottle of active study drug/placebo. The unique Treatment Number was printed on the study medication bottle, where also a sticker for the case report form (CRF) was positioned. The bottles with study drug/placebo were packed in boxes marked with eGFR 15-59 mL/min/1.73 $m^2$ or eGFR 60-90 mL/min/1.73 $m^2$ according to the stratification. Study drug/placebo was kept in two separate sets, one set of study drug/placebo for patients with eGFR 15-59 mL/min/1.73 $m^2$ and one set for patients with eGFR values of 60-90 mL/min/1.73 $m^2$. Each study drug/placebo box was marked with a unique code (eGFR 15-59 mL/min/1.73 $m^2$ was marked 1-001, 1-002, etc. and eGFR 60-90 mL/min/1.73 $m^2$ was marked 2-001, 2-002, etc.).

The allocation to study drug/placebo was performed manually by the same designated study staff who prepared the syringe with study drug/placebo. Once the patient had been admitted to the operation ward and inclusion/exclusion criteria had been re-checked, the study patient was allocated to receive study drug or placebo according to the following steps:

1. Depending on the eGFR before surgery, the research nurse took the next bottle from either a box labelled eGFR 15-59 mL/min/1.73 $m^2$ or a box labelled eGFR 60-90 mL/min/1.73 $m^2$.
2. One tear-off label from the bottle with the unique Treatment Number (i.e. the code to if the bottle contained ciclosporin or placebo) and the box serial number (e.g. 1-100) was added to the patient's CRF.
3. Two separate labels were marked and placed on two 50 mL syringes.
4. The correct volume of study medication was aspirated into one or two syringes, depending on the patient's weight, according to the Study Drug Manual.
5. Patient name, identifier (Swedish social security number), Treatment Number, study box serial number (e.g. 1-001) and date were entered into the Enrolment List.
6. The syringe(s) was immediately taken to the operating room where the patient ID was checked and the drug was administrated according to the Study Drug Manual.

#### 9.4.3.2 Blinding and Unblinding

The IMPs (ciclosporin and placebo) were delivered, labelled and packed in a dispatch box containing randomised colourless glass vials, sealed with a rubber stopper, containing a nominal fill volume of 100 mL. Each patient had one vial of 100 mL prepared (the given dose should be 0.5 mL/kg body weight). A number of dispatch boxes with randomised vials were available in the hospital pharmacy. The IMP was labelled in such a manner that the patient and study staff were unable to determine from the dispensed packaging to which treatment group the patient had been assigned.

The qualitative composition of CicloMulsion® and its matching placebo only differed in the presence or absence of ciclosporin, thus, the final emulsions were visually indistinguishable.

The treatment each patient received was not disclosed to the investigator, trial site staff, the patient, the sponsor, their representatives/designees, or NeuroVive Pharmaceutical AB until after the study database had been formally locked. The Treatment Number codes were held by FoU Skåne.

Individual code breaking sealed envelopes were available for the investigators if there was a safety issue requiring un-blinding on individual basis.

### 9.4.4 Selection of Dose and Timing of Dose for Each Patient

Selection of Dose

Ciclosporin is a well-established immunosuppressant that has been initially administered as an i.v. dose of 3–5 mg/kg/day to patients undergoing solid and bone marrow transplants (44). Once transplant patients are able to tolerate oral administration, they can receive ciclosporin capsules on an ongoing basis at a maintenance dose of 2–6 mg/kg, the exact dose being determined by target trough levels of ciclosporin in blood.

The current study is the first study conducted within the indication 'protection of renal function in cardiac surgery'. Compared with the long-term daily administration of ciclosporin in transplant patients, the selected dose of CicloMulsion® for the current study, is a single i.v. bolus dose of 2.5 mg/kg (0.5 mL/kg). Thus, it was anticipated that AEs arising from administration of CicloMulsion® would be less frequent, milder and of shorter duration than those arising from long-term dosing of the marketed ciclosporin product, Sandimmun® and generic equivalents.

Timing of Dose for Each Patient
CicloMulsion® or placebo was administered during 10 minutes through a central venous line, which was inserted immediately after anaesthetic induction when the patient was in a stable circulatory state and before the patient was connected to the ECC.

### 9.4.5 Treatment Compliance

The research/assigned study nurse designated by the principal investigator was in charge of the accountability of the IMP, and had to maintain an adequate record of the arrival and distribution of all IMP, in the Site Master Investigator File.

The volume of the study drug given to each patient was noted in the CRF.

The person responsible for monitoring, or the delegated person, checked that the study drug management was done in a satisfactory way and ensured that the destruction of unused and returned drugs were handled in accordance with supplier recommendations and by clinical routine. Any unused product or waste material was to be disposed of in accordance with local requirements and after approval from the monitor.

For a patient to be considered as compliant and to be included in the per protocol analysis, he/she had to have received at least 90% of the intended dose and not have any major protocol deviations.

### 9.4.6 Prior and Concomitant Therapy

#### 9.4.6.1 Therapy Allowed at Enrolment, on/during Day of Surgery (Day 0) and on Days 1 to 30 Post-surgery

The study did not affect study patients' concomitant medication with the exceptions mentioned below. The patient's concomitant medication was according to routine indication. As per routine clinical procedure, each patient had their normal maintenance drugs withdrawn 24 hours before the CABG operation, excepted were β-blockers and proton-pump inhibitors, which were given in the morning of surgery. In addition, a benzodiazepine (diazepam) was given as sedative pre-medication. All the patient's ongoing/concomitant medications were assessed by the investigator.

In this study population with well-known cardio-vascular diseases and other co-morbidities, the risk with drug interactions when obtaining one single i.v. injected dose with statins or verapamil (CYP3A4 inhibitors/inducers) has been judged to be of less risk vs the assessed benefit for these patients. Both statins and calcium channel blockers were therefore allowed medications at enrolment in this study.

Therapy allowed at enrolment:

- Statins, calcium-channel blockers, verapamil
- Acetylsalicylic acid (ASA)

Therapy allowed on/during day of surgery (Day 0):

- Diazepam, proton pump inhibitors (e.g. omeprazole), beta-blockers

There were no restrictions regarding therapy allowed on Days 1-30 post-surgery:

In the intensive care unit (ICU), transfusion of blood products was according to clinical routine.

#### 9.4.6.2 Non-Allowed and Restricted Ongoing and Concomitant Medications

Ciclosporin, a calcineurin inhibitor, is a substrate for cytochrome P450 3A4. Drug interactions mainly occur when ciclosporin is co-administered with either inhibitors or inducers of CYP3A4. Combining ciclosporin with CYP3A4 inhibitors increases the ciclosporin exposure, whereas combining ciclosporin with a CYP3A4 inducer decreases the ciclosporin exposure.

##### 9.4.6.2.1 Non-allowed Medications at Enrolment and during Day 0

Ongoing treatment with any of the following was not allowed:

- St John's Wort and bosentan (CYP3A4 inducers decrease the blood levels of ciclosporin)
- Dabigatran etexilate, aliskiren, stiripentol (CYP3A4 substrates, which can be affected by ciclosporin)
- Glibenclamid
- Other ongoing immunosuppressive treatment (e.g. tacrolimus or ciclosporin) and non-steroidal anti-inflammatory drugs (NSAIDs)
- Per-operative treatment with inhalation anaesthetics: isoflurane (45, 46) and sevoflurane (47, 48). These drugs may have nephroprotective effects.

##### 9.4.6.2.2 Restricted Medications at Enrolment and during Day 0

Ongoing treatment with any of the following was to be assessed by the investigator:

- All inducers of CYP3A4 are expected to decrease ciclosporin levels, e.g. barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, ticlopidine, sulfinpyrazone, terbinafine and rifampicin.
- All inhibitors of CYP3A4 may lead to increased levels of ciclosporin, e.g. nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone, telaprevir, amiodarone, macrolide antibiotics (erythromycin, clarithromycin and azithromycin), azole antibiotics (ketoconazole, fluconazole, itraconazole and voriconazole).

The study protocol referred to the Investigator's Brochure (IB) for a more extensive list of medications interacting with ciclosporin.

Restricted drugs during surgery included:

- Diuretics, e.g. furosemide (affects diuresis in a random manner)
- Ketamine
- Remifentanil

### 9.5 Efficacy and Safety Variables

#### 9.5.1 Efficacy and Safety Measurements Assessed and Schedule of Assessments

Table 1 depicts the events and assessments that do not belong to the normal care of patients.

**Table 1: Schedule of study events and assessments**

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| **Day/Month in relation to surgery day** | **Day -1** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Month 1** |
| Informed consent | X | | | | | | |
| Inclusion/ exclusion criteria | X | X | | | | | |
| Randomisation | | X | | | | | |
| Study drug | | X | | | | | |
| AE and SAE recording and reporting | | X | X | X | X | X | X |
| Blood ciclosporin concentration | | X | X | | | | |
| Blood tests efficacy: CyC, creatinine | X | | X | X | X | X | |
| Analysis urine TIMP-2, urine IGFBP7. U-albumin/creatinine | | X | X | | | | |
| Blood tests safety: $Mg^{2+}$, $K^{+}$, urea, myoglobin, ALAT, bilirubin, ALP, GT, leukocytes, CRP, CK, Hb, thrombocytes | X | | X | X | X | X | |
| Exploratory immunologic tests | | X | X | | | | |
| Blood tests cardiac: TnT, CK MB | X | X | X | X | X | X | |
| Blood test cerebral: S-S100B | X | | X | X | | | |
| Documentation of hourly diuresis, bleeding at 12 hours and total, time to extubation, time in ICU and fluid balance. | | X | X | | | | |
| Temperature, blood pressure | X | | X | X | X | X | |
| Scoring of leg wound infection | | | | | | X | |

Day -1 corresponds to the day before surgery, usually the same as admission day. Day 0 corresponds to the surgery day and Day 1 corresponds to the day after surgery and so on. Baseline blood tests were renewed if taken more than 5 days before surgery.
ALP: alkaline phosphatase; Hb: haemoglobin

#### 9.5.1.1 Primary Efficacy Measurement

P-CyC was measured by an immunometric method by Roche.

#### 9.5.1.2 Secondary Efficacy Measurements

Kidney, cardiac and brain function parameters and markers were assessed daily during the study:

- P-creatinine was measured by an enzymatic colorimetric method.
- eGFR was calculated using both creatinine (MDRD) and CyC. The lowest eGFR value was used for the inclusion criterion assessment.
- AKI was calculated according to RIFLE (based on creatinine and/or eGFR). AKI was also estimated based on CyC eGFR.
- Postoperatively, U-TIMP-2 and U-GFBP7 were measured repeatedly during 24 hours (Nephrocheck Bedside analyser, Astute Medical, San Diego, California, US). These molecules are markers of early AKI (49, 50).
- Urinary output was monitored and recorded during surgery and postoperatively until the patient was discharged from the ICU.
- CK MB and P-TnT are markers of cardiac injury and were followed to evaluate a suggested cardioprotective effect of ciclosporin (36, 37).
- S-S100 B, a marker of brain injury, was followed to evaluate a possible brain protective effect of ciclosporin (51).

#### 9.5.1.3 Safety - Adverse Events

##### 9.5.1.3.1 General

A designated safety partner was assigned by the sponsor to handle all safety-related tasks. The designated partner assessed seriousness, causality and expectedness of SAE as reported by the investigator. The evaluation of the expectedness was defined by the designated safety partner using the IB as reference document. The sponsor or the designated safety partner was responsible for reporting of all relevant safety information, including SUSARs, New Safety Issues and annual Development Safety Update Reports (DSURs), to the competent authorities and to the IEC concerned.

##### 9.5.1.3.2 Definition of Terms

Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavourable and unintended sign (e.g. tachycardia, enlarged liver) or abnormal results of an investigation (e.g. laboratory finding, electrocardiography [ECG]), or symptom (e.g. nausea, chest pain) or disease temporally associated with the use of a medical (investigational) product, whether or not related to the medicinal (investigational) product.

Events not to be considered as AEs:

- A pre-existing condition (i.e. a disorder present before the AE reporting period started and noted on the medical history/physical examination form) should not be reported as an AE unless the condition worsened or episodes increased in frequency during the AE reporting period.
- Procedures to support the treatment regimens.

Clinical normal signs and symptoms due to the procedure of CABG were only to be reported as AEs if they were:

- Serious events according to the definition or were not expected in relation to the surgical procedure as judged by the investigator.

Definition of Serious Adverse Event
A serious adverse event (SAE) is an AE occurring during any part of the study that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth effect
- Other important medical event

Events that do not meet the definition of a Serious Adverse Event:

- Elective surgery or other scheduled hospitalisation periods that were planned before the patient was included in the study were not to be reported as SAEs.
- Hospitalisation following the surgical procedure should not be reported as SAE.

Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)
The definition of an unexpected adverse reaction is an AE, which has not been documented or reported earlier. The reference document is the reference safety information in the IB. All SUSARs had to be evaluated including an assessment of relationship to the IMP.

If the responsible investigator/sponsor regarded the SAE as being a SUSAR, it had to be promptly reported to the sponsor's designated safety partner, who was responsible for reporting SUSARs to the regulatory authorities.

#### 9.5.1.3.3 Recording of Adverse Events

Assessment of Severity

- Mild: Awareness of sign or symptom, but easily tolerated and caused no interference with daily activities.
- Moderate: Discomfort enough to cause interference with daily activities.
- Severe: Incapacitating with inability to perform normal daily activities.

Causal Relationship to the Investigational Medicinal Product (IMP)
The investigator judged whether or not, in his/her opinion; the AE was associated with the study treatment.

- Probably: An AE, which might be due to the use of the drug. The relationship in time was suggestive (e.g. confirmed by dechallenge). An alternative explanation was less likely, e.g. concomitant drug(s), concomitant disease(s).
- Possibly: An AE, which might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), was inconclusive. The relationship in time was reasonable; therefore, the causal relationship could not be excluded.
- Unlikely: An AE for which an alternative explanation was more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggested that a causal relationship was unlikely.

Diagnosis
A diagnosis was to be recorded if available. If no diagnosis was available, each sign and symptom was be recorded as individual AE.

Outcome
Outcome of the AE had to be judged by the investigator by the following terms:

- Recovered
- Recovered with sequelae (if recovered with sequelae, sequelae to be specified)
- Not recovered
- Fatal

#### 9.5.1.3.4 Reporting of Adverse Events

Reporting of Adverse Events
All AEs, as defined above, that occurred in patients during the AE reporting period had to be reported in the AE section of the CRF, whether or not the event was assessed as related to the study drug. If the event was serious, the SAE report forms also had to be completed.

All AEs, spontaneously reported by the subject or reported in response to the open question from the study personnel: “Have you had any health problems since previous you were asked”: or revealed by observation or result from an investigation were collected and recorded in the CRF.

The following variables were recorded in the CRF for each AE; description, start and stop date, severity, SAE or not, causality rating, action taken and outcome of the AE.

The reporting of AE began after the start of study medication and lasted until the follow-up phone call was made 1 month after the operation day. All AEs that were not resolved at the last visit/last contact were to be followed up by the investigator until they were resolved or up to 6 months with recording in the CRF.

Reporting of Serious Adverse Events
SAEs were reported throughout the study including the follow-up period. The following variables were recorded in the CRF for each SAE; description, start and stop date, study medication, concomitant medication and disease, medical history, seriousness, causality and outcome.

All SAEs were reported to the sponsor’s designated safety partner within 24 hours after the investigator/sponsor became aware of it according to the separate Safety Management Plan.

All SAEs that were not resolved at the last visit were to be followed until they were resolved or up to 6 months.

Reporting of SUSARs
If the responsible investigator/sponsor regarded the SAE as being a SUSAR, it had to be reported within 24 hours of awareness to the sponsor’s designated partner, who was responsible for reporting SUSARs to the regulatory authorities and the IEC:

- Fatal or life-threatening SUSARs had to be reported to the sponsor’s designated partner within 24 hours and the IEC within 7 days after the principal investigator

became aware of the incident. Updates to complete the report had to be sent to the sponsor's designated partner within 48 hours.

- SUSARs which were not fatal or life-threatening had to be reported to the sponsor's designated partner within 24 hours and IEC within 15 days after the principal investigator became aware of the incident. Updates to complete the report had to be sent to the sponsor's designated partner as soon as possible.

All SUSARs had to be followed until they were resolved or up to 6 months.

#### 9.5.1.4 Safety – Clinical Laboratory Evaluation

Besides the biomarkers that were evaluated in this study primarily regarded as efficacy variables (see Sections 9.5.1.1 and 9.5.1.2 ), blood tests for safety included: $Mg^{2+}$, $K^{+}$, urea, myoglobin, ASAT, ALAT, bilirubin, ALP, GT, leukocytes, CRP, CK, Hb and thrombocytes (Table 1).

#### 9.5.1.5 Safety – Vital Sign Measurements

Vital signs were followed including continuous monitoring of blood pressure via an arterial catheter from arrival to the operating theatre until the patient left the ICU. Thereafter, blood pressure was measured daily non-invasively.

#### 9.5.1.6 Safety – Physical Examination

A physical examination was performed at baseline (before surgery).

### 9.5.2 Appropriateness of Measurements

CABG surgery may induce injury to the kidneys, heart and the brain. To estimate a possible organ-protective effect of ciclosporin, i.e. the efficacy in this study, a number of biomarkers were evaluated. P-CyC, P-creatinine, U-TIMP-2 and U-GFBP7 are markers of AKI (49, 50), CK MB and P-TnT are markers of cardiac injury (36, 37) and S-S 100 B is a marker of brain injury (51).

Besides conventional monitoring of AEs and SAEs throughout the study, several other safety measures were applied. Hourly diuresis was followed at the ICU together with the need for diuretics and i.v. fluids to maintain a satisfactory diuresis. All the renal biomarkers were immediately available for the clinician in charge for continuous evaluation of renal function. Other safety blood chemistry parameters included daily myoglobin, creatine kinase (CK), $Mg^{2+}$, $K^{+}$, urea levels, leukocytes, CRP and hepatic function tests. Vital signs were followed including continuous monitoring of blood pressure via an arterial catheter from arrival to the operating room until the patient left the ICU.

### 9.5.3 Pharmacokinetic Measurements

This study was not designed as a PK study. However, B-ciclosporin concentrations were measured in arterial blood samples collected immediately after administration of IMP and on Day 1.

In accordance with the study protocol, samples for clinical chemistry measurements were obtained on Days -1 to 4 (but not at the follow-up visit on Day 30 as incorrectly stated in the document 'Exploratory Graphical Analysis of the CiPRICS study' (Appendix 16.1.9).

The purpose of the PK analysis was to perform a graphical analysis of PK and clinical chemistry measurements obtained to explore:

- The PK characteristics of ciclosporin after i.v. administration.
- The longitudinal changes in clinical chemistry of interest.
- Potential relationships between ciclosporin exposure and changes in key clinical chemistry measurements (P-CyC, creatinine, CK MB, P-TnT and S-S 100 B).

The analysis was performed in the following steps:
1. Exploratory graphical analysis of the covariates, and the correlation between covariates in the analysis data set.
2. Exploratory graphical analysis of the ciclosporin plasma concentration vs time profiles in the analysis data set.
3. Calculation of the ciclosporin AUC for subjects receiving active treatment (ciclosporin).
4. Exploratory graphical analysis of the clinical chemistry measurements vs time profiles in the analysis data set.
5. Exploratory graphical analysis of the relationships between the ciclosporin concentration or AUC and the change in key clinical chemistry measurements.

In addition, in the exploratory graphical analysis of covariates, the univariate and multivariate covariate distributions were visualized to identify possible outliers and to explore the correlation structure.

Individual ciclosporin plasma concentration vs time profiles were plotted on linear-linear, logarithmic-linear, and logarithmic-logarithmic scales. The graphs were inspected for outliers, and differences between study groups (high vs low eGFR at baseline). A smooth was added to the plots when relevant.

Individual $AUC_{0\text{-}24h}$ was calculated for subjects receiving active treatment (ciclosporin). $AUC_{0\text{-}24h}$ was defined as the AUC from the first PK observation to the time of the third PK observation, which occurred about 24 hours after dosing. No attempts were made to include the AUC remaining after the third PK observation in the AUC calculations. The subjects with ciclosporin concentrations below the lower limit of quantification (LLOQ) in the third sample were assigned a ciclosporin concentration of 15 ng/mL (LLOQ/2). $AUC_{0\text{-}24h}$ was not computed for subjects who did not have at least 3 ciclosporin concentration measurements. The $AUC_{0\text{-}24h}$ calculations were done using a non-compartmental analysis (NCA) approach. Based on the calculated $AUC_{0\text{-}24h}$ and the administered dose, the individual clearance (CL) values were computed according to the following equation: $CL = Dose/ AUC_{0\text{-}24h}$

### 9.5.4 Other Measurements

All concomitant diseases were registered in the CRF before study start.

Besides the study events and assessments outlined in Table 1, all other necessary assessments were included in the routine care and were routinely registered in all cardiac surgery patient records in the department, e.g. documentation of thoracic drain bleeding at 12 hours post-operatively, total thoracic drain bleeding during ICU stay, transfusion, reoperation because of bleeding, stroke (transient or persistent), mediastinitis, atrial fibrillation, myocardial infarction (using department definition, ASAT >2.0 and ECG changes specific for ischaemia), post-

operative cardiac failure (using department definition, i.e. inotropes more than 24 hours postoperatively) and length of stay after surgery.

### 9.6 Data Quality Assurance

A record is kept of patients who were enrolled in the pre-trial screening, including also patients who were not enrolled in the study (i.e. patient screening log).

Case Report Form
After inclusion, a CRF was opened for the patient. The CRF was not added to the medical records. The study data should always be confidential. Medical journal data and other applicable data were entered into the CRF during the stay. After discharge from the hospital, all CRFs are stored in a locked room. Electronical datasets are stored on the hospital servers.

Individual patients cannot be identified from the presentation of data.

The data collected for each patient in the study were recorded in the same patient's unique CRF. The CRF was designed specifically for recording of the data in the current study. CRFs are in paper form.

The study patient forms are designed for each study patient. Study patients are identified as patient numbers that were given them after enrolment in the study. Every study patient has a unique study number.

All questions in the CRF had to be answered. If any question could not be answered, these fields were be completed by ND="Not done", NA="Not applicable", nk="not known".
The study patient data contained in medical records had to be consistent with the data in the CRF.

Monitoring
The purpose of the monitoring and quality control was to ensure the scientific integrity, the data quality, the safety and integrity of the participating subjects and that the study was compliant with the current version of the Declaration of Helsinki, ICH GCP and national regulations. The sponsor delegated the monitoring to FoU-centrum Skåne, an independent party, which performed on-site monitoring before, during, and after the study.

The monitoring activities included source data verification. To enable this, the monitor was given access to relevant study patient medical records. Before start of monitoring, the patient was informed and consent was given to this. Moreover, a secrecy undertaking had to be signed by the person responsible for the study patient medical records and the monitor.

FoU-centrum Skåne, which was delegated the monitoring function, ensured the following

- That study patient privacy and safety were met.
- The protocol was followed.
- The recruitment and inclusion of patients in the study were according to study plan.
- That correct data were collected in the study-developed CRF.
- That all AEs (except those that were normal clinical signs and symptoms due to the procedure of CABG according to the investigator) were reported according to LVFS 2011:19.

- The management of medicines was done in accordance with regulations for clinical trials, including storage, management and documentation.
- That access to the original data and study-related documents was available and that all study documents were archived according to regulations.
- That there were resources available for implementation of the study.
- That the trial was conducted according to regulations and guidelines, national and international.

The principal investigator/sponsor ensured that the monitor had access to the CRF, as well as original medical records of laboratory data, etc. to ensure that source data were relevant to the study, without compromising the patient privacy. The principal investigator was also aware that inspection by the authority could be implemented.

The study-specific details and extent of the monitoring activities are described in a monitoring plan by the sponsor.

Source Data Verification
Study patient data in the CRF were verified. The study patient data contained in medical records had to be consistent with the data written in the CRF but not vice versa. Study-specific data which were not relevant to study patient care and treatment could be written directly into the CRF and constitute the source data.

Record Keeping and Archiving
The principal investigator should keep the CRF and study patient identifier list, the original of study patient information and obtained consent for the study out of reach of unauthorised persons. Although patients in the study can be identified by those responsible for the study.

Study documents and source data should be filed for at least 10 years after the study report is written and submitted to the MPA.

Data Management
All study patient data were processed by the investigators named in the clinical study protocol. All processed data should be stored on the hospitals data servers with the same level of security as patient electronical records.

All deviations from the protocol were to be registered in the CRF.

## 9.7 Statistical Analysis Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical Plans

#### 9.7.1.1 General Approaches

Descriptive statistics was to be presented for all variables as appropriate. Continuous variables were to be summarised by descriptive statistics (sample size [n], mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum values). Categorical data were to be summarised by sample size (n), number and percentage of occurrences, and number of missing values (n).

All statistical tests were to be conducted at the two-sided 5% level unless otherwise specified. Where appropriate, model-based point estimates, together with their 95% confidence intervals (CIs) were to be presented along with the two-sided p-value for the test.

The SAP dated 28-Sep-2016 (based on blinded data) clarified that:

- t-test was to be used to assess group differences for continuous variables if not otherwise specified, Mann-Whitney U-test was to be performed to assess group differences when analysing ordinal variables and Fisher's exact test was to be used to assess group differences for dichotomous endpoints.
- Relative change from baseline was to be analysed by the means of linear mixed model with group and stratification variable as fixed factors to assess group differences.
- Linear mixed models were to be used to assess group differences when analysing repeated measures. Post-hoc tests could be performed where relevant.
- Some analyses were to be accompanied with a line graph depicting the randomised groups with 95% CI for the mean and the reference limits for the endpoint and some analyses were to be accompanied with a bar graph depicting the randomised groups with error bars.
- The linear mixed model analysis was to be performed with different covariance structures. For those models that converge, AIC (Akaike information criterion) was to be used to assess the best fit between models. The model with the smallest AIC was to be used. If linear mixed models did not converge using any covariance structure, repeated measures ANOVA (analysis of variance) or t-tests were to be performed.
- If assumptions for parametric analysis were clearly violated, data transformations or a non-parametric approach were to be applied.
- The exploratory analyses of the effects of ECC- and cross clamp duration on the primary objective, P-CyC and P-creatinine, were to be performed after delivery of the full statistical analysis report.

#### 9.7.1.2 Primary Efficacy Endpoint Methodology

The hypothesis in this study was that ciclosporin, administered as a single i.v. bolus dose preoperatively in CABG surgery, would reduce the level of renal dysfunction after this type of surgery.

The primary comparison was to investigate the difference in relative change in CyC from baseline to the third post-operative day between CicloMulsion® and placebo in the total intent-to-treat (ITT) population. However, in accordance with the statistical analysis plan (SAP), the modified ITT (mITT) population, defined as all patients treated, i.e. receiving the study drug and who did not fulfil any predefined eligibility violations was to be used.

According to the study protocol, the primary endpoint, change in P-CyC from baseline to the third post-operative day, was to be analysed using analysis of covariance (ANCOVA) including treatment and baseline P-CyC as explanatory variables. However, since the relative change from Day -1 to Day 3 is the primary efficacy variable, a mixed linear model was regarded more suitable as described in the SAP (Appendix 16.1.9). Two-sided p-values below 0.05 were to be considered to indicate statistically significant differences. The corresponding 95% two-sided CI for the difference was also to be constructed.

#### 9.7.1.3 Secondary Efficacy Endpoint and Safety Endpoint Methodology

The treatment difference between ciclosporin and placebo in secondary efficacy endpoints and safety biochemistry was to be tested.

Secondary endpoints were mainly to be analysed by using ANCOVA, following the same conventions as in the analysis of the primary endpoint.

The following secondary endpoints related to kidney function were defined in the SAP:

- P-CyC on Days -1, 1, 2, 3, 4
- P-CyC AUC on Days -1, 1, 2, 3, 4
- Relative change in P-creatinine from Day -1 to Day 3
- P-creatinine on Days -1, 1, 2, 3, 4
- P-creatinine AUC Days -1, 1, 2, 3, 4
- TIMP-2 IGFBP7 on Day 0 (before and at 4 and 12 hours after ECC surgery)
- U-albumin/creatinine ratio before and at 4 and 12 hours after ECC
- eGFR P-CyC on Days -1, 1, 2, 3, 4
- eGFR P-CyC/creatinine on Days -1, 1, 2, 3, 4
- eGFR based on P-creatinine ($eGFR_{MDRD}$) on Days -1, 1, 2, 3, 4
- RIFLE (based on creatinine) classifications 0, R (risk), I (injury) and F (failure) on Day 3
- RIFLE (based on eGFR) classifications 0, R (risk), I (injury) and F (failure) on Day 3 (52).

The following safety endpoints relating to AEs, SAEs and SUSARs were defined in the SAP:

- AEs on Days 0-4 presented as lowest level MedDRA term.
- SAEs and SUSARs on Days 0-30, i.e. during the whole study period, presented as lowest level MedDRA term.

The following biochemistry safety endpoints were defined in the SAP:

- P-$K^+$, P-$Mg^{2+}$, P-urea, P-myoglobin, P-CK, P-bilirubin, P-ASAT, P-ALAT, P-GT, P-ALP, P-CRP, B-leucocytes, B-haemoglobin and B-thrombocytes on Days -1, 1, 2, 3 and 4.

The following vital sign safety endpoints were defined in the SAP:

- Body temperature, and systolic and diastolic blood pressure on Days -1, 1, 2, 3 and 4.

Other safety endpoint defined in the SAP:

- Leg wound infection on Day 4.

Exploratory endpoint defined in the SAP:
Two subgroups, patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$, were to be analysed according to the same plan as outlined for the primary objective.

Covariates and factors for the primary endpoint defined in the SAP:

- The stratification variable, i.e. pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ used in the randomisation.

Covariates and factors for the continuous secondary endpoints defined in the SAP:

- The baseline variable of the endpoint.
- The stratification variable, i.e. pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ used in the randomisation.

Covariates and factors for the secondary endpoints and clinical outcomes defined in the SAP:

- The baseline variable of the endpoint.

#### 9.7.1.4 Pharmacokinetic and Pharmacodynamic Endpoints Methodology

There were no pharmacokinetic or pharmacodynamic endpoints in this study.

#### 9.7.1.5 Other Endpoint Methodology

Exploratory analyses were to be performed of several quality indices including e.g. time on mechanical ventilator, time in ICU, extent of bleeding, incidence of atrial fibrillation, time on ECC and immunologic parameters.

### 9.7.2 Determination of Sample Size

It was estimated that approximately 170 patients were to be enrolled to have 150 evaluable patients (defined as per protocol [PP] study patients in the clinical study protocol) with approximately 75 patients in each treatment arm. Approximately 50 patients were to be stratified to a pre-defined subgroup of patients with an eGFR of 15-59 mL/min/1.73 $m^2$, and the rest stratified to a subgroup of patients with an eGFR of 60-90 mL/min/1.73 $m^2$.

The relative difference between groups in change from baseline CyC to the third post-operative day was to serve as primary end-point. In a previous study (5), the response within each subject group was normally distributed with a standard deviation (SD) of 27%, Figure 2. With 75 study patients receiving the active substance and 75 study patients receiving placebo, it was estimated that we would be able to detect a true difference in the primary end-point of -13% or 13% (i.e. half a SD) with a power of 0.8. The Type I error probability associated with this test, i.e. that the population means of the experimental and control groups are equal, is 0.05. The study was to continue until the planned number of study patients had finalised the protocol.

| | Valid N | Mean | Std.Dev. | Change from baseline | SD for change |
|---|---|---|---|---|---|
| CyC preop | 70 | 1.53 | 0.31 | | |
| CyC Day1 | 70 | 1.53 | 0.53 | 98.9% | 22.8% |
| CyC Day2 | 69 | 1.97 | 0.71 | 127.3% | 34.5% |
| CyC Day3 | 70 | 1.98 | 0.67 | 128.0% | 27.8% |
| CyC Day4 | 69 | 1,81 | 0.66 | 118.1% | 29.2% |

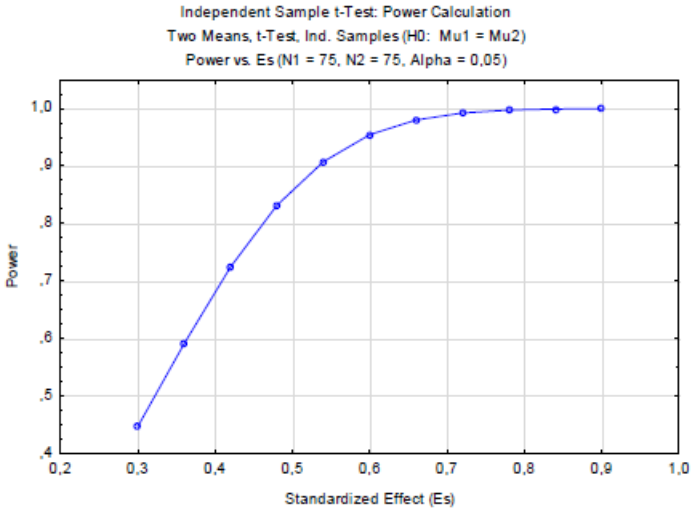


**Figure 2: Power vs standardised effect**
Data based on the parameters from a previous study (5) for Day 3 after surgery.

Table 2 shows the outcome of a sensitivity analysis at different power levels on Day 3.

**Table 2: Sensitivity analysis at different power levels on Day 3 in a previous study**

| Power | Change in CyC from baseline |
|---|---|
| 70% | 11.4% |
| 80% | 12.8% |
| 90% | 15.0% |
| 95% | 16.5% |

## 9.8 Changes in the Conduct of the Study or Planned Analyses

### 9.8.1 Changes in the Conduct of the Study

There was one amendment to the study protocol, dated 02-May-2016 (i.e. before unblinding). The major changes introduced in this amendment were:

- Based on the patient population available at the site, the size of the stratum was changed from “at least 60” to “approximately 50” patients from the group with an eGFR of 15-59 mL/min/1.73 $m^2$.
- Exploratory immunologic biomarkers were no longer included as a secondary safety endpoint.
- The flow chart was updated to show that blood samples for exploratory immunologic biomarkers were to be collected on Day 0 and Day 1.

### 9.8.2 Changes in the Planned Analysis

The following changes in the planned analyses were introduced in the protocol amendment dated 02-May-2016 (i.e. before unblinding):

- It was clarified that the primary comparison (difference in CyC change from baseline to the third post-operative day between ciclosporin and placebo) was to be performed on the ITT population and not the modified ITT population (mITT). (This was later changed back to the mITT in the SAP dated 28-Sep-2016.)
- It was clarified that the primary endpoint to be analysed using ANCOVA was the change, and not the relative change, in CyC from baseline to the third post-operative day. (This was later changed back to the relative change in the SAP dated 28-Sep-2016. For further changes, see below.)
- It was omitted that type I error would be protected by performing a fixed-sequence multiple-testing procedure.
- The following was added: "The treatment difference between CicloMulsion® and placebo in secondary efficacy endpoints and safety biochemistry (including but not limited to the Endpoints described in Section 4.4 of the study protocol) will be tested."
- It was omitted that if the primary comparison was statistically significant, the treatment difference in a number of secondary analyses of renal function, cardiac injury and cerebral injury were to be tested in a specified order, where each step was only to be considered confirmatory providing the that the previous step(s) was/were successful and if any of the previous steps were not successful, the analysis of the following steps were to be considered descriptive.
- It was omitted that exploratory endpoints should be analysed using ANCOVA.

### 9.8.3 Changes Following Study Unblinding and Post-hoc Analyses

Unblinding of data took place on 04-Oct-2016.

Exploratory analyses of how ECC- and cross clamp duration may affect the result of the primary objective have not been performed. However, the actual durations of the ECC and aortic cross clamp are presented (see Section 11.3.3).

AE tables in the Statistical Report in Appendix 16.1.9 were supplemented with conventional AE tables presenting percentage of patients reporting AEs based on all patients exposed to IMP (presented in Section 12.1 and Section 14.3 of this document).

Based on the outcome of the study, a retrospective post-hoc follow-up safety analysis was performed of plasma creatinine at 1-6 months after surgery. Retrospective data from patient medical records were used for this purpose.

# 10 STUDY PATIENTS

## 10.1 Disposition of Patients

A total of 446 patients were assessed for eligibility of whom 155 were randomised (see Figure 3 for reasons for exclusion). All randomised patients received IMP (76 patients allocated to the ciclosporin group and 79 allocated to the placebo group).

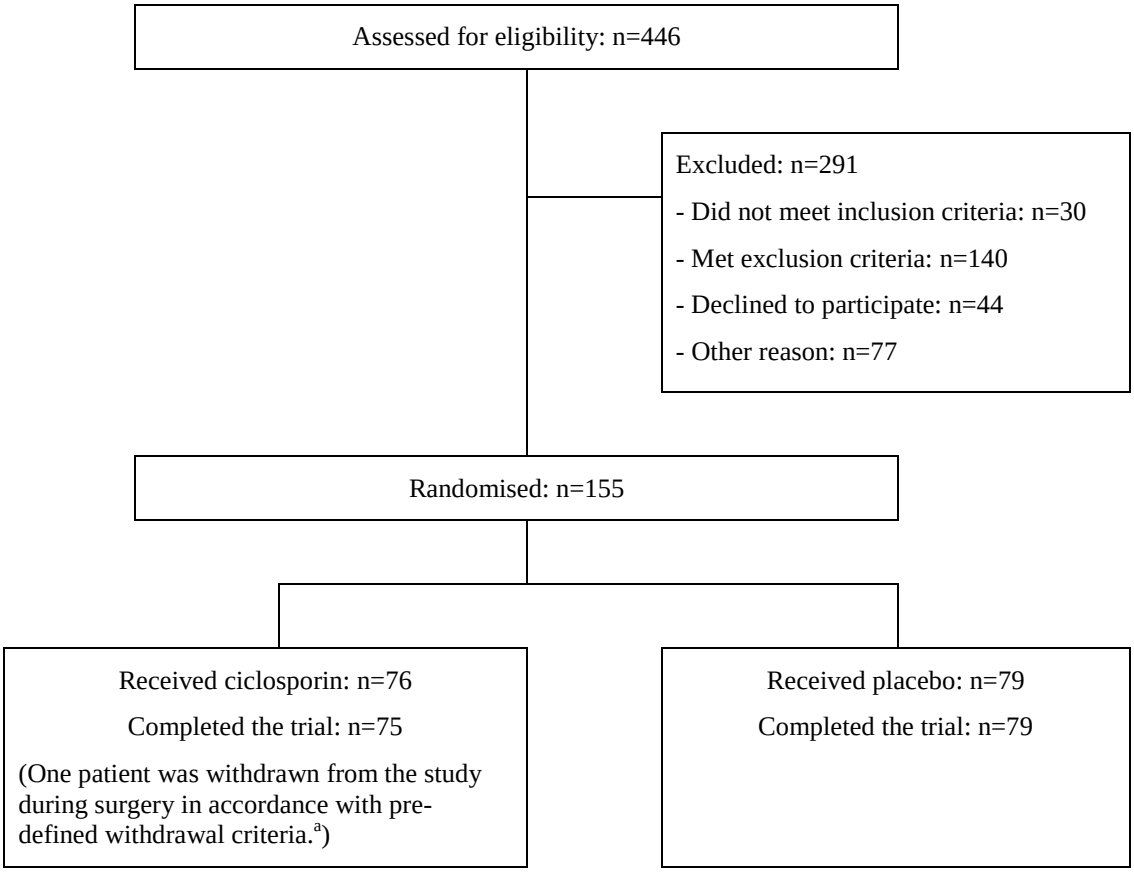


**Figure 3: Disposition of patients**

[a] During surgery (after IMP dosing), Patient No. [Redacted] in the ciclosporin group was found to need additional surgery besides CABG surgery (operated also with an aortic valve) and was withdrawn from the study in accordance with the pre-defined withdrawal criteria.

## 10.2 Protocol Deviations

No major protocol deviations were reported (all patients 100% of the intended dose and no other major protocol deviations were reported).

## 10.3 Data Sets Analysed

The strictly defined ITT population also includes patients that consented to the study but never underwent the surgical procedures or were treated with the IMP. According to the SAP, the Full Analysis Set (FAS) would be the modified ITT (mITT) population, defined as all patients treated, i.e. receiving the study drug and who did not fulfil any predefined eligibility violations.

Safety Analysis Set
All 76 patients allocated to ciclosporin and all 79 patients allocated to placebo received the intended IMP and are included in the safety analysis set, Figure 4.

Efficacy Analysis Set (Identical to the FAS, mITT Population and the PP Population)
Patient No. [Redacted] in the ciclosporin group, who was found during surgery (after IMP dosing) to need additional surgery besides CABG (operated also with an aortic valve) is excluded from the efficacy analysis set. Thus, 75 patients in the ciclosporin group are included in the efficacy analysis set.

All 79 patients who received placebo are included in the efficacy analysis set (of whom 1 patient had no P-CyC value from Day 3, please see Section 11.2.2 for handling of missing data).

Based on blinded data, it was concluded that the per-protocol (PP) population is identical to the mITT population as no major protocol deviations were reported. (For a patient to be considered compliant and to be included in the PP analysis, he/she had to have received at least 90% of the intended dose and not have any major protocol deviations.)

PK Analysis Set
All 76 patients who received ciclosporin are included in the PK analysis set, i.e. the patient who was excluded from the efficacy analyses due to the need for additional surgery is included in the PK analysis set.

Of the 79 patients who received placebo, one patient (No. [Redacted]) was incorrectly recorded to have received ciclosporin. At the PK analyses, the patient was found to have ciclosporin levels below the LLOQ and the patient was therefore excluded from the PK analyses. Thus, 78 patients in the placebo group are included in the PK analysis set.

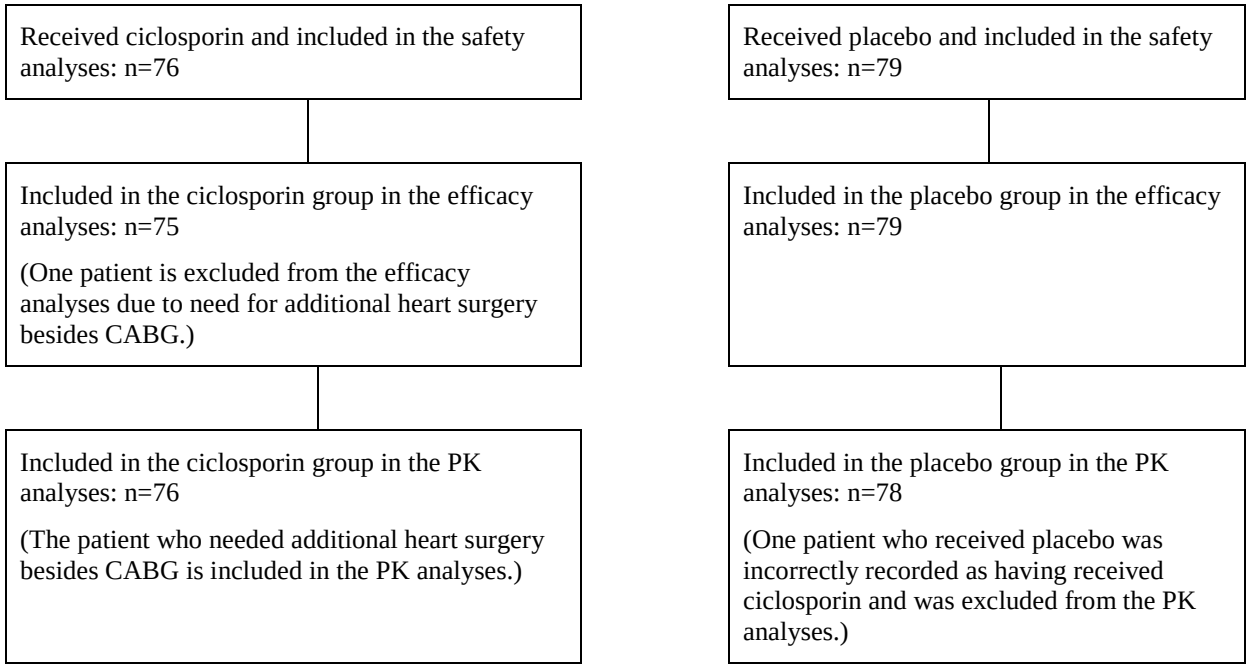


**Figure 4: No. of patients included in the safety, efficacy and PK analysis datasets**

## 10.4 Demographic and Other Baseline Characteristics

### 10.4.1 Demographic and Other Baseline Characteristics Including Concurrent/Previous Illnesses and Concomitant Treatments

Gender, age, height and weight were similar between the treatment groups. Overall, 82.7% of the patients in the ciclosporin group and 86.1% in the placebo group were men. The mean age was 69.7 years (range: 47 to 87 years) in the ciclosporin group and 69.1 years (range: 36 to 86 years) in the placebo group. The mean weight was 82.3 kg (range: 55 to 122 kg) in the ciclosporin group and 86.1 kg (range: 61 to 122 kg) in the placebo group.

Mean systolic and diastolic blood pressure (ciclosporin: 134.4/72.5 mmHg; placebo: 137.4/74.9 mmHg) and percentage of patients with hypertension (ciclosporin: 72.0%; placebo: 78.5%) was similar between the treatment groups at baseline.

Some differences were observed in concurrent illnesses and concomitant treatments between the treatment groups (Table 3), however, these are not believed to have had any major clinical impact on the overall conclusions of the study.

**Table 3: Demographics and other baseline characteristics including concurrent and previous illnesses, and concomitant medications**

| | | Ciclosporin N=75 | Placebo N=79 |
|---|---|---|---|
| Gender (male) | n (%) | 62 (82.7%) | 68 (86.1%) |
| Age (years) | Mean (SD)<br>Median (range) | 69.7 (8.1)<br>70.0 (47.0–87.0) | 69.1 (8.3)<br>69.0 (36.0–86.0) |
| Height (cm) | Mean (SD)<br>Median (range) | 174.1 (8.6)<br>176.0 (152.0–193.0) | 174.7 (7.9)<br>176.0 (150.0–189.0) |
| Weight (kg) | Mean (SD)<br>Median (range) | 82.3 (13.3)<br>82.0 (55.0–122.0) | 86.1 (14.7)<br>87.0 (61.0–122.0) |
| Systolic blood pressure (mmHg) | Mean (SD)<br>Median (range) | 134.4 (17.4)<br>135.0 (104.0–187.0) | 137.4 (18.5)<br>136.0 (105.0–200.0) |
| Diastolic blood pressure (mmHg) | Mean (SD)<br>Median (range) | 72.5 (9.1)<br>73.0 (50.0–94.0) | 74.9 (8.1)<br>75.0 (60.0–95.0) |
| Hypertension | n (%) | 54 (72.0) | 62 (78.5) |
| Pre-op eGFR MDRD (mL/min/1.73 $m^2$) | Mean (SD)<br>Median (range) | 72.1 (15.6)<br>71.7 (32.9–105.3) | 71.1 (17.0)<br>72.3 (37.0–101.8) |
| Pre-op eGFR CKD-EPI (mL/min/1.73 $m^2$) | Mean (SD)<br>Median (range) | 69.0 (20.0)<br>69.4 (24.4–110.5) | 65.1 (18.9)<br>65.7 (16.0–119.0) |
| Chronic heart failure | n (%) | 10 (13.3) | 15 (19.0) |
| LVEF <30% | n (%) | 2 (2.7) | 3 (3.8) |
| LVEF 30–50% | n (%) | 9 (12.0) | 14 (17.7) |
| LVEF >50% | n (%) | 62 (82.7) | 59 (74.7) |
| COPD | n (%) | 4 (5.3) | 0 (0.0) |
| Diabetes | n (%) | 14 (18.7) | 26 (32.9) |
| Peripheral vascular disease | n (%) | 4 (5.3) | 5 (6.3) |
| Previous cardiovascular infarction | n (%) | 6 (8.0) | 5 (6.3) |
| Thyroid disease | n (%) | 3 (4.0) | 8 (10.1) |
| Chronic atrial fibrillation | n (%) | 1 (1.3) | 4 (5.1) |
| Paroxysmal atrial fibrillation | n (%) | 5 (6.7) | 6 (7.6) |
| Diuretics | n (%) | 10 (13.3) | 23 (29.1) |
| ACE inhibitor/ARB | n (%) | 59 (78.7) | 60 (76.0) |
| Beta-blocker | n (%) | 62 (82.7) | 64 (81.0) |
| Statins | n (%) | 69 (92.0) | 76 (96.2) |
| Warfarin | n (%) | 1 (1.3) | 2 (2.5) |
| ASA | n (%) | 68 (90.7) | 73 (92.4) |
| Clopidrogel/prasurgel | n (%) | 5 (6.7) | 3 (3.8) |
| Antithrombotic treatment | n (%) | 16 (21.3) | 20 (25.3) |
| Antibiotics | n (%) | 1 (1.3) | 4 (5.1) |

Source: Table 1 in the Statistical Report (Appendix 16.1.9)
ACE: angiotensin-converting enzyme/ inhibitor; ARB: angiotensin-receptor blocker; CKD-EPI: Chronic Kidney Disease - Improved Prediction Equations (method to estimate GFR); COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction
Note: Patient No. [Redacted], included in the safety analyses but not in the efficacy analyses (due to additional surgery besides than CABG), is not included in this table, see Appendix 16.2.4 for demographics and baseline data collected from this patient.

## 10.5 Measurements of Treatment Compliance

The IMP, i.e. active study drug or placebo, was given as a single i.v. dose after anaesthesia induction.

For a patient to be considered as compliant and to be included in the per protocol analysis, he/she had to have received at least 90% of the intended dose. It was confirmed by the

Investigator that all patients received 100% of the dose. The analysis of the ciclosporin plasma concentration-time profiles confirmed that all patients in the ciclosporin group had adequate exposure of ciclosporin except for one patient who correctly received placebo but for whom the IMP number was incorrectly recorded (a number corresponding to ciclosporin). This patient was consequently excluded from the PK analyses.

None of the patients in the placebo group had detectable ciclosporin plasma concentrations.

### 10.6 Extent of Exposure

All 155 randomised patients received a single dose of IMP (ciclosporin: 76 patients; placebo: 79).

Ciclosporin or placebo was administered as a single i.v. bolus dose injection, 0.5 mL/kg body weight. This corresponds to a dose of 2.5 mg/kg ciclosporin if the study patient was randomised to active study drug.

# 11 EFFICACY AND OTHER EVALUATIONS

## 11.1 Efficacy Results

### 11.1.1 Primary Efficacy Endpoint

The hypothesis was that ciclosporin, administered as a single i.v. bolus dose preoperatively in CABG surgery, would reduce the level of renal dysfunction. Compared to placebo, ciclosporin was expected to reduce the concentration of the AKI marker P-CyC. The primary comparison was to investigate the relative difference in P-CyC change from baseline (Day -1) to the third post-operative day (Day 3) between ciclosporin and placebo.

The primary endpoint was not met as a larger increase in P-CyC was observed in the ciclosporin group (mean: 36.4%) than in the placebo group (mean: 15.9%), Table 4. The efficacy analysis of relative change from Day -1 to Day 3 based on LN (natural logarithm)-transformed values are shown in Table 5. The treatment difference in relative change from Day -1 to Day 3 based on LN-transformed values (mean difference: 0.158; standard error [SE]: 0.036) was statistically significant in favour of placebo (p<0.001), Table 5.

**Table 4: Primary efficacy endpoint, descriptive analysis: relative change[a] in P-CyC from Day -1 to Day 3**

| Group | n | Mean (SD) | Median (Q1–Q3) | Min-Max | N missing |
|---|---|---|---|---|---|
| Ciclosporin | 75 | 136.38 (35.64) | 128.72 (110.83–151.02) | 79.28–258.25 | 0 |
| Placebo | 78 | 115.87 (30.82) | 109.13 (100.00–119.51) | 81.10–284.07 | 1 |

[a] quotient of Day 3 value divided by Day -1 value multiplied by 100
Source: Table 2a in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

**Table 5: Primary efficacy endpoint based on LN-transformed values of the relative change (multiplied by 100) in P-CyC from Day -1 to Day 3**

| | Est (SE) | 95% CI | p-value |
|---|---|---|---|
| Ciclosporin | 4.885 (0.026) | 4.833–4.937 | |
| Placebo | 4.727 (0.026) | 4.676–4.778 | |
| Treatment difference (Ciclosporin – Placebo) | 0.158 (0.036) | 0.087-0.230 | <0.001[a, b, c] |

Est: estimate
Source: Tables 3a and 3b in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154
[a] Linear mixed model with group and stratification variable as fixed factors
[b] LN transformation
[c] Residuals not symmetric

**Sensitivity Analysis of the Primary Endpoint**
The sensitivity analysis (Table 6 and Table 7) resulted in almost identical results as the analysis of the primary endpoint presented in Table 4 and Table 5. For further details on the sensitivity analysis, see Table 3c in the Statistical Report in Appendix 16.1.9).

**Table 6: Primary efficacy endpoint, descriptive analysis: relative change (multiplied by 100) in P-CyC from Day -1 to Day 3. Sensitivity analysis.**

| Group | n | Mean (SD) | Median (Q1–Q3) | Min-Max | N missing |
|---|---|---|---|---|---|
| Ciclosporin | 75 | 136.38 (35.64) | 128.72 (110.83–151.02) | 79.28–258.25 | 0 |
| Placebo | 79 | 115.80 (30.63) | 109.16 (100.00–119.51) | 81.10–284.07 | 0 |

Source: Table 2b in the Statistical Report (Appendix 16.1.9)
N=154

**Table 7: Primary efficacy endpoint: treatment difference in relative change in P-CyC from Day -1 to Day 3 based on LN-transformed values. Sensitivity analysis.**

| | Est (SE) | 95% CI | p-value |
|---|---|---|---|
| Ciclosporin | 4.885 (0.026) | 4.833–4.937 | |
| Placebo | 4.726 (0.026) | 4.676–4.777 | |
| Treatment difference (Ciclosporin – Placebo) | 0.159 (0.036) | 0.087-0.230 | <0.001[a, b, c] |

Source: Tables 3c and 3d in the Statistical Report (Appendix 16.1.9)
N=154
[a] Linear mixed model with group and stratification variable as fixed factors
[b] LN transformation
[c] Residuals not symmetric

### 11.1.2 Secondary Efficacy Endpoints

#### 11.1.2.1 Secondary Efficacy Endpoints – Kidney Function

**P-CyC Concentrations on Days -1, 1, 2, 3, 4**

The mean P-CyC concentration was 1.13 mg/L in the ciclosporin group and 1.18 mg/L in the placebo group on Day -1 (normal range: 0.84-1.25 mg/L). The highest mean P-CyC concentrations were observed on Day 3 in both groups (ciclosporin: 1.57 mg/L; placebo: 1.36 mg/L), Table 8.

**Table 8: P-CyC concentrations on Days -1, 1, 2, 3 and 4**

| | | Ciclosporin | Placebo |
|---|---|---|---|
| Day -1 | Mean (SD), (mg/L)<br>Median (range), (mg/L)<br>n | 1.13 (0.30)<br>1.07 (0.76–2.21)<br>75 | 1.18 (0.31)<br>1.10 (0.75–2.57)<br>79 |
| Day 1 | Mean (SD), (mg/L)<br>Median (range), (mg/L)<br>n | 1.08 (0.36)<br>1.01 (0.54–2.84)<br>75 | 1.06 (0.38)<br>0.96 (0.52–2.94)<br>79 |
| Day 2 | Mean (SD), (mg/L)<br>Median (range), (mg/L)<br>n | 1.48 (0.64)<br>1.31 (0.76–4.32)<br>75 | 1.33 (0.48)<br>1.19 (0.69–3.51)<br>78 |
| Day 3 | Mean (SD), (mg/L)<br>Median (range), (mg/L)<br>n | 1.57 (0.69)<br>1.34 (0.81–4.64)<br>75 | 1.36 (0.51)<br>1.19 (0.78–3.66)<br>78 |
| Day 4 | Mean (SD), (mg/L)<br>Median (range), (mg/L)<br>n | 1.51 (0.79)<br>1.18 (0.81–5.18)<br>75 | 1.32 (0.45)<br>1.22 (0.81–3.55)<br>78 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in LN-transformed values of P-CyC was 0.001 in favour of placebo on Days 1-4 (combined), for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**P-CyC $AUC_{Day-1\ to\ Day\ 4}$**
The mean P-CyC $AUC_{Day-1\ to\ Day\ 4}$ (in mg/L x h), was 135.8 in the ciclosporin group and 127.9 in the placebo group, Table 9.

**Table 9: P-CyC $AUC_{Day-1\ to\ Day\ 4}$**

| | Ciclosporin | Placebo |
|---|---|---|
| Mean (SD), (mg/L x h) | 135.80 (42.93) | 127.85 (34.02) |
| Median (range), (mg/L x h) | 124.92 (87.72–325.20) | 117.84 (81.12–296.16) |
| n | 75 | 79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in LN-transformed values of P-CyC $AUC_{Day-1\ to\ Day\ 4}$ was 0.108, see Table 5a in the Statistical Report in Appendix 16.1.9.

**P-creatinine Concentrations on Days -1, 1, 2, 3 and 4**
The mean P-creatinine concentration was 89.3 µmol/L in the ciclosporin group and 91.9 µmol/L in the placebo group on Day -1 (normal range: 60-105 µmol/L). The highest (worst) mean P-creatinine concentration was observed on Day 3 in the ciclosporin group (123.9 µmol/L) and on Day 2 in the placebo group (107.9 µmol/L), Table 10.

**Table 10: P-creatinine concentrations on Days -1, 1, 2, 3 and 4**

| | P-creatinine (µmol /L) | Ciclosporin | Placebo |
|---|---|---|---|
| Day -1 | Mean (SD) | 89.25 (19.36) | 91.94 (19.13) |
| | Median (range) | 86.0 (59–158) | 91.0 (57–157) |
| | n | 75 | 79 |
| Day 1 | Mean (SD) | 91.80 (23.60) | 88.61 (23.18) |
| | Median (range) | 86.0 (51–163) | 83.0 (48–160) |
| | n | 75 | 79 |
| Day 2 | Mean (SD) | 121.97 (48.10) | 107.92 (40.88) |
| | Median (range) | 109.0 (59–311) | 99.0 (59–309) |
| | n | 75 | 79 |
| Day 3 | Mean (SD) | 123.87 (55.85) | 106.25 (49.35) |
| | Median (range) | 106.0 (48–377) | 94.0 (54–383) |
| | n | 75 | 79 |
| Day 4 | Mean (SD) | 112.47 (56.71) | 102.10 (48.06) |
| | Median (range) | 93.0 (50–411) | 91.0 (55–368) |
| | n | 75 | 79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in LN-transformed values of P-creatinine was <0.001 (Days 1-4 combined) in favour of placebo, for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**Relative Change in P-Creatinine from Day -1 to Day 3**
The mean increase in P-creatinine from Day -1 to Day 3 was 38.6% in the ciclosporin group vs 15.8% in the placebo group, for further details see Table 4 in the Statistical Report (Appendix 16.1.9).

The treatment difference in LN-transformed value of relative change in P-creatinine from Day -1 to Day 3 was in favour of placebo (p<0.001), see Table 5a in the Statistical Report in Appendix 16.1.9.

**P-Creatinine $AUC_{Day\text{-}1\ to\ Day\ 4}$**

The mean P-creatinine $AUC_{Day\text{-}1\ to\ Day\ 4}$ (measured as µmol/L x h), was 10524 in the ciclosporin group and 9595 in the placebo group, for further details see Table 4 in the Statistical Report (Appendix 16.1.9).

The higher P-creatinine concentrations in the ciclosporin group as compared to the placebo group are in agreement with the results of the primary efficacy variable, i.e. a worsening in the renal function when the patients received ciclosporin.

The p-value for the treatment difference in LN-transformed values of P-creatinine $AUC_{Day\text{-}1\ to\ Day\ 4}$ was 0.044, see Table 5a in the Statistical Report in Appendix 16.1.9.

**TIMP-2 IGFBP7 before and at 4 and 12 Hours after ECC**

The mean TIMP-2 IGFBP7 concentrations (measured in $[ng/mL]^2/1000$) decreased from 0.47 at before ECC to 0.18 at 12 hours after ECC in the ciclosporin group and from 0.57 to 0.15 in the placebo group, Table 11. The normal range of TIMP-2 IGFBP7 is 0.04-2.22 $(ng/mL)^2/1000$.

**Table 11: TIMP-2 IGFBP7 before and at 4 and 12 hours after ECC surgery**

| | TIMP-2 IGFBP7 $(ng/mL)^2/1000$ | Ciclosporin | Placebo |
|---|---|---|---|
| Baseline | Mean (SD)<br>Median (range)<br>n | 0.47 (0.51)<br>0.38 (0.03–3.54)<br>74 | 0.57 (0.59)<br>0.33 (0.02–2.52)<br>79 |
| 4 hours after ECC | Mean (SD)<br>Median (range)<br>n | 0.21 (0.35)<br>0.12 (0.02–2.00)<br>75 | 0.18 (0.34)<br>0.10 (0.02–2.25)<br>79 |
| 12 hours after ECC | Mean (SD)<br>Median (range)<br>n | 0.18 (0.21)<br>0.12 (0.02–1.30)<br>75 | 0.15 (0.12)<br>0.12 (0.02–0.62)<br>79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in LN-transformed values of TIMP-2 IGFBP7 was 0.254 (combined), for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**U-Albumin/creatinine ratio before and at 4 and 12 Hours after ECC)**

The mean U-albumin/creatinine ratio was lower in the ciclosporin group (mean: 2.3; SD: 5.4) than in the placebo group (mean: 8.2; SD: 35.5) at baseline (normal range: <3.0). However, it is difficult to draw any firm conclusions as a few high values may have influenced the results, which is reflected by the median values which were identical (0.85) in the two treatment groups. At 4 hours, this ratio was higher in the ciclosporin group (mean: 11.5; SD: 27.5) than in the placebo group (mean: 7.6; SD: 8.9), but median values were similar (ciclosporin: 3.2; placebo: 3.8). At 12 hours, the U-albumin/creatinine ratio was similar between the treatment groups (ciclosporin, mean: 7.1, SD: 11.2; placebo, mean: 7.0, 9.8), for further details see Table 4 in the Statistical Report (Appendix 16.1.9).

The p-value for the treatment difference in LN-transformed values of U-albumin/creatinine ratio was 0.709 (combined), for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**eGFR Based on P-CyC on Days -1, 1, 2, 3 and 4**

The mean eGFR based on P-CyC was 68.4 mL/min/1.73 $m^2$ in the ciclosporin group and 65.2 mL/min/1.73 $m^2$ in the placebo group on Day -1. The lowest (worst) mean eGFR based on P-CyC was observed on Day 3 in both groups and was lower in the ciclosporin group than in the placebo group (ciclosporin: 50.2 mL/min/1.73 $m^2$; placebo: 57.2 mL/min/1.73 $m^2$), Table 12.

**Table 12: eGFR based on P-CyC on Days -1, 1, 2, 3 and 4**

| | **$eGFR_{P\text{-}CyC}$** (mL/min/1.73 $m^2$) | **Ciclosporin** | **Placebo** |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 68.35 (19.62)<br>67.43 (24.38–110.50)<br>75 | 65.20 (18.91)<br>65.29 (21.07–118.90)<br>79 |
| Day 1 | Mean (SD)<br>Median (range)<br>n | 74.01 (23.88)<br>73.05 (17.80–118.81)<br>75 | 76.41 (24.82)<br>79.49 (17.62–142.74)<br>79 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 53.35 (22.09)<br>51.77 (10.01–109.89)<br>75 | 59.05 (21.67)<br>59.24 (13.93–123.95)<br>79 |
| Day 3 | Mean (SD)<br>Median (range)<br>n | 50.18 (21.81)<br>49.93 (9.27–106.64)<br>75 | 57.22 (21.15)<br>59.62 (13.18–116.59)<br>78 |
| Day 4 | Mean (SD)<br>Median (range)<br>n | 53.95 (22.14)<br>54.92 (8.01–106.64)<br>75 | 58.07 (20.75)<br>57.99 (13.72–113.25)<br>79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in eGFR based on P-CyC was 0.005 in favour of placebo on Days 1-4 (combined), for further details see the Statistical Report in Appendix 16.1.9.

**eGFR Based on P-CyC/P-Creatinine on Days -1, 1, 2, 3 and 4**

The mean eGFR based on P-CyC/P-creatinine was 71.4 mL/min/1.73 $m^2$ in the ciclosporin group and 69.0 mL/min/1.73 $m^2$ in the placebo group on Day -1. The lowest (worst) mean eGFR based on P-CyC/P-creatinine was observed on Day 3 (ciclosporin group) and Day 2 (placebo group) and was lower in the ciclosporin group than in the placebo group (ciclosporin: 53.7 mL/min/1.73 $m^2$; placebo: 61.9 mL/min/1.73 $m^2$), Table 13.

**Table 13: eGFR based on P-CyC/P-creatinine on Days -1, 1, 2, 3 and 4**

| | **$eGFR_{P\text{-}CyC/P\text{-}creatinine}$** (mL/min/1.73 $m^2$) | **Ciclosporin** | **Placebo** |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 71.38 (17.03)<br>71.94 (27.77–101.99)<br>75 | 68.99 (17.48)<br>70.38 (29.61–106.58)<br>79 |
| Day 1 | Mean (SD)<br>Median (range)<br>n | 74.03 (21.10)<br>75.69 (25.45–114.01)<br>75 | 77.04 (22.31)<br>81.63 (24.40–135.27)<br>79 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 55.10 (21.19)<br>54.04 (11.37–105.16)<br>75 | 61.89 (21.44)<br>63.59 (18.78–117.94)<br>79 |
| Day 3 | Mean (SD)<br>Median (range)<br>n | 53.68 (22.12)<br>53.89 (10.08–100.35)<br>75 | 61.96 (21.78)<br>63.21 (14.05–111.81)<br>79 |
| Day 4 | Mean (SD)<br>Median (range)<br>n | 58.99 (22.63)<br>62.80 (8.85–101.83)<br>75 | 63.67 (21.46)<br>65.58 (14.39–108.20)<br>79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in eGFR based on P-CyC/P-creatinine was <0.001 in favour of placebo on Days 1-4 (combined), for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**eGFR Based on Creatinine ($eGFR_{MDRD}$) on Days -1, 1, 2, 3 and 4**

The mean $eGFR_{MDRD}$ was 73.1 mL/min/1.73 $m^2$ in the ciclosporin group and 71.7 mL/min/1.73 $m^2$ in the placebo group on Day -1. The lowest mean $eGFR_{MDRD}$ was observed on Day 2 in both groups and was lower in the ciclosporin group than in the placebo group (ciclosporin: 55.9 mL/min/1.73 $m^2$; placebo: 63.8 mL/min/1.73 $m^2$), Table 14.

**Table 14: $eGFR_{MDRD}$ on Days -1, 1, 2, 3 and 4**

| | **$eGFR_{MDRD}$** (mL/min/1.73 $m^2$) | **Ciclosporin** | **Placebo** |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 73.09 (16.09)<br>72.08 (32.88–110.92)<br>75 | 71.67 (16.71)<br>71.65 (37.04–105.65)<br>79 |
| Day 1 | Mean (SD)<br>Median (range)<br>n | 72.35 (18.92)<br>72.48 (31.30–120.87)<br>75 | 76.58 (20.95)<br>79.50 (30.55–125.26)<br>79 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 55.92 (18.94)<br>55.71 (14.78–89.58<br>75 | 63.77 (20.50)<br>65.14 (17.64–108.89)<br>79 |
| Day 3 | Mean (SD)<br>Median (range)<br>n | 56.77 (21.23)<br>57.57 (13.42–113.67)<br>75 | 66.67 (22.17)<br>68.84 (13.77–115.98)<br>79 |
| Day 4 | Mean (SD)<br>Median (range)<br>n | 63.38 (21.68)<br>66.78 (12.14–108.44)<br>75 | 69.86 (23.16)<br>69.86 (14.42–123.14)<br>79 |

Source: Table 4 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

The p-value for the treatment difference in $eGFR_{MDRD}$ was 0.001 in favour of placebo on Days 1-4 (combined), for further details see Table 5a in the Statistical Report in Appendix 16.1.9.

**RIFLE Classification on Day 3 Based on Creatinine**
When the RIFLE classification was based on creatinine, 52 patients (69.3%) in the ciclosporin group vs 72 patients (91.1%) in the placebo group did not fulfil the RIFLE criteria for risk of acute renal failure (category 0) on Day 3.

On Day 3, 15 patients (20.0%) in the ciclosporin group vs 3 patients (3.8%) in the placebo group fulfilled the RIFLE criteria for risk (R) of acute renal failure, 5 patients (6.7%) in the ciclosporin group vs 2 (2.5%) in the placebo group fulfilled the criteria for injury (I) and 3 patients (4.0%) in the ciclosporin group vs 2 (2.5%) in the placebo group fulfilled the criteria for failure (F) classification (the worst category of R, I and F), Table 15.

**Table 15: Number and percentage of patients by RIFLE classification on Day 3 (based on creatinine)**

| | **Ciclosporin N=75** n (%) | **Placebo N=79** n (%) | **p-value** |
|---|---|---|---|
| 0 | 52 (69.3) | 72 (91.1) | 0.001 [a] |
| R (risk) | 15 (20.0) | 3 (3.8) | 0.001 [a] |
| I (injury) | 5 (6.7) | 2 (2.5) | 0.192 [a] |
| F (failure) | 3 (4.0) | 2 (2.5) | 0.522 [a] |

[a] Logistic regression with stratification variable specified as strata, Exact conditional score test
Source: Tables 4 and 5a in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

**RIFLE Classification on Day 3 Based on eGFR**
When the RIFLE classification was based on eGFR, 34 patients (45.3%) in the ciclosporin group vs 62 patients (78.5%) in the placebo group did not fulfil the RIFLE criteria for risk of acute renal failure (category 0) on Day 3.

On Day 3, 27 patients (36.0%) in the ciclosporin group vs 11 (13.9%) in the placebo group fulfilled the RIFLE criteria for risk (R) of acute renal failure, 12 patients (16.0%) in the ciclosporin group vs 5 (6.3%) in the placebo group fulfilled the criteria for injury (I) and 2 patients (2.7%) in the ciclosporin group vs 1 (1.3%) in the placebo group fulfilled the criteria for failure (F) classification, Table 16.

**Table 16: Number and percentage of patients by RIFLE classification on Day 3 (based on eGFR)**

| | **Ciclosporin N=75** n (%) | **Placebo N=79** n (%) | **p-value** |
|---|---|---|---|
| 0 | 34 (45.3) | 62 (78.5) | <0.001 [a] |
| R (risk) | 27 (36.0) | 11 (13.9) | 0.002 [a] |
| I (injury) | 12 (16.0) | 5 (6.3) | 0.055 [a] |
| F (failure) | 2 (2.7) | 1 (1.3) | 0.428 [a] |

[a] Logistic regression with stratification variable specified as strata, Exact conditional score test
Analysis set: mITT (PP); N=154
Source: Tables 4 and 5a in the Statistical Report (Appendix 16.1.9)

Both the RIFLE classification based on creatinine and the RIFLE classification based on eGFR support the results of the primary efficacy variable since a larger proportion of patients in the ciclosporin group than in the placebo group fulfilled the criteria for risk of acute renal failure.

For further data on the secondary efficacy endpoints, see the Statistical Report in Appendix 16.1.9.

#### 11.1.2.2 Secondary Efficacy Endpoints – Heart Function

**P-Troponin T (P-TnT) before and after ECC**

The mean P-TnT concentration was 35.3 ng/L in the ciclosporin group and 42.8 ng/L in the placebo group on Day -1 (normal range: <15 ng/L). The highest mean P-TnT concentration was observed at 8 hours after surgery in both groups (ciclosporin: 366.2 ng/L; placebo: 390.0 ng/L). By Day 4, the mean P-TnT concentration was 312.5 ng/L in the ciclosporin group vs 221.0 ng/L in the placebo group, Table 17.

**Table 17: P-TnT concentrations before and after ECC**

| | P-TnT (ng/L) | Ciclosporin | Placebo |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 35.33 (126.44)<br>10.0 (5–1042)<br>75 | 42.76 (123.08)<br>13.0 (5–861)<br>79 |
| 4 hours | Mean (SD)<br>Median (range)<br>n | 333.50 (163.99)<br>299.5 (70–835)<br>74 | 381.14 (201.94)<br>355.0 (93–991)<br>79 |
| 8 hours | Mean (SD)<br>Median (range)<br>n | 366.23 (204.05)<br>302.0 (80–1041)<br>74 | 389.97 (183.99)<br>368.5 (95–1005)<br>78 |
| 12 hours | Mean (SD)<br>Median (range)<br>n | 361.51 (331.06)<br>252.0 (90–2158)<br>75 | 331.67 (175.54)<br>302.0 (95–1269)<br>79 |
| 24 hours | Mean (SD)<br>Median (range)<br>n | 286.60 (294.56)<br>198.0 (73–2105)<br>73 | 269.19 (189.23)<br>223.0 (74–1395)<br>77 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 330.40 (900.20)<br>168.0 (48–7865)<br>75 | 251.32 (222.91)<br>183.5 (45–1200)<br>78 |
| Day 3 | Mean (SD)<br>Median (range)<br>n | 327.23 (1152.6)<br>140.0 (28–9999)<br>74 | 221.79 (213.11)<br>151.0 (29–1387)<br>78 |
| Day 4 | Mean (SD)<br>Median (range)<br>n | 312.49 (1093.8)<br>112.0 (17–9491)<br>75 | 220.99 (271.45)<br>130.5 (22–1547)<br>76 |

Analysis set: mITT (PP); N=154
Source: Table 11 in the Statistical Report (Appendix 16.1.9)

The P-TnT $AUC_{Day\ -1\ –\ Day\ 4}$ (in ng/L x h) was higher in the ciclosporin group (mean: 30377; SD: 68508) than in the placebo group (mean: 24614; SD: 18030), see Table 11 in the Statistical Report (Appendix 16.1.9) for further details.

**P-CK-MB before and after ECC**

The mean P-CK-MB concentration was 2.8 µg/L in the ciclosporin group and 2.7 µg/L in the placebo group on Day -1 (normal range: <5.0 µg/L). The highest mean P-CK-MB concentration was observed at 12 hours after surgery in both groups and was similar between the treatment groups (ciclosporin: 16.1 µg/L; placebo: 15.7 µg/L). By Day 4, the mean P-TnT concentration was 2.3 µg/L in the ciclosporin group and 2.6 µg/L in the placebo group, Table 18.

**Table 18: P-CK-MB before and after ECC**

| | P-CK-MB (µg/L) | Ciclosporin | Placebo |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 2.81 (3.04)<br>2.00 (1.0–23.1)<br>75 | 2.67 (1.67)<br>2.30 (1.0–10.6)<br>79 |
| 4 hours | Mean (SD)<br>Median (range)<br>n | 14.58 (5.39)<br>13.35 (4.6–29.7)<br>74 | 14.95 (5.96)<br>13.90 (6.2–40.7)<br>79 |
| 8 hours | Mean (SD)<br>Median (range)<br>n | 15.67 (9.90)<br>12.75 (5.0–64.8)<br>74 | 15.49 (9.39)<br>13.90 (6.0–79.2)<br>78 |
| 12 hours | Mean (SD)<br>Median (range)<br>n | 16.12 (15.85)<br>12.30 (5.3–102.8)<br>75 | 15.72 (15.85)<br>12.40 (4.5–141.3)<br>79 |
| 24 hours | Mean (SD)<br>Median (range)<br>n | 14.02 (21.15)<br>9.10 (3.4–175.6)<br>74 | 14.37 (18.18)<br>9.30 (2.7–145.3)<br>77 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 7.30 (17.29)<br>4.40 (1.2–152.3)<br>75 | 6.76 (8.19)<br>4.25 (1.3–49.2)<br>78 |
| Day 3 | Mean (SD)<br>Median (range)<br>n | 3.63 (7.99)<br>2.50 (1.0–70.5)<br>74 | 3.25 (2.72)<br>2.40 (1.0–16.3)<br>78 |
| Day 4 | Mean (SD)<br>Median (range)<br>n | 2.27 (2.31)<br>1.80 (1.0–20.6)<br>75 | 2.58 (2.28)<br>2.20 (1.0–18.7)<br>77 |

Source: Table 11 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

Consequently, the P-CK-MB $AUC_{Day\ -1\ –\ Day\ 4}$ (in µg/L x h) was also similar between the ciclosporin group (mean: 797.3; SD: 1137.6) and the placebo group (mean: 780.9; SD: 667.3), see Table 11 in the Statistical Report (Appendix 16.1.9) for further details.

### 11.1.2.3 Secondary Efficacy Endpoints – Brain Function

**S-S 100B before and after ECC**

The mean S-S 100B concentration was similar between the treatments on Day -1 (ciclosporin: 0.06 µg/L; placebo: 0.07 µg/L) as well as post-surgery on Day 1 (0.16 µg/L in both groups) and Day 2 (ciclosporin: 0.13 µg/L; placebo: 0.14 µg/L), Table 19. The normal range for S-S 100B is <0.10 µg/L.

**Table 19: S-S 100B concentrations before and after ECC**

| | S-S 100B (µg/L) | Ciclosporin | Placebo |
|---|---|---|---|
| Day -1 | Mean (SD)<br>Median (range)<br>n | 0.06 (0.03)<br>0.06 (0.02–0.18)<br>71 | 0.07 (0.08)<br>0.05 (0.02–0.68)<br>78 |
| Day 1 | Mean (SD)<br>Median (range)<br>n | 0.16 (0.07)<br>0.14 (0.06–0.38)<br>74 | 0.16 (0.17)<br>0.14 (0.03–1.50)<br>79 |
| Day 2 | Mean (SD)<br>Median (range)<br>n | 0.13 (0.06)<br>0.12 (0.06–0.50)<br>72 | 0.14 (0.15)<br>0.11 (0.03–1.20)<br>78 |

Source: Table 12 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP); N=154

### 11.1.3 *Post-hoc* Analyses

As plasma creatinine was defined as an efficacy variable, a retrospective post-hoc safety follow-up analysis of this variable at 1-3 months and 3-6 months is presented in this section.

At 1-6 months, mean values of plasma creatinine concentrations had decreased to values similar to the baseline values in both treatment groups. More specifically, the mean plasma creatinine concentrations were 89.9 µmol/L in the ciclosporin group vs 93.4 µmol/L in the placebo group at 1-3 months and 91.7 µmol/L in the ciclosporin group vs 94.5 µmol/L in the placebo group at 3-6 months. The p-value for the differences between the treatment groups was 0.498 at 1-3 months and 0.643 at 3-6 months, Table 20.

**Table 20: Post-hoc safety follow-up of plasma creatinine at 1-3 months and 3-6 months**

| | P-creatinine (µmol /L) | Ciclosporin | Placebo | p-value |
|---|---|---|---|---|
| Day -1 | Mean (SD)<br>n | 89.25 (19.36)<br>75 | 91.94 (19.13)<br>79 | |
| Day 1 | Mean (SD)<br>n | 91.80 (23.60)<br>75 | 88.61 (23.18)<br>79 | 0.009[a] |
| Day 2 | Mean (SD)<br>n | 121.97 (48.10)<br>75 | 107.92 (40.88)<br>79 | 0.001[a] |
| Day 3 | Mean (SD)<br>n | 123.87 (55.85)<br>75 | 106.25 (49.35)<br>79 | <0.001[a] |
| Day 4 | Mean (SD)<br>n | 112.47 (56.71)<br>75 | 102.10 (48.06)<br>79 | 0.019 [a] |
| 1-3 months | Mean (SD)<br>n | 89.9 (22.0)<br>n=55 | 93.4 (33.0)<br>n=68 | 0.498[b] |
| 3-6 months | Mean (SD)<br>n | 91.7 (24.2)<br>n=37 | 94.5 (29.0)<br>n=41 | 0.643[b] |

[a] Analysed by repeated measures linear mixed model
[b] Analysed by t-test

For post-hoc safety follow-up of individual laboratory values (plasma creatinine), see Section 12.3.2.3.

## 11.2 Results of Statistical Issues Encountered during the Analysis

### 11.2.1 Adjustment of Covariates

An exploratory graphical analysis was performed to assess the exposure-response (PK/PD) relationship and to identify covariates impacting the response.

### 11.2.2 Handling of Withdrawals, Discontinuations or Missing Data

For patients with any missing value of P-CyC on Day -1 or Day 3, the missing value was to be replaced by the last value carried forward, which was done for one patient who was found during the blinded review to have a missing value of P-CyC on Day 3. The imputed value was used in the sensitivity analysis of the primary endpoint. Not detectable values were to be replaced by the limit value. No other values were to be replaced.

See the Statistical Report in Appendix 16.1.9 for number of values replaced by the lowest/highest detection limit.

### 11.2.3 Interim Analyses and Data Monitoring

Two interim safety analyses were planned; one after the completion of 50 patients and one after completion of 100 patients. Unblinded data were analysed and evaluated by an independent interim safety analysis group. The major purpose of these analyses was to evaluate any signals for increased incidence of AKI, as compared to the EPRICS study (5), a study with similar design.

The independent interim safety analysis group working principles and team members were outlined in a charter.

### 11.2.4 Multicentre Studies

Not applicable since this was a single centre study.

### 11.2.5 Multiple Comparison/Multiplicity

No correction for multiple testing was performed.

### 11.2.6 Use of an "Efficacy Subset" of Patients

Not applicable.

### 11.2.7 Examination of Subgroups

Pre-defined sub-groups were patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ and patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$.

As expected, the mean P-CyC concentrations were higher in the sub-group of patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ (1.39 mg/L in the ciclosporin group and 1.47 mg/L in the placebo group on Day -1) than in the sub-group of patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ (0.97 mg/L in the ciclosporin group and 1.00 mg/L in the placebo group on Day -1). The normal range for P-CyC is 0.84-1.25 mg/L. The lowest mean P-CyC concentrations were observed on Day 1 in both sub-groups. The highest mean P-CyC concentrations were observed on Day 3 both in the sub-group of patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ (ciclosporin: 1.99 mg/L; placebo: 1.65 mg/L) and in the sub-group of patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ (ciclosporin: 1.31 mg/L; placebo: 1.19 mg/L), Table 21.

**Table 21: P-CyC concentrations on Days -1, 1, 2, 3 and 4 by pre-operative eGFR**

| | P-CyC (mg/L) | Pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ | | Pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ | |
|---|---|---|---|---|---|
| | | Ciclosporin | Placebo | Ciclosporin | Placebo |
| Day -1 | Mean (SD)<br>n | 1.39 (0.33)<br>28 | 1.47 (0.32)<br>30 | 0.97 (0.11)<br>47 | 1.00 (0.11)<br>49 |
| Day 1 | Mean (SD)<br>n | 1.33 (0.44)<br>28 | 1.36 (0.44)<br>30 | 0.93 (0.19)<br>47 | 0.88 (0.16)<br>49 |
| Day 2 | Mean (SD)<br>n | 1.88 (0.83)<br>28 | 1.62 (0.54)<br>30 | 1.24 (0.31)<br>47 | 1.14 (0.32)<br>48 |
| Day 3 | Mean (SD)<br>n | 1.99 (0.87)<br>28 | 1.65 (0.55)<br>30 | 1.31 (0.39)<br>47 | 1.19 (0.39)<br>48 |
| Day 4 | Mean (SD)<br>n | 1.94 (1.00)<br>28 | 1.62 (0.52)<br>30 | 1.25 (0.48)<br>47 | 1.13 (0.26)<br>48 |

Source: Tables 21 and 23 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP)

A larger increase in P-CyC was observed in the ciclosporin group than in the placebo group in both subgroups: The relative increase from Day -1 to Day 3 was 39.8% in the ciclosporin group vs 11.5% in the placebo group in the subgroup of patients with an eGFR of 15-59 mL/min/1.73 m: p<0.001. The relative increase from Day -1 to Day 3 was 34.4% in the ciclosporin group vs 18.6% in the placebo group in the subgroup of patients with an eGFR of 60-90 mL/min/1.73 $m^2$: p=0.011, Table 22.

**Table 22: Relative change in P-CyC from Day -1 to Day 3 by pre-operative eGFR**

| P-CyC (mg/L) | Pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ | | Pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ | |
|---|---|---|---|---|
| | Ciclosporin | Placebo | Ciclosporin | Placebo |
| Mean (SD)<br>n | 139.79 (35.24)<br>28 | 111.47 (23.71)<br>30 | 134.35 (36.10)<br>47 | 118.62 (34.49)<br>48 |

Source: Tables 20 and 22 in the Statistical Report (Appendix 16.1.9)
Analysis set: mITT (PP)

For further data on the subgroup analyses, please see the Statistical Report in Appendix 16.1.9.

### 11.2.8 Tabulation of Individual Response

Individual response data are presented in Appendix 16.2.6.

## 11.3 Pharmacokinetic, Pharmacodynamic and Other Analyses Results

### 11.3.1 Drug Dose, Drug Concentration and Relationships to Response

**Ciclosporin Plasma Concentration vs Time**

The analysis of the ciclosporin plasma concentration-time profiles confirmed that all patients in the ciclosporin group had adequate exposure of ciclosporin except for one patient who correctly received placebo but for whom the IMP number was incorrectly recorded (a number corresponding to ciclosporin). This patient was consequently excluded from the PK analyses. The graph of ciclosporin plasma concentration vs time shows a multi-exponential elimination profile. With only 3 plasma concentration observations per subject, any NCA-based exposure predictions, such as $AUC_{0-24h}$, would be biased. However, the $AUC_{0-24h}$ indicates whether a subject had a higher or lower ciclosporin exposure than the typical patient in the CiPRICS

study and the individual $AUC_{0-24h}$ predictions were therefore used, together with the observed plasma concentrations at the time point of the clinical chemistry measurements, in the exploratory analysis of the exposure-response relationships. It should be noted that, due to the expected bias in the $AUC_{0-24h}$ predictions, the CL estimates are also biased and should not be compared to CL estimates based on more dense sampling schedules.

Plots of the ciclosporin plasma concentrations vs time, stratified by low or high eGFR, are presented on linear and semi-logarithmic scales in Figure 5.

The mean $AUC_{0-24h}$ of ciclosporin was 10028 ng/mL x h in the ciclosporin group. The subjects in the low eGFR group had a lower mean $AUC_{0-24h}$ of ciclosporin (9359 ng/mL x h) than the high eGFR group (10429 ng/mL x h). The mean ciclosporin dose was 40.6 mL in the low eGFR group and 42.8 mL in the high eGFR group. The differences in the $AUC_{0-24h}$ between the low and high eGFR groups can partly be explained by the differences in the ciclosporin dose.

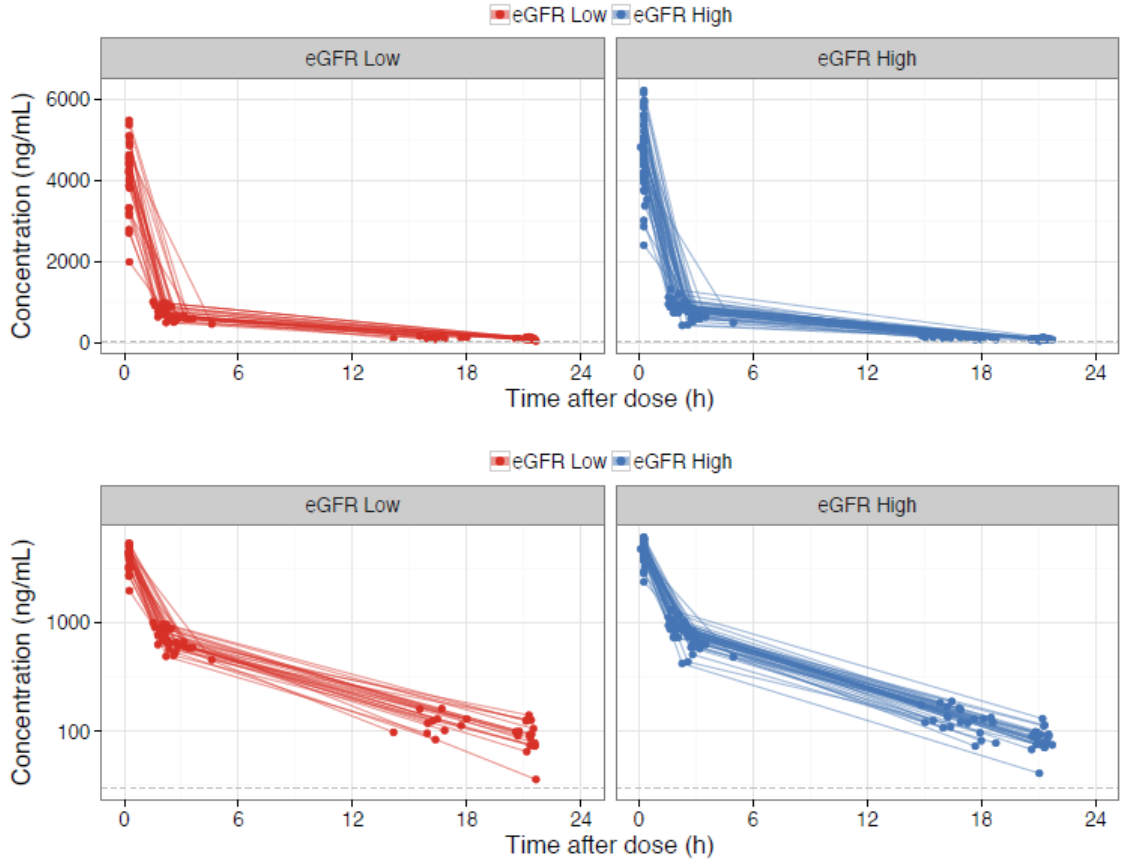


**Figure 5: Observed plasma concentrations vs time, stratified by eGFR**
Each line represents the data for one subject. The upper panels represent the data on a linear scale and the bottom panels represent the data on a semi-logarithmic scale. The grey dashed line represents the LLOQ.
Source: Figure 3 in the document 'Exploratory Graphical Analysis of the CiPRICS study' (Appendix 16.1.9)

**P-CyC vs Time**

Subjects receiving ciclosporin had in general higher P-CyC levels at 48, 72, and 96 hours after dosing than subjects receiving placebo (Figure 6), but there did not appear to be any clear relationship between the ciclosporin concentration or $AUC_{0\text{-}24h}$ and the change from baseline in P-CyC at 24, 48, 72, or 96 hours after dosing. Subjects with high eGFR had lower P-CyC levels than subjects with low eGFR, but there were no clear differences in the change from baseline in P-CyC between the two eGFR groups. Moreover, there were no obvious trends in the response magnitude for subjects with different eGFR MDRD levels at baseline, please see the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9 for further details).

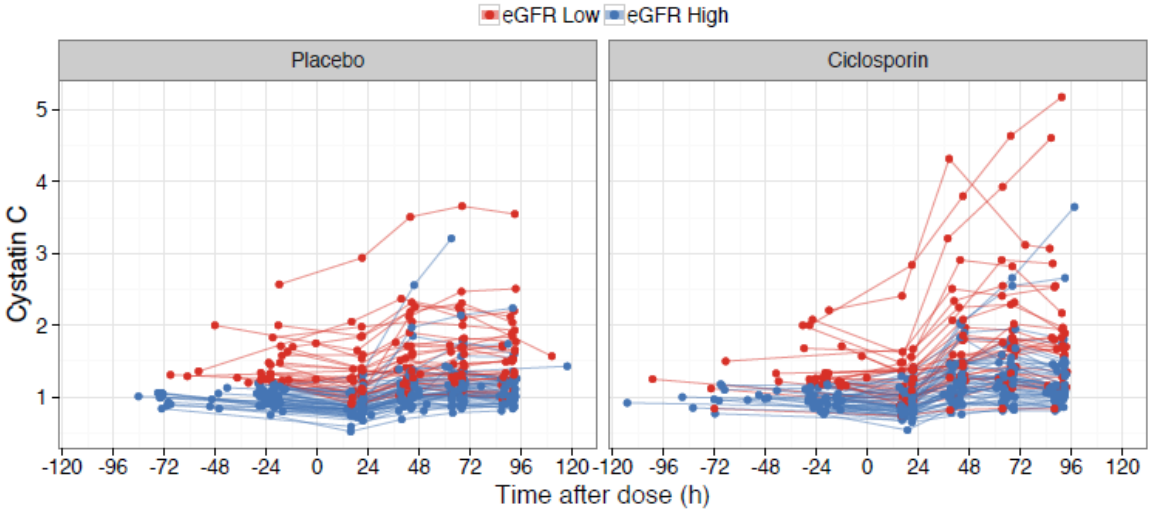


**Figure 6: Observed P-CyC vs time**

Each line represents the data for one subject.

Source: Figure 7 in the document 'Exploratory Graphical Analysis of the CiPRICS study' (Appendix 16.1.9)

**Creatinine vs Time**
Subjects receiving ciclosporin had in general higher creatinine levels at 48, 72, and 96 hours after dosing than subjects receiving placebo, but there did not appear to be any clear relationship between the ciclosporin concentration or $AUC_{0-24h}$ and the change from baseline in creatinine at 24, 48, 72, or 96 hours after dosing. Subjects with high eGFR had lower creatinine levels compared to subjects with low eGFR, but there were no clear differences in change in the fraction of creatinine from baseline between the two eGFR groups, please see the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9 for further details.

**CK MB vs Time**
The CK MB levels increased after dosing both in the placebo group and in the ciclosporin group but returned to baseline values within 96 hours after dosing. There were no clear differences in the magnitude or the time course of the response between the treatment groups, between subjects with low or high eGFR at baseline, or between the eGFR MDRD levels, please see the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9 for further details.

**P-Troponin T (P-TnT) vs Time**
The P-TnT levels increased after dosing both in the placebo group and in the ciclosporin group but started to return to the baseline values within 96 hours after dosing. There were no clear differences in the magnitude or the time course of the response between the treatment groups, between subjects with low or high eGFR at baseline, or between the eGFR MDRD levels, please see the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9 for further details..

**S-S 100 B vs Time**
The S-S 100 B levels increased after dosing in both treatment groups but started to return to the baseline values within 48 hours after dosing. There were no substantial differences in the magnitude or the time course of the response between the treatment groups, between subjects with low or high eGFR at baseline, or between the eGFR MDRD levels.

There may be a weak relationship between the ciclosporin plasma concentrations after about 24 hours and the S-S 100 B response, as well as between the $AUC_{0-24h}$ and the change from baseline in S-S 100 B at 24 or 48 hours after dosing. However, the range of the S-S 100 B response in the ciclosporin group was similar to that of the placebo group, please see the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9 for further details.

**Summary of the Exploratory Graphical Analysis**
The mean $AUC_{0-24h}$ of ciclosporin was 10 028 ng/mL x h in the ciclosporin group.

The exploratory graphical analysis showed a more pronounced increase in the P-CyC and creatinine levels in the ciclosporin group than in the placebo group. However, no strong relationships between the ciclosporin exposure and the magnitude or time course of the response in any of the clinical chemistry measurements (P-CyC, creatinine, CK MB, P-TnT or S-S 100 B) could be established.

### 11.3.2 Drug-Drug and Drug-Disease Interactions

Drug-drug or drug –disease interactions were not investigated in this study.

### 11.3.3 Other Endpoints

The mean ECC duration was 77.2 min (SD: 29.7 min) in the ciclosporin group vs. 73.7 min (SD: 26.8 min) in the placebo group. The mean aortic cross clamp duration was 47.4 min (SD: 20.1 min) in the ciclosporin group vs. 46.1 min (SD: 16.2 min) in the placebo group, for further details see the Statistical Report (Appendix 16.1.9).

In addition, data on the following endpoints are presented in the Statistical Report (Appendix 16.1.9):

- Number of distal coronary grafts on Day 0
- Leg wound length on Day 0
- Number of suture lines on Day 0
- Triclosan suture used on Day 0
- Wound closed before ECC on Day 0
- Number of drains on Day 0
- Staples used on Day 0
- Experience harvesting > 2 years on Day 0
- Experience closing on Day 0
- Fluid balance during surgery
- Fluid balance on Day 0
- Diuresis before ECC on Day 0
- Diuresis during ECC on Day 0
- Total diuresis during operation
- Anaesthesia according to protocol on Day 0
- Intraop dose dobutamine on Day 0
- Total dose dobutamine on Day 0
- Intraop dose noradrenaline at the thoracic intensive care unit (THIVA) on Day 0
- Total dose noradrenaline at THIVA on Day 0
- Diuresis the first 12 hours at THIVA on Day 0
- Bleeding 12 hours at THIVA on Day 0
- Total bleeding on Day 0
- Time in ICU on Day 1
- Time to extubation
- Concomitant medications on Days 0, 1, 2, 3 and 4 (mannitol, furosemide, amiloride, metolazone, noradrenaline and dobutamine)
- Telephone contact on Day 30
- Contact primary care on Day 30
- Contact hospital on Day 30
- Received antibiotics on Day 30
- Graft leg healed on Day 30
- Reoperation because of bleeding
- Stroke
- Mediastinitis
- Atrial fibrillation
- Myocardial infarction
- Heart failure

### 11.4 Efficacy Results Summary

Kidney Function

The primary endpoint was not met as a larger increase in P-CyC was observed in the ciclosporin group (mean: 36.4%) than in the placebo group (mean: 15.9%). The treatment difference in relative change from Day -1 to Day 3 based on LN-transformed values was in favour of placebo ($p<0.001$).

The mean P-CyC concentration was 1.13 mg/L in the ciclosporin group and 1.18 mg/L in the placebo group on Day -1 (normal range: 0.84-1.25 mg/L). The highest mean P-CyC concentrations were observed on Day 3 in both groups (ciclosporin: 1.57 mg/L; placebo: 1.36 mg/L).

The increase in P-creatinine from Day -1 to Day 3 was 38.6% in the ciclosporin group vs 15.8% in the placebo group. The higher P-creatinine concentrations in the ciclosporin group as compared to the placebo group are in agreement with the results of the primary efficacy variable, i.e. a worsening in the liver function when the patients received ciclosporin.

Mean values of TIMP-2 IGFBP7 were within normal range before and at 4 and 12 hours after ECC.

The lowest (worst) mean eGFR values based on P-CyC, P-CyC/P-creatinine or P-creatinine were generally observed on Day 2 or Day 3 in both groups and was lower in the ciclosporin group than in the placebo group.

On Day 3, 15 patients (20.0%) in the ciclosporin group vs 3 patients (3.8%) in the placebo group fulfilled the creatinine-based RIFLE criteria for risk (R) of acute renal failure, 5 patients (6.7%) in the ciclosporin group vs 2 (2.5%) in the placebo group fulfilled the criteria for injury (I) and 3 patients (4.0%) in the ciclosporin group vs 2 (2.5%) in the placebo group fulfilled the criteria for failure (F) classification (the worst category of R, I and F). On Day 3, 27 patients (36.0%) in the ciclosporin group vs 11 (13.9%) in the placebo group fulfilled the eGFR-based RIFLE criteria for risk (R) of acute renal failure, 12 patients (16.0%) in the ciclosporin group vs 5 (6.3%) in the placebo group fulfilled the criteria for injury (I) and 2 patients (2.7%) in the ciclosporin group vs 1 (1.3%) in the placebo group fulfilled the criteria for failure (F) classification.

The pre-specified sub-group analysis showed that the mean P-CyC concentrations were higher in the sub-group of patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ than in the sub-group of patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ at all time points. The highest mean P-CyC concentrations were observed on Day 3 both in the sub-group of patients with a pre-operative eGFR of 15-59 mL/min/1.73 $m^2$ (ciclosporin: 1.99 mg/L; placebo: 1.65 mg/L) and in the sub-group of patients with a pre-operative eGFR of 60-90 mL/min/1.73 $m^2$ (ciclosporin: 1.31 mg/L; placebo: 1.19 mg/L).

Heart Function

The highest mean P-TnT concentration, a biomarker of cardiac injury, was observed at 8 hours after surgery in both groups (ciclosporin: 366.2 ng/L; placebo: 390.0 ng/L). By Day 4, the mean P-TnT concentration was 312.5 ng/L in the ciclosporin group vs 221.0 ng/L in the placebo group.

The highest mean P-CK-MB concentration was observed at 12 hours after surgery in both groups and was similar between the treatment groups.

Thus, no cardioprotective effect of ciclosporin was observed in this study.

Brain Function
The mean S-S 100B concentration was similar between the treatments at all time points. Thus, no brain protective effect of ciclosporin was observed in this study.

Exploratory PK Analysis
The mean ciclosporin dose was 40.6 mL in the low eGFR group and 42.8 mL in the high eGFR group.

The exploratory graphical analysis based on PK data of ciclosporin showed a more pronounced increase in the P-CyC and creatinine levels in the ciclosporin group than in the placebo group. However, no strong relationship between the ciclosporin exposure and the magnitude or time course of the response in P-CyC, P-creatinine, CK MB, P-TnT or S-S 100 B could be established.

Post-hoc Results
A retrospective post-hoc safety follow-up analysis was performed of plasma creatinine for safety reasons. The mean values decreased over time in both treatment groups and were similar between the treatment groups at 1-3 months or 3-6 months.

# 12 SAFETY EVALUATION

## 12.1 ADVERSE EVENTS (AEs)

### 12.1.1 Brief Summary of Adverse Events

A total of 41 patients (26%) reported at least one AE, 21 (28%) in the ciclosporin group and 20 (25%) in the placebo group. The distribution of AEs was similar between the treatment groups with 28 AEs in the ciclosporin group and 29 in the placebo group. Five AEs were assessed as related to the IMP; 3 in the ciclosporin group and 2 in the placebo group. Ten patients (13%) in the ciclosporin group had a total of 12 SAEs and 11 patients (14%) in the placebo group had a total of 14 SAEs, Table 23.

**Table 23: Summary display of AEs (safety population)**

| | Ciclosporin N=76 | Placebo N=79 | Total N=155 |
|---|---|---|---|
| Total number of unique AEs [a] | 28 | 29 | 57 |
| Total number of AEs | 28 | 29 | 57 |
| Total number of subjects with at least one AE | 21 (28%) | 20 (25%) | 41 (26%) |
| Total number of unique related AEs[a] | 3 | 2 | 5 |
| Total number of related AEs | 3 | 2 | 5 |
| Total number of subjects with at least one related AE | 3 (4%) | 2 (3%) | 5 (3%) |
| Total number of unique SAEs [a] | 12 | 14 | 26 |
| Total number of SAEs | 12 | 14 | 26 |
| Total number of subjects with at least one SAE | 10 (13%) | 11 (14%) | 21 (14%) |

[a] Unique Preferred Term are only calculated once within each subject
Source: Appendix 16.2.7 and Table 14.3.1.1

### 12.1.2 Most Frequently Reported Adverse Events (AEs)

When analysing AEs by system organ class (SOC), most of the AEs were classified as 'Infections and infestations' (ciclosporin: 8 AEs in 7 patients [9%]; placebo: 6 AEs in 5 patients [6%]), 'Respiratory, thoracic and mediastinal disorders' (ciclosporin: 9 AEs in 9 patients [12%]; placebo: 3 AEs in 3 patients [4%]) or 'Cardiac disorders' (ciclosporin: 3 AEs in 3 patients [4%]; placebo: 4 AEs in 4 patients [5%]). The most frequently reported AEs (preferred terms; PTs) were pleural effusion reported by 8 patients (ciclosporin: 6 AEs in 6 patients [8%]; placebo: 2 AEs in 2 patients [3%]), pneumonia reported by 5 patients (ciclosporin: 4 AEs in 4 patients [5%]; placebo: 1 AE in 1 patient [1%]) and postoperative wound infection reported by 3 patients (ciclosporin: 1 AE in 1 patient [1%]; placebo: 2 AEs in 2 patients [3%]), Table 24.

**Table 24: No. of unique AEs by SOC, preferred term (PT) and treatment (safety population)**

| | | Ciclosporin N=76 | Placebo N=79 | Total N=155 |
|---|---|---|---|---|
| Infections and Infestations | Subjects | 7 (9%) | 5 (6%) | 12 (8%) |
| | AEs | 8 | 6 | 14 |
| | Related | 2 | 2 | 4 |
| | Pneumonia | 4 (5%) 4 | 1 (1%) 1 | 5 (3%) 5 |
| | Postoperative Wound Infection | 1 (1%) 1 | 2 (3%) 2 | 3 (2%) 3 |
| | Urinary Tract Infection | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Colon Gangrene | 1 (1%) 1 | | 1 (1%) 1 |
| | Infection | | 1 (1%) 1 | 1 (1%) 1 |
| | Mediastinitis | | 1 (1%) 1 | 1 (1%) 1 |
| | Respiratory Infection | 1 (1%) 1 | | 1 (1%) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Subjects | 9 (12%) | 3 (4%) | 12 (8%) |
| | AEs | 9 | 3 | 12 |
| | Pleural Effusion | 6 (8%) 6 | 2 (3%) 2 | 8 (5%) 8 |
| | Pneumothorax | 2 (3%) 2 | | 2 (1%) 2 |
| | Cough | | 1 (1%) 1 | 1 (1%) 1 |
| | Dyspnoea | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders | Subjects | 3 (4%) | 4 (5%) | 7 (5%) |
| | AEs | 3 | 4 | 7 |
| | Pericardial Effusion | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Angina Pectoris | | 1 (1%) 1 | 1 (1%) 1 |
| | Atrial Fibrillation | 1 (1%) 1 | | 1 (1%) 1 |
| | Cardiac Disorder | | 1 (1%) 1 | 1 (1%) 1 |
| | Cardiac Failure | 1 (1%) 1 | | 1 (1%) 1 |
| | Ventricular Arrhythmia | | 1 (1%) 1 | 1 (1%) 1 |
| Investigations | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Liver Function Test Abnormal | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Hepatic Enzyme Increased | | 1 (1%) 1 | 1 (1%) 1 |
| Nervous System Disorders | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Cerebrovascular Accident | | 2 (3%) 2 | 2 (1%) 2 |
| | Syncope | 1 (1%) 1 | | 1 (1%) 1 |
| Psychiatric Disorders | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Delirium | | 2 (3%) 2 | 2 (1%) 2 |
| | Sleep Disorder | 1 (1%) 1 | | 1 (1%) 1 |
| Gastrointestinal Disorders | Subjects | | 2 (3%) | 2 (1%) |
| | AEs | | 2 | 2 |
| | Diarrhoea | | 1 (1%) 1 | 1 (1%) 1 |
| | Gastrointestinal Haemorrhage | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Chest Pain | 1 (1%) 1 | | 1 (1%) 1 |
| | Non-Cardiac Chest Pain | | 1 (1%) 1 | 1 (1%) 1 |
| Renal and Urinary Disorders | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Renal Failure | 1 (1%) 1 | | 1 (1%) 1 |
| | Urinary Retention | | 1 (1%) 1 | 1 (1%) 1 |
| Vascular Disorders | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Related | 1 | | 1 |
| | Deep Vein Thrombosis | | 1 (1%) 1 | 1 (1%) 1 |

| | | Ciclosporin N=76 | Placebo N=79 | Total N=155 |
|---|---|---|---|---|
| | Hypertension | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders, Respiratory, Thoracic and Mediastinal Disorders | | | | |
| | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Cardiac Arrest, Myocardial Infarction, Pulmonary Oedema | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Gastrointestinal Haemorrhage, Cardiac Arrest | 1 (1%) 1 | | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Chest Pain, Nausea, Vomiting | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Investigations | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Pyrexia, C-Reactive Protein Increased | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Postpericardiotomy Syndrome | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Vascular Graft Occlusion, Myocardial Infarction | 1 (1%) 1 | | 1 (1%) 1 |
| Renal and Urinary Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Hydronephrosis, Ureteral Stenosis | | 1 (1%) 1 | 1 (1%) 1 |

Subjects= Number of Subjects in SOC, i.e. each subject is calculated only once
AEs=Number of unique AEs in SOC, i.e. each preferred term is only calculated once within a subject
Related=Number of unique related AEs in SOC
For each preferred term the number of subjects in n and (%) is given together with the actual number of occurren ce for the preferred term
MedDRA version 18.0
Source: Appendix 16.2.7 and Table 14.3.1.2

### 12.1.3 Categorisation of All Adverse Events

**Causality**

Five AEs were assessed as possibly related to the IMP (ciclosporin: 3; placebo: 2). The 3 possibly related AEs in the ciclosporin group (1 event each of respiratory infection, pneumonia and hypertension) were all of mild severity and resolved. Also the 2 possibly related AEs in the placebo group (1 event of pneumonia of mild severity and 1 event of mediastinitis of severe severity) resolved during the study, Table 25.

**Table 25: Listing of AEs of assessed as possibly related to the IMP**

| Group | Events (PT MedDRA Term) | SAE | Causality | Severity | Outcome |
|---|---|---|---|---|---|
| Ciclosporin | Respiratory infection | No | Possible | Mild | Recovered |
| Ciclosporin | Pneumonia | No | Possible | Mild | Recovered |
| Ciclosporin | Hypertension | No | Possibly | Mild | Recovered |
| Placebo | Pneumonia | Yes | Possibly | Mild | Recovered |
| Placebo | Mediastinitis | Yes | Possibly | Severe | Recovered |

Source: Extracted from Appendix 16.2.7

**Intensity**
A majority of the AEs were of mild (ciclosporin: 13; placebo: 11) or moderate severity (ciclosporin: 13; placebo: 11). Nine AEs were severe (ciclosporin: 2; placebo: 7; all of which were serious and are therefore listed in Table 27). See Table 14.3.1.4 and Appendix 16.2.7 for further details.

## 12.2 Analysis of Deaths, Other Serious Adverse Events and Other Clinically Meaningful Adverse Events

### 12.2.1 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Adverse Events of Special Interest

#### 12.2.1.1 Deaths

There was one death in this study, a cerebrovascular accident occurring in the placebo group. The event was assessed as unlikely related to the IMP, please see Section 14.3.3 for the narrative.

#### 12.2.1.2 Other Serious Adverse Events

Ten patients (13%) in the ciclosporin group had 12 SAEs and 11 patients (14%) in the placebo group had 14 SAEs, Table 23. Pleural effusion was the most commonly reported SAE (3 patients in the ciclosporin group) followed by pneumonia (1 patient in each group), pericardial effusion (1 patient in each group) and cerebrovascular accident (2 patients in the placebo group), Table 26.

**Table 26: No. of unique SAEs by SOC, PT and treatment (safety population)**

| | | Ciclosporin N=76 | Placebo N=79 | Total N=155 |
|---|---|---|---|---|
| Infections and Infestations | Subjects | 3 (4%) | 3 (4%) | 6 (4%) |
| | AEs | 3 | 3 | 6 |
| | Related | | 2 | 2 |
| | Pneumonia | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Colon Gangrene | 1 (1%) 1 | | 1 (1%) 1 |
| | Infection | | 1 (1%) 1 | 1 (1%) 1 |
| | Mediastinitis | | 1 (1%) 1 | 1 (1%) 1 |
| | Postoperative Wound Infection | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders | Subjects | 3 (4%) | 2 (3%) | 5 (3%) |
| | AEs | 3 | 2 | 5 |
| | Pericardial Effusion | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Atrial Fibrillation | 1 (1%) 1 | | 1 (1%) 1 |
| | Cardiac Disorder | | 1 (1%) 1 | 1 (1%) 1 |
| | Cardiac Failure | 1 (1%) 1 | | 1 (1%) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Subjects | 3 (4%) | | 3 (2%) |
| | AEs | 3 | | 3 |
| | Pleural Effusion | 3 (4%) 3 | | 3 (2%) 3 |
| Nervous System Disorders | Subjects | | 2 (3%) | 2 (1%) |
| | AEs | | 2 | 2 |
| | Cerebrovascular Accident | | 2 (3%) 2 | 2 (1%) 2 |
| Cardiac Disorders, Respiratory, Thoracic and Mediastinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Cardiac Arrest, Myocardial Infarction, Pulmonary Oedema | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Gastrointestinal Haemorrhage | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Gastrointestinal Haemorrhage, Cardiac Arrest | 1 (1%) 1 | | 1 (1%) 1 |
| General Disorders and administration Site Conditions | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Non-Cardiac Chest Pain | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Chest Pain, Nausea, Vomiting | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Postpericardiotomy Syndrome | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Vascular Graft Occlusion, Myocardial Infarction | 1 (1%) 1 | | 1 (1%) 1 |
| Investigations | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Liver Function Test Abnormal | 1 (1%) 1 | | 1 (1%) 1 |
| Renal and Urinary Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Hydronephrosis, Ureteral Stenosis | | 1 (1%) 1 | 1 (1%) 1 |
| Vascular Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Deep Vein Thrombosis | | 1 (1%) 1 | 1 (1%) 1 |

Subjects= Number of Subjects in SOC, i.e. each subject is calculated only once
AEs=Number of unique AEs in SOC, i.e. each preferred term is only calculated once within a subject
Related=Number of unique related AEs in SOC
For each preferred term the number of subjects in n and (%) is given together with the actual number of occurren ce of the preferred term
MedDRA version 18.0
Source: Appendix 16.2.7 and Table 14.3.1.3

None of the 12 SAEs in the ciclosporin group was assessed as related to the IMP, while 2 SAEs in the placebo group were assessed as possibly related to the IMP, Table 27. Two SAEs in the ciclosporin group were of severe severity (1 SAE of vascular graft occlusion and myocardial infarction, and 1 SAE of gastrointestinal haemorrhage and cardiac arrest) and 7 in the placebo group (2 SAEs of cerebrovascular accident and 1 SAE each of gastrointestinal haemorrhage, cardiac disorder and mediastinitis, 1 SAE of cardiac arrest, myocardial infarction and pulmonary oedema and 1 SAE of hydronephrosis, ureteral stenosis), Table 27.
No fatal SAE occurred in the ciclosporin group, 10 SAEs were resolved, 1 resulted in sequelae (colon gangrene) and 1 was still ongoing (atrial fibrillation) at the last follow up.
One fatal SAE occurred in the placebo group (cerebrovascular accident), 11 SAEs were resolved and 2 resulted in sequelae (1 SAE of cardiac arrest, myocardial infarction and pulmonary oedema and 1 SAE of hydronephrosis and ureteral stenosis), Table 27.
No action was taken with regard to IMP in this single dose study (Appendix 16.2.7).

**Table 27: Listing of all SAEs**

| Group | Events (PT MedDRA Term) | Start date | Stop date | Causality | Severity | Outcome |
|---|---|---|---|---|---|---|
| Ciclosporin | Pleural effusion | 2015-07-16 | 2015-07-18 | Unlikely | Moderate | Recovered |
| Ciclosporin | Vascular graft occlusion, myocardial infarction | 2015-09-23 | 2015-10-05 | Unlikely | Severe | Recovered |
| Ciclosporin | Pericardial effusion | 2015-11-14 | 2015-11-30 | Unlikely | Moderate | Recovered |
| | Pleural effusion | 2015-11-14 | 2015-11-30 | Unlikely | Moderate | Recovered |
| Ciclosporin | Pneumonia | 2015-12-23 | 2015-12-27 | Unlikely | Moderate | Recovered |
| Ciclosporin | Pleural effusion | 2016-02-19 | 2016-02-29 | Unlikely | Moderate | Recovered |
| Ciclosporin | Atrial fibrillation | 2016-03-16 | | Unlikely | Mild | Ongoing |
| Ciclosporin | Liver function test abnormal | 2016-03-04 | 2016-03-08 | Unlikely | Mild | Recovered |
| Ciclosporin | Cardiac failure | 2016-04-05 | 2016-04-11 | Unlikely | Moderate | Recovered |
| Ciclosporin | Gastrointestinal haemorrhage, Cardiac arrest | 2016-05-21 | 2016-05-24 | Unlikely | Severe | Recovered |
| | Colon gangrene | 2016-05-14 | 2016-05-16 | Unlikely | Moderate | Recovered with sequelae |
| Ciclosporin | Postoperative wound infection | 2016-06-17 | 2016-07-01 | Unlikely | Moderate | Recovered |
| Placebo | Deep vein thrombosis | 2015-05-13 | 2015-05-14 | Unlikely | Moderate | Recovered |
| Placebo | Cerebrovascular accident | 2015-06-24 | 2015-06-29 | Unlikely | Severe | Recovered |
| Placebo | Pneumonia | 2015-09-05 | 2015-09-14 | Possibly | Mild | Recovered |
| Placebo | Gastrointestinal haemorrhage | 2015-11-03 | 2015-11-05 | Unlikely | Severe | Recovered |
| Placebo | Cardiac disorder | 2015-12-14 | 2015-12-17 | Unlikely | Severe | Recovered |
| Placebo | Non-cardiac chest pain | 2016-03-04 | 2016-03-16 | Unlikely | Moderate | Recovered |
| | Chest pain, Nausea, Vomiting | 2016-03-17 | 2016-03-22 | Unlikely | Moderate | Recovered |
| Placebo | Postpericardiotomy syndrome | 2016-03-16 | 2016-03-18 | Unlikely | Moderate | Recovered |
| Placebo | Mediastinitis | 2016-03-28 | 2016-06-09 | Possibly | Severe | Recovered |
| Placebo | Cardiac arrest, Myocardial infarction, Pulmonary oedema | 2016-05-07 | 2020-05-07 | Unlikely | Severe | Recovered with sequelae |
| | Hydronephrosis, Ureteral stenosis | 2016-05-07 | 2016-05-24 | Unlikely | Severe | Recovered with sequelae |
| Placebo | Cerebrovascular accident | 2016-05-14 | 2016-06-07 | Unlikely | Severe | Fatal |
| Placebo | Pericardial effusion | 2016-06-18 | 2016-06-22 | Unlikely | Moderate | Recovered |
| | Infection | 2016-06-18 | 2016-06-22 | Unlikely | Moderate | Recovered |

Source: Extracted from Appendix 16.2.7

### 12.2.1.3 Discontinuations due to Adverse Events

There were no discontinuations due to AEs in this single dose study.

#### 12.2.1.4 Other Adverse Events of Special Interest

There were no other AEs of special interest

### 12.2.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Clinically Meaningful Adverse Events

Narratives of the one death in the placebo group and the 25 non-fatal SAEs are included in Section 14.3.3.

## 12.3 CLINICAL LABORATORY EVALUATION

### 12.3.1 Individual Laboratory Measurements by Patient and Abnormal Laboratory Values

In accordance with the study protocol, clinical normal signs and symptoms due to the procedure of CABG were only to be reported as AEs if they constituted serious events or were not expected in relation to the surgical procedure as judged by the investigator.

Four patients (1 patient in the ciclosporin group and 3 in the placebo group) had any abnormal laboratory value reported as an AE, 3 events of increased liver enzymes and 1 event of increased CRP. One event of increased liver enzymes in the ciclosporin group was reported as an SAE. None of these AEs was assessed as related to the IMP and all resolved. All events were of mild severity and no action was taken, Table 29.

All individual laboratory measurements are listed by patient in Appendix 16.2.8.

### 12.3.2 Evaluation of Laboratory Values

#### 12.3.2.1 Laboratory Values Over Time

Laboratory values (mean, median, min, max) are shown by treatment group and study day in Table 28. For a graphical presentation of the distribution of the variables and the results of the statistical tests, see the Statistical Report in Appendix 16.1.9. Please note that, based on the distribution of the variables, statistical tests were based on LN-transformed where appropriate.

As seen from the minimum and maximum values in Table 28, out-of-range values were recorded for a large number of laboratory measurements, which is normally seen after the CABG procedure.

Based on the outcome of the study, a retrospective post-hoc safety follow-up analysis was performed of plasma creatinine (defined as an efficacy variable in this study), at 1-6 months for safety reasons. The mean values decreased over time in both treatment groups and were similar between the treatment groups at 1-3 months or 3-6 months, see Table 20 in Section 11.1.3.

**Table 28: Laboratory values by treatment group and study day**

| Endpoint | | Group | n | Mean (SD) | Median | (Min–Max) | Reference value |
|---|---|---|---|---|---|---|---|
| P-Potassium (mmol/L) | | | | | | | 3.5-4.4 |
| | Day -1 | Ciclosporin | 73 | 4.1 (0.3) | 4.1 | (3.1–4.9) | |
| | Day 1 | Ciclosporin | 74 | 4.6 (0.3) | 4.6 | (4.0–5.8) | |
| | Day 2 | Ciclosporin | 75 | 4.3 (0.3) | 4.3 | (3.6–5.3) | |
| | Day 3 | Ciclosporin | 75 | 4.1 (0.3) | 4.2 | (3.2–4.8) | |
| | Day 4 | Ciclosporin | 75 | 4.2 (0.4) | 4.2 | (3.3–5.2) | |
| | Day -1 | Placebo | 76 | 4.1 (0.3) | 4.1 | (3.6–4.8) | |
| | Day 1 | Placebo | 79 | 4.5 (0.3) | 4.5 | (3.9–5.5) | |
| | Day 2 | Placebo | 79 | 4.1 (0.4) | 4.1 | (3.3–6.1) | |
| | Day 3 | Placebo | 79 | 4.1 (0.3) | 4.1 | (3.0–5.2) | |
| | Day 4 | Placebo | 78 | 4.2 (0.4) | 4.2 | (3.0–5.1) | |
| P-Mg (mmol/L) | | | | | | | 0.70-0.95 |
| | Day -1 | Ciclosporin | 75 | 0.8 (0.1) | 0.8 | (0.5–1.0) | |
| | Day 1 | Ciclosporin | 74 | 1.1 (0.2) | 1.1 | (0.8–1.8) | |
| | Day 2 | Ciclosporin | 75 | 0.9 (0.2) | 0.9 | (0.8–1.5) | |
| | Day 3 | Ciclosporin | 74 | 0.9 (0.3) | 0.8 | (0.7–2.9) | |
| | Day 4 | Ciclosporin | 75 | 0.9 (0.2) | 0.9 | (0.7–1.6) | |
| | Day -1 | Placebo | 79 | 0.8 (0.1) | 0.8 | (0.6–1.1) | |
| | Day 1 | Placebo | 79 | 1.1 (0.2) | 1.1 | (0.9–2.0) | |
| | Day 2 | Placebo | 78 | 0.9 (0.1) | 0.9 | (0.6–1.5) | |
| | Day 3 | Placebo | 78 | 0.9 (0.1) | 0.8 | (0.6–1.4) | |
| | Day 4 | Placebo | 78 | 0.9 (0.1) | 0.8 | (0.6–1.4) | |
| P-Urea (mmol/L) | | | | | | | 3.5-8.2 |
| | Day -1 | Ciclosporin | 75 | 6.4 (2.2) | 5.9 | (3.5–16.6) | |
| | Day 1 | Ciclosporin | 74 | 5.4 (2.1) | 5.2 | (3.0–18.9) | |
| | Day 2 | Ciclosporin | 75 | 7.1 (2.6) | 6.8 | (3.5–20.0) | |
| | Day 3 | Ciclosporin | 75 | 8.6 (3.9) | 7.4 | (3.7–23.9) | |
| | Day 4 | Ciclosporin | 75 | 8.8 (4.8) | 7.1 | (3.7–29.1) | |
| | Day -1 | Placebo | 79 | 6.9 (2.3) | 6.4 | (3.6–14.9) | |
| | Day 1 | Placebo | 79 | 5.3 (1.9) | 4.9 | (2.9–14.2) | |
| | Day 2 | Placebo | 78 | 6.4 (2.8) | 5.8 | (2.4–19.4) | |
| | Day 3 | Placebo | 78 | 7.1 (3.2) | 6.3 | (3.4–20.1) | |
| | Day 4 | Placebo | 77 | 7.4 (3.5) | 6.4 | (2.5–21.3) | |
| P-Myoglobin (µg/L) | | | | | | | 28-72 |
| | Day -1 | Ciclosporin | 74 | 48.7 (35.9) | 39.5 | (22.0–271.0) | |
| | Day 1 | Ciclosporin | 74 | 275.3 (206.7) | 206.0 | (85.0–1256.0) | |
| | Day 2 | Ciclosporin | 75 | 285.2 (321.7) | 160.0 | (60.0–1853.0) | |
| | Day 3 | Ciclosporin | 74 | 131.4 (137.8) | 78.5 | (31.0–888.0) | |
| | Day 4 | Ciclosporin | 75 | 81.7 (73.0) | 54.0 | (22.0–362.0) | |
| | Day -1 | Placebo | 78 | 45.0 (24.1) | 37.5 | (22.0–122.0) | |
| | Day 1 | Placebo | 79 | 301.5 (238.7) | 235.0 | (76.0–1076.0) | |
| | Day 2 | Placebo | 78 | 223.0 (275.0) | 154.5 | (33.0–2102.0) | |
| | Day 3 | Placebo | 78 | 124.2 (167.2) | 78.0 | (24.0–1110.0) | |
| | Day 4 | Placebo | 77 | 78.8 (101.8) | 57.0 | (22.0–875.0) | |
| P-Creatine kinase (CK), (µkat/L) | | | | | | | 0.70-4.7 |
| | Day -1 | Ciclosporin | 73 | 1.7 (1.3) | 1.3 | (0.5–9.7) | |
| | Day 1 | Ciclosporin | 74 | 9.1 (6.3) | 7.6 | (2.5–46.0) | |
| | Day 2 | Ciclosporin | 75 | 10.7 (9.8) | 7.8 | (2.2–65.0) | |
| | Day 3 | Ciclosporin | 74 | 7.6 (9.1) | 5.2 | (1.4–71.0) | |
| | Day 4 | Ciclosporin | 74 | 4.6 (5.0) | 3.2 | (0.7–37.0) | |
| | Day -1 | Placebo | 79 | 1.7 (1.2) | 1.4 | (0.4–7.1) | |
| | Day 1 | Placebo | 79 | 10.3 (6.5) | 8.1 | (2.4–32.0) | |
| | Day 2 | Placebo | 78 | 11.8 (11.7) | 8.1 | (1.4–74.0) | |
| | Day 3 | Placebo | 78 | 8.1 (9.1) | 5.1 | (0.8–55.0) | |

| Endpoint | | Group | n | Mean (SD) | Median | (Min–Max) | Reference value |
|---|---|---|---|---|---|---|---|
| | Day 4 | Placebo | 78 | 4.6 (4.7) | 3.0 | (0.5–30.0) | |
| P-Bilirubin (µmol/L) | | | | | | | 5-25 |
| | Day -1 | Ciclosporin | 75 | 7.6 (3.8) | 7.0 | (3.0–27.0) | |
| | Day 1 | Ciclosporin | 74 | 13.5 (7.0) | 12.0 | (4.0–44.0) | |
| | Day 2 | Ciclosporin | 74 | 12.7 (8.0) | 11.0 | (3.0–51.0) | |
| | Day 3 | Ciclosporin | 73 | 11.1 (6.6) | 9.0 | (4.0–52.0) | |
| | Day 4 | Ciclosporin | 75 | 10.8 (5.6) | 9.0 | (4.0–38.0) | |
| | Day -1 | Placebo | 79 | 8.4 (4.3) | 7.0 | (3.0–29.0) | |
| | Day 1 | Placebo | 79 | 12.2 (5.3) | 11.0 | (6.0–30.0) | |
| | Day 2 | Placebo | 77 | 11.0 (4.7) | 10.0 | (3.0–28.0) | |
| | Day 3 | Placebo | 79 | 9.8 (4.9) | 9.0 | (3.0–31.0) | |
| | Day 4 | Placebo | 77 | 9.9 (5.1) | 9.0 | (4.0–40.0) | |
| P-ASAT (µkat/L) | | | | | | | 0.25-0.75 |
| | Day -1 | Ciclosporin | 75 | 0.7 (0.4) | 0.5 | (0.3–2.2) | |
| | Day 1 | Ciclosporin | 75 | 0.9 (0.8) | 0.7 | (0.4–4.5) | |
| | Day 2 | Ciclosporin | 75 | 1.0 (3.3) | 0.6 | (0.3–29.0) | |
| | Day 3 | Ciclosporin | 74 | 1.3 (6.1) | 0.5 | (0.2–53.0) | |
| | Day 4 | Ciclosporin | 75 | 0.9 (2.7) | 0.5 | (0.2–24.0) | |
| | Day -1 | Placebo | 79 | 0.5 (0.3) | 0.5 | (0.2–2.4) | |
| | Day 1 | Placebo | 79 | 0.8 (0.4) | 0.7 | (0.4–2.7) | |
| | Day 2 | Placebo | 78 | 0.7 (0.4) | 0.6 | (0.3–2.2) | |
| | Day 3 | Placebo | 79 | 0.6 (0.3) | 0.5 | (0.2–1.7) | |
| | Day 4 | Placebo | 78 | 0.7 (1.0) | 0.5 | (0.2–8.7) | |
| P-ALAT (µkat/L) | | | | | | | 0.15-1.1 |
| | Day -1 | Ciclosporin | 75 | 1.0 (1.0) | 0.7 | (0.2–7.2) | |
| | Day 1 | Ciclosporin | 75 | 0.9 (0.8) | 0.6 | (0.2–4.7) | |
| | Day 2 | Ciclosporin | 75 | 1.1 (3.8) | 0.5 | (0.1–33.0) | |
| | Day 3 | Ciclosporin | 74 | 1.3 (5.9) | 0.5 | (0.2–51.0) | |
| | Day 4 | Ciclosporin | 75 | 1.1 (4.5) | 0.5 | (0.2–39.0) | |
| | Day -1 | Placebo | 79 | 0.7 (0.5) | 0.7 | (0.2–3.3) | |
| | Day 1 | Placebo | 79 | 0.6 (0.6) | 0.5 | (0.2–4.9) | |
| | Day 2 | Placebo | 78 | 0.5 (0.4) | 0.5 | (0.2–2.9) | |
| | Day 3 | Placebo | 79 | 0.5 (0.3) | 0.4 | (0.1–2.4) | |
| | Day 4 | Placebo | 78 | 0.7 (1.3) | 0.5 | (0.2–12.0) | |
| P-GT (µkat/L) | | | | | | | 0.20-1.9 |
| | Day -1 | Ciclosporin | 75 | 0.9 (0.9) | 0.5 | (0.2–5.5) | |
| | Day 1 | Ciclosporin | 74 | 0.7 (0.7) | 0.4 | (0.1–3.5) | |
| | Day 2 | Ciclosporin | 75 | 0.7 (0.6) | 0.4 | (0.1–3.3) | |
| | Day 3 | Ciclosporin | 74 | 0.8 (0.8) | 0.5 | (0.2–4.7) | |
| | Day 4 | Ciclosporin | 75 | 1.0 (1.1) | 0.7 | (0.2–8.2) | |
| | Day -1 | Placebo | 79 | 1.2 (2.1) | 0.6 | (0.2–14.0) | |
| | Day 1 | Placebo | 79 | 0.9 (1.4) | 0.5 | (0.2–9.5) | |
| | Day 2 | Placebo | 78 | 0.8 (1.3) | 0.5 | (0.2–8.6) | |
| | Day 3 | Placebo | 79 | 1.0 (1.5) | 0.6 | (0.2–10.0) | |
| | Day 4 | Placebo | 78 | 1.3 (1.7) | 0.6 | (0.2–10.0) | |
| P-ALP (µkat/L) | | | | | | | 0.60-1.8 |
| | Day -1 | Ciclosporin | 75 | 1.4 (0.6) | 1.3 | (0.6–3.5) | |
| | Day 1 | Ciclosporin | 74 | 1.0 (0.5) | 0.9 | (0.5–2.8) | |
| | Day 2 | Ciclosporin | 75 | 1.1 (0.4) | 1.0 | (0.5–2.8) | |
| | Day 3 | Ciclosporin | 74 | 1.2 (0.7) | 1.1 | (0.6–5.5) | |
| | Day 4 | Ciclosporin | 75 | 1.5 (1.2) | 1.3 | (0.6–10.0) | |
| | Day -1 | Placebo | 79 | 1.4 (0.7) | 1.2 | (0.7–4.7) | |
| | Day 1 | Placebo | 79 | 1.0 (0.4) | 0.9 | (0.4–2.9) | |
| | Day 2 | Placebo | 78 | 1.0 (0.4) | 0.9 | (0.5–2.7) | |
| | Day 3 | Placebo | 79 | 1.1 (0.5) | 1.0 | (0.6–3.0) | |
| | Day 4 | Placebo | 78 | 1.3 (0.9) | 1.1 | (0.6–6.4) | |
| P-CRP (mg/L) | | | | | | | <3.0 |

| Endpoint | | Group | n | Mean (SD) | Median | (Min–Max) | Reference value |
|---|---|---|---|---|---|---|---|
| | Day -1 | Ciclosporin | 75 | 4.0 (6.1) | 2.0 | (0.6–33.0) | |
| | Day 1 | Ciclosporin | 74 | 59.0 (33.0) | 50.0 | (14.0–192.0) | |
| | Day 2 | Ciclosporin | 73 | 196.9 (75.5) | 197.0 | (77.0–385.0) | |
| | Day 3 | Ciclosporin | 74 | 223.3 (82.9) | 227.0 | (41.0–419.0) | |
| | Day 4 | Ciclosporin | 75 | 175.4 (74.2) | 167.0 | (23.0–352.0) | |
| | Day -1 | Placebo | 79 | 6.1 (9.0) | 2.1 | (0.6–48.0) | |
| | Day 1 | Placebo | 79 | 63.4 (27.8) | 61.0 | (15.0–180.0) | |
| | Day 2 | Placebo | 78 | 171.8 (67.9) | 165.0 | (48.0–417.0) | |
| | Day 3 | Placebo | 79 | 185.5 (73.2) | 173.0 | (50.0–411.0) | |
| | Day 4 | Placebo | 79 | 141.2 (73.6) | 124.0 | (37.0–475.0) | |
| B-Leukocytes ($10^9$/L) | | | | | | | 3.5-8.8 |
| | Day -1 | Ciclosporin | 75 | 7.5 (1.7) | 7.0 | (4.9–13.9) | |
| | Day 1 | Ciclosporin | 75 | 13.5 (3.5) | 12.9 | (7.1–25.5) | |
| | Day 2 | Ciclosporin | 75 | 13.5 (3.3) | 12.9 | (7.1–20.9) | |
| | Day 3 | Ciclosporin | 73 | 12.0 (2.5) | 11.7 | (7.7–17.8) | |
| | Day 4 | Ciclosporin | 75 | 10.1 (2.2) | 9.9 | (5.8–15.7) | |
| | Day -1 | Placebo | 79 | 7.7 (1.8) | 7.3 | (5.0–12.3) | |
| | Day 1 | Placebo | 78 | 11.8 (3.5) | 11.5 | (6.9–21.1) | |
| | Day 2 | Placebo | 79 | 11.8 (2.8) | 11.2 | (7.2–20.3) | |
| | Day 3 | Placebo | 79 | 11.1 (2.7) | 10.7 | (6.2–17.6) | |
| | Day 4 | Placebo | 79 | 9.7 (2.5) | 9.3 | (4.5–16.4) | |
| B-Haemoglobin (g/L) | | | | | | | 134-170 |
| | Day -1 | Ciclosporin | 73 | 135.6 (13.7) | 136.0 | (93.0–165.0) | |
| | Day 1 | Ciclosporin | 74 | 108.9 (12.4) | 111.0 | (74.0–146.0) | |
| | Day 2 | Ciclosporin | 75 | 101.8 (11.4) | 100.0 | (78.0–139.0) | |
| | Day 3 | Ciclosporin | 73 | 99.1 (11.1) | 100.0 | (75.0–129.0) | |
| | Day 4 | Ciclosporin | 75 | 101.5 (10.9) | 101.0 | (83.0–136.0) | |
| | Day -1 | Placebo | 78 | 137.8 (15.8) | 137.0 | (88.0–179.0) | |
| | Day 1 | Placebo | 78 | 111.8 (13.1) | 112.0 | (86.0–147.0) | |
| | Day 2 | Placebo | 79 | 103.2 (12.8) | 103.0 | (74.0–135.0) | |
| | Day 3 | Placebo | 79 | 104.1 (11.9) | 103.0 | (77.0–136.0) | |
| | Day 4 | Placebo | 78 | 105.7 (12.4) | 104.0 | (81.0–144.0) | |
| B-Thrombocytes ($10^9$/L) | | | | | | | 145-348 |
| | Day -1 | Ciclosporin | 74 | 242.3 (63.2) | 240.0 | (134.0–471.0) | |
| | Day 1 | Ciclosporin | 74 | 187.5 (53.0) | 185.5 | (82.0–313.0) | |
| | Day 2 | Ciclosporin | 73 | 164.9 (44.3) | 164.0 | (80.0–275.0) | |
| | Day 3 | Ciclosporin | 72 | 173.5 (47.5) | 171.5 | (71.0–270.0) | |
| | Day 4 | Ciclosporin | 74 | 210.4 (55.1) | 207.0 | (89.0–352.0) | |
| | Day -1 | Placebo | 79 | 237.5 (60.6) | 233.0 | (95.0–448.0) | |
| | Day 1 | Placebo | 77 | 186.0 (47.0) | 179.0 | (109.0–312.0) | |
| | Day 2 | Placebo | 78 | 169.3 (46.0) | 167.5 | (43.0–287.0) | |
| | Day 3 | Placebo | 79 | 183.2 (47.8) | 179.0 | (65.0–285.0) | |
| | Day 4 | Placebo | 79 | 225.2 (56.8) | 225.0 | (81.0–364.0) | |

Analysis set: mITT (PP); N=154
Source: Table 6 in the Statistical Report (Appendix 16.1.9)

#### 12.3.2.2 Individual Patient Changes in Laboratory Values

Individual patient changes in P-CyC, P-creatinine, P-CK MB, P-TnT and S-S 100 B are presented graphically in the document 'Exploratory Graphical Analysis of the CiPRICS study' in Appendix 16.1.9.

#### 12.3.2.3 Individual Clinically Meaningful Abnormalities

According to the study protocol, clinical normal signs and symptoms due to the procedure of CABG were only to be reported as AEs if they were SAEs according to the definition or were not expected in relation to the surgical procedure as judged by the investigator.

Four patients (1 patient in the ciclosporin group and 3 in the placebo group) had any abnormal laboratory value reported as an AE, 3 events of increased liver enzymes and 1 event of increased CRP. One event of increased liver enzymes in the ciclosporin group was reported as an SAE. None of these AEs was assessed as related to the IMP and all resolved. All events were of mild severity and no action was taken, Table 29.

**Table 29: Abnormal laboratory values reported as AEs**

| Patient No. | Group | Event (PT MedDRA term) | Start date | Stop date | SAE | Causality | Severity | Action taken | AE caused patient to discontinue | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| [Redacted] | Placebo | Hepatic enzyme increased | 2015-12-15 | 2015-12-18 | No | Unlikely | Mild | No | No | Recovered |
| [Redacted] | Placebo | C-reactive protein increased | 2016-02-16 | 2016-02-16 | No | Unlikely | Mild | No | No | Recovered |
| [Redacted] | Ciclosporin | Liver function test abnormal | 2016-03-04 | 2016-03-08 | Yes | Unlikely | Mild | No | No | Recovered |
| [Redacted] | Placebo | Liver function test abnormal | 2016-05-27 | 2016-08-07 | No | Unlikely | Mild | No | No | Recovered |
| MedDRA version 18.0 | | | | | | | | | | |

Source: Extracted from Appendix 16.2.7

**Post-hoc Safety Follow-up of Individual Laboratory Values**
Five patients, 3 in the ciclosporin group (Nos. [Redacted], [Redacted] and [Redacted]) and 2 in the placebo group (Nos. [Redacted] and [Redacted]) qualified for the RIFLE classification of kidney failure (F) based on creatinine values on Day 3, see Table 15. Three of these patients, 2 in the ciclosporin arm (Nos. [Redacted] and [Redacted]) and 1 in the placebo arm (No. [Redacted]), are the same as those who qualified for the RIFLE classification of kidney failure (F), based on eGFR on Day 3, see Table 16. Medical records of these 5 patients were reviewed separately as part of the retrospective post-hoc safety follow-up.

Three of the patients, 2 in the ciclosporin-arm and 1 in the placebo arm had plasma creatinine concentration within the reference range (males: 60-105 µmol/L; females: 45-90 µmol/L), at 1-3 months, while 2 patients, one in each treatment group, still had elevated creatinine concentrations. The patient in the ciclosporin group with an elevated creatinine concentration of 183 µmol/L at 1-3 months still had an elevated creatinine value of 161 µmol/L at 3-6 months, but this value was almost identical to the baseline value of 158 µmol/L, Table 30.

**Table 30: Creatinine concentrations (µmol/L) by study Day and at the post-hoc safety follow-up in patients fulfilling the RIFLE criteria for kidney failure on Day 3**

| Treatment group | Patient No. | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | 1-3 months | 3-6 months |
|---|---|---|---|---|---|---|---|---|
| Ciclosporin | [Redacted] | 66 | 79 | 174 | 232 | 231 | 72 | 82 |
| Ciclosporin | [Redacted] | 69 | 75 | 184 | 282 | 301 | 80 | 78 |
| Placebo | [Redacted] | 91 | 97 | 309 | 383 | 368 | 91 | 109 |
| Ciclosporin | [Redacted] | 158 | 128 | 311 | 377 | 411 | 183 | 161 |
| Placebo | [Redacted] | 97 | 100 | 272 | 314 | 311 | 131 | Not available |

## 12.4 VITAL SIGNS, PHYSICAL EXAMINATIONS AND OTHER OBSERVATIONS RELATED TO SAFETY

### 12.4.1 Vital Signs

No clear trends were observed in mean values of body temperature, SBP and DBP over time and no obvious differences in vital signs were observed between the treatment groups, Table 31.

**Table 31: Vital signs by treatment group and study Day**

| Endpoint | | Group | n | Mean (SD) | Median | (Min–Max) | n miss |
|---|---|---|---|---|---|---|---|
| Body temperature (°C) | | | | | | | |
| | Day 1 | Ciclosporin | 75 | 37.3 (0.6) | 37.2 | (35.8–38.7) | 0 |
| | Day 2 | Ciclosporin | 75 | 37.0 (0.7) | 37.0 | (34.9–38.4) | 0 |
| | Day 3 | Ciclosporin | 75 | 36.7 (0.6) | 36.8 | (35.5–38.6) | 0 |
| | Day 4 | Ciclosporin | 74 | 36.6 (0.6) | 36.6 | (35.0–37.9) | 1 |
| | Day 1 | Placebo | 79 | 37.4 (0.4) | 37.4 | (36.4–38.3) | 0 |
| | Day 2 | Placebo | 78 | 36.9 (0.6) | 37.0 | (35.0–38.1) | 1 |
| | Day 3 | Placebo | 77 | 36.7 (0.6) | 36.6 | (35.4–37.9) | 2 |
| | Day 4 | Placebo | 77 | 36.6 (0.6) | 36.7 | (35.1–37.8) | 2 |
| SBP (mmHg) | | | | | | | |
| | Day -1 | Ciclosporin | 75 | 134.4 (17.4) | 135.0 | (104.0–187.0) | 0 |
| | Day 1 | Ciclosporin | 75 | 119.1 (17.4) | 117.0 | (88.0–159.0) | 0 |
| | Day 2 | Ciclosporin | 75 | 123.6 (16.8) | 124.0 | (73.0–163.0) | 0 |
| | Day 3 | Ciclosporin | 74 | 124.9 (15.5) | 125.0 | (91.0–168.0) | 1 |
| | Day 4 | Ciclosporin | 75 | 129.7 (14.7) | 130.0 | (100.0–170.0) | 0 |
| | Day -1 | Placebo | 79 | 137.4 (18.5) | 136.0 | (105.0–200.0) | 0 |
| | Day 1 | Placebo | 79 | 120.9 (17.8) | 120.0 | (79.0–162.0) | 0 |
| | Day 2 | Placebo | 79 | 123.0 (20.0) | 120.0 | (70.0–180.0) | 0 |
| | Day 3 | Placebo | 79 | 129.0 (18.3) | 129.0 | (95.0–180.0) | 0 |
| | Day 4 | Placebo | 79 | 130.4 (17.9) | 130.0 | (89.0–182.0) | 0 |
| DBP (mmHg) | | | | | | | |
| | Day -1 | Ciclosporin | 75 | 72.5 (9.1) | 73.0 | (50.0–94.0) | 0 |
| | Day 1 | Ciclosporin | 75 | 57.5 (9.7) | 55.0 | (37.0–85.0) | 0 |
| | Day 2 | Ciclosporin | 75 | 66.6 (11.9) | 65.0 | (45.0–98.0) | 0 |
| | Day 3 | Ciclosporin | 74 | 67.0 (11.2) | 69.0 | (35.0–96.0) | 1 |
| | Day 4 | Ciclosporin | 74 | 72.7 (8.6) | 70.5 | (55.0–96.0) | 1 |
| | Day -1 | Placebo | 79 | 74.9 (8.1) | 75.0 | (60.0–95.0) | 0 |
| | Day 1 | Placebo | 79 | 59.3 (9.1) | 57.0 | (38.0–90.0) | 0 |
| | Day 2 | Placebo | 78 | 67.7 (11.2) | 70.0 | (30.0–97.0) | 1 |
| | Day 3 | Placebo | 78 | 72.5 (11.4) | 70.0 | (45.0–101.0) | 1 |
| | Day 4 | Placebo | 79 | 73.5 (10.3) | 75.0 | (46.0–100.0) | 0 |

Analysis set: mITT (PP); N=154
Source: Table 7 in the Statistical Report (Appendix 16.1.9)

### 12.4.2 Physical Examination Findings

No physical examination findings were reported.

### 12.4.3 Other Observations Related to Safety

The mean leg wound infection scoring was 5.0 in the ciclosporin group and 4.0 in the placebo group on Day 4 (p=0.087 for the difference between treatments). For further details, see Table 15 in the Statistical Report (Appendix 16.1.9).

## 12.5 Safety Results Summary

A total of 41 patients (26%) reported at least one AE, 21 (28%) in the ciclosporin group and 20 (25%) in the placebo group. The distribution of AEs was similar between the treatment groups with 28 AEs in the ciclosporin group and 29 in the placebo group.

The most frequently reported AEs were pleural effusion (ciclosporin: 6 patients [8%]; placebo: 2 patients [3%]), pneumonia (ciclosporin: 4 patients [5%]; placebo: 1 patient [1%]) and postoperative wound infection (ciclosporin: 1 patient [1%]; placebo: 2 patients [3%]).

Five AEs were assessed as possibly related to the IMP (ciclosporin: 3; placebo: 2). The 3 possibly related AEs in the ciclosporin group (1 event each of respiratory infection, pneumonia and hypertension) were all of mild severity and resolved. Also the 2 possibly related AEs in the placebo group (1 event of pneumonia of mild severity and 1 event of mediastinitis of severe severity) resolved during the study.

Ten patients (13%) in the ciclosporin group had 12 SAEs and 11 patients (14%) in the placebo group had 14 SAEs. Pleural effusion was the most commonly reported SAE (3 patients in the ciclosporin group) followed by pneumonia (1 patient in each group), pericardial effusion (1 patient in each group) and cerebrovascular accident (2 patients in the placebo group). None of the SAEs in the ciclosporin group was assessed as related to the IMP, while 2 SAEs in the placebo group were assessed as possibly related to the IMP. No fatal SAE occurred in the ciclosporin group, while 1 fatal SAE occurred in the placebo group (cerebrovascular accident). One SAE in the ciclosporin group (colon gangrene) and 2 in the placebo group (1 SAE of cardiac arrest, myocardial infarction and pulmonary oedema and 1 SAE of hydronephrosis and ureteral stenosis) resulted in sequelae.

Based on the outcome of the study, a retrospective post-hoc safety follow-up analysis was performed of plasma creatinine at 1-6 months for safety reasons. The mean plasma creatinine values decreased over time in both treatment groups and were similar between the treatment groups at 1-3 months or 3-6 months. The 5 patients (3 in the ciclosporin group and 2 in the placebo group) who qualified for the RIFLE classification of kidney failure based on creatinine values on Day 3 were reviewed separately as part of the retrospective post-hoc safety follow-up. Two of the 3 patients in the ciclosporin group had plasma creatinine concentrations within the reference range at 1-3 months. The third patient in the ciclosporin group had a high plasma creatinine concentration already before surgery and at 3-6 months, the creatinine value was still elevated but had decreased to the baseline value.

No clear trends were observed in mean values of body temperature, SBP and DBP over time and no obvious differences in vital signs were observed between the treatment groups.

## 13 DISCUSSION AND OVERALL CONCLUSIONS

Ciclosporin has been used since the early 1980's as an immunosuppressant in kidney and other solid organ transplantation. In addition to its well-known immunosuppressive properties, ciclosporin is a potent inhibitor of mitochondrial permeability transition, and several animal studies have indicated that ciclosporin can limit ischaemia-reperfusion injury under experimental conditions (11-14) and in various organs (13, 15, 16) including the kidney (17-20).

Previous clinical studies investigating the effects of ciclosporin against injury after ischemia and reperfusion in the heart and trauma to the brain have not revealed any ciclosporin-induced safety concerns (35-40).

The current study was the first clinical study investigating the possible renoprotective effect of ciclosporin after ischemia-reperfusion in humans.

Ciclosporin did not protect the kidneys from AKI after CABG. In contrast, ciclosporin resulted in statistically significantly higher levels of the renal biomarkers P-CyC and P-creatinine than placebo on Day 3 after surgery.

The exploratory graphical analysis based on PK data of ciclosporin supported the efficacy results and showed more pronounced increases in the P-CyC and creatinine levels in the ciclosporin group than in the placebo group. However, no strong relationship between the ciclosporin exposure and the magnitude or time course of the response in P-CyC, P-creatinine, CK MB, P-TnT or S-S 100 B could be established.

A retrospective post-hoc safety analysis of plasma creatinine at 1-6 months showed no lasting effects. No other unexpected safety issues were observed and the overall frequencies of AEs and SAEs were comparable between the ciclosporin group and the placebo group.

Based on the negative outcome of this study and taking the transient increase in biomarkers of kidney injury into account, no further studies are planned with ciclosporin within this indication.

# 14 TABLES AND FIGURES

## 14.1 Demographic Data

Baseline characteristics are tabulated in the Statistical Report in Appendix 16.1.9.

## 14.2 Efficacy Data

Tables and figures of efficacy data are tabulated in the Statistical Report in Appendix 16.1.9.

## 14.3 Safety Data

### 14.3.1 Displays of Adverse Events

**Table 14.3.1.1 Summary Display of Adverse Events (safety population)**

| | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|
| Total number of unique AEs [a] | 28 | 29 | 57 |
| Total number of AEs | 28 | 29 | 57 |
| Total number of subjects with at least one AE | 21 (28%) | 20 (25%) | 41 (26%) |
| Total number of unique related AEs[a] | 3 | 2 | 5 |
| Total number of related AEs | 3 | 2 | 5 |
| Total number of subjects with at least one related AE | 3 (4%) | 2 (3%) | 5 (3%) |
| Total number of unique SAEs [a] | 12 | 14 | 26 |
| Total number of SAEs | 12 | 14 | 26 |
| Total number of subjects with at least one SAE | 10 (13%) | 11 (14%) | 21 (14%) |

[a] Unique Preferred Term are only calculated once within each subject
Source: Appendix 16.2.7

**Table 14.3.1.2 Number of Unique Adverse Events by System Organ Class, Preferred Term and Treatment (safety population)**

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| Infections and Infestations | Subjects | 7 (9%) | 5 (6%) | 12 (8%) |
| | AEs | 8 | 6 | 14 |
| | Related | 2 | 2 | 4 |
| | Pneumonia | 4 (5%) 4 | 1 (1%) 1 | 5 (3%) 5 |
| | Postoperative Wound Infection | 1 (1%) 1 | 2 (3%) 2 | 3 (2%) 3 |
| | Urinary Tract Infection | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Colon Gangrene | 1 (1%) 1 | | 1 (1%) 1 |
| | Infection | | 1 (1%) 1 | 1 (1%) 1 |
| | Mediastinitis | | 1 (1%) 1 | 1 (1%) 1 |
| | Respiratory Infection | 1 (1%) 1 | | 1 (1%) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Subjects | 9 (12%) | 3 (4%) | 12 (8%) |
| | AEs | 9 | 3 | 12 |
| | Pleural Effusion | 6 (8%) 6 | 2 (3%) 2 | 8 (5%) 8 |
| | Pneumothorax | 2 (3%) 2 | | 2 (1%) 2 |
| | Cough | | 1 (1%) 1 | 1 (1%) 1 |
| | Dyspnoea | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders | Subjects | 3 (4%) | 4 (5%) | 7 (5%) |
| | AEs | 3 | 4 | 7 |
| | Pericardial Effusion | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Angina Pectoris | | 1 (1%) 1 | 1 (1%) 1 |
| | Atrial Fibrillation | 1 (1%) 1 | | 1 (1%) 1 |
| | Cardiac Disorder | | 1 (1%) 1 | 1 (1%) 1 |
| | Cardiac Failure | 1 (1%) 1 | | 1 (1%) 1 |
| | Ventricular Arrhythmia | | 1 (1%) 1 | 1 (1%) 1 |

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| Investigations | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Liver Function Test Abnormal | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Hepatic Enzyme Increased | | 1 (1%) 1 | 1 (1%) 1 |
| Nervous System Disorders | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Cerebrovascular Accident | | 2 (3%) 2 | 2 (1%) 2 |
| | Syncope | 1 (1%) 1 | | 1 (1%) 1 |
| Psychiatric Disorders | Subjects | 1 (1%) | 2 (3%) | 3 (2%) |
| | AEs | 1 | 2 | 3 |
| | Delirium | | 2 (3%) 2 | 2 (1%) 2 |
| | Sleep Disorder | 1 (1%) 1 | | 1 (1%) 1 |
| Gastrointestinal Disorders | Subjects | | 2 (3%) | 2 (1%) |
| | AEs | | 2 | 2 |
| | Diarrhoea | | 1 (1%) 1 | 1 (1%) 1 |
| | Gastrointestinal Haemorrhage | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Chest Pain | 1 (1%) 1 | | 1 (1%) 1 |
| | Non-Cardiac Chest Pain | | 1 (1%) 1 | 1 (1%) 1 |
| Renal and Urinary Disorders | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Renal Failure | 1 (1%) 1 | | 1 (1%) 1 |
| | Urinary Retention | | 1 (1%) 1 | 1 (1%) 1 |

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| Vascular Disorders | Subjects | 1 (1%) | 1 (1%) | 2 (1%) |
| | AEs | 1 | 1 | 2 |
| | Related | 1 | | 1 |
| | Deep Vein Thrombosis | | 1 (1%) 1 | 1 (1%) 1 |
| | Hypertension | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders, Cardiac Disorders, Respiratory, Thoracic and Mediastinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Cardiac Arrest, Myocardial Infarction, Pulmonary Oedema | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Gastrointestinal Haemorrhage, Cardiac Arrest | 1 (1%) 1 | | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Gastrointestinal Disorders, Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Chest Pain, Nausea, Vomiting | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Investigations | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Pyrexia, C-Reactive Protein Increased | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Postpericardiotomy Syndrome | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| | AEs | 1 | | 1 |
| | Vascular Graft Occlusion, Myocardial Infarction | 1 (1%) 1 | | 1 (1%) 1 |
| Renal and Urinary Disorders, Renal and Urinary Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Hydronephrosis, Ureteral Stenosis | | 1 (1%) 1 | 1 (1%) 1 |

Subjects= Number of Subjects in SOC, i.e. each subject is calculated only once
AEs=Number of unique AEs in SOC, i.e. each preferred term is only calculated once within a subject
Related=Number of unique related AEs in SOC
For each preferred term the number of subjects in n and (%) is given together with the actual number of occurrence for the preferred term
MedDRA version 18.0
Source: Appendix 16.2.7

**Table 14.3.1.3 Number of Unique Serious Adverse Events by System Organ Class, Preferred Term and Treatment (safety population)**

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| Infections and Infestations | Subjects | 3 (4%) | 3 (4%) | 6 (4%) |
| | AEs | 3 | 3 | 6 |
| | Related | | 2 | 2 |
| | Pneumonia | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Colon Gangrene | 1 (1%) 1 | | 1 (1%) 1 |
| | Infection | | 1 (1%) 1 | 1 (1%) 1 |
| | Mediastinitis | | 1 (1%) 1 | 1 (1%) 1 |
| | Postoperative Wound Infection | 1 (1%) 1 | | 1 (1%) 1 |
| Cardiac Disorders | Subjects | 3 (4%) | 2 (3%) | 5 (3%) |
| | AEs | 3 | 2 | 5 |
| | Pericardial Effusion | 1 (1%) 1 | 1 (1%) 1 | 2 (1%) 2 |
| | Atrial Fibrillation | 1 (1%) 1 | | 1 (1%) 1 |
| | Cardiac Disorder | | 1 (1%) 1 | 1 (1%) 1 |
| | Cardiac Failure | 1 (1%) 1 | | 1 (1%) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Subjects | 3 (4%) | | 3 (2%) |
| | AEs | 3 | | 3 |
| | Pleural Effusion | 3 (4%) 3 | | 3 (2%) 3 |
| Nervous System Disorders | Subjects | | 2 (3%) | 2 (1%) |
| | AEs | | 2 | 2 |
| | Cerebrovascular Accident | | 2 (3%) 2 | 2 (1%) 2 |
| Cardiac Disorders, Cardiac Disorders, Respiratory, Thoracic and Mediastinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| | Cardiac Arrest, Myocardial Infarction, Pulmonary Oedema | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Gastrointestinal Haemorrhage | | 1 (1%) 1 | 1 (1%) 1 |
| Gastrointestinal Disorders, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Gastrointestinal Haemorrhage, Cardiac Arrest | 1 (1%) 1 | | 1 (1%) 1 |
| General Disorders and administration Site Conditions | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Non-Cardiac Chest Pain | | 1 (1%) 1 | 1 (1%) 1 |
| General Disorders and administration Site Conditions, Gastrointestinal Disorders, Gastrointestinal Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Chest Pain, Nausea, Vomiting | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Postpericardiotomy Syndrome | | 1 (1%) 1 | 1 (1%) 1 |
| Injury, Poisoning and Procedural Complications, Cardiac Disorders | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Vascular Graft Occlusion, Myocardial Infarction | 1 (1%) 1 | | 1 (1%) 1 |
| Investigations | Subjects | 1 (1%) | | 1 (1%) |
| | AEs | 1 | | 1 |
| | Liver Function Test Abnormal | 1 (1%) 1 | | 1 (1%) 1 |

| | | Ciclosporin N=(76) | Placebo N=(79) | Total N=(155) |
|---|---|---|---|---|
| Renal and Urinary Disorders, Renal and Urinary Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Hydronephrosis, Ureteral Stenosis | | 1 (1%) 1 | 1 (1%) 1 |
| Vascular Disorders | Subjects | | 1 (1%) | 1 (1%) |
| | AEs | | 1 | 1 |
| | Deep Vein Thrombosis | | 1 (1%) 1 | 1 (1%) 1 |

Subjects= Number of Subjects in SOC, i.e. each subject is calculated only once
AEs=Number of unique AEs in SOC, i.e. each preferred term is only calculated once within a subject
Related=Number of unique related AEs in SOC
For each preferred term the number of subjects in n and (%) is given together with the actual number of occurrence for the preferred term
MedDRA version 18.0
Source: Appendix 16.2.7

**Table 14.3.1.4 Adverse Events: Number of Subjects by Treatment, System Organ Class, Preferred Term and Intensity (safety population)**

**Treatment: Ciclosporin**

| | | Mild | | Moderate | | Severe | | Total | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | | R | NR | R | NR | R | NR | R | NR | R+NR |
| Respiratory, thoracic and mediastinal disorders | Pleural effusion | | 1 (1%) | | 5 (7%) | | | | 6 (8%) | 6 (8%) |
| | Pneumothorax | | 1 (1%) | | 1 (1%) | | | | 2 (3%) | 2 (3%) |
| | Dyspnoea | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Infections and infestations | Colon gangrene | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| | Postoperative wound infection | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| | Respiratory infection | 1 (1%) | | | | | | 1 (1%) | | 1 (1%) |
| | Urinary tract infection | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| | Pneumonia | 1 (1%) | 2 (3%) | | 1 (1%) | | | 1 (1%) | 3 (4%) | 4 (5%) |
| Cardiac disorders | Atrial fibrillation | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| | Cardiac failure | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| | Pericardial effusion | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| Gastrointestinal disorders, Cardiac disorders | Gastrointestinal haemorrhage, Cardiac arrest | | | | | | 1 (1%) | | 1 (1%) | 1 (1%) |
| General disorders and administration site conditions | Chest pain | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Injury, poisoning and procedural complications, cardiac disorders | Vascular graft occlusion, myocardial infarction | | | | | | 1 (1%) | | 1 (1%) | 1 (1%) |
| Investigations | Liver function test abnormal | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Nervous system disorders | Syncope | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Psychiatric disorders | Sleep disorder | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |

| | | Mild | | Moderate | | Severe | | Total | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | | R | NR | R | NR | R | NR | R | NR | R+NR |
| Renal and urinary disorders | Renal failure | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Vascular disorders | Hypertension | 1 (1%) | | | | | | 1 (1%) | | 1 (1%) |

R=Related (Possibly), NR=Not Related (Unlikely)
If a subject had the same preferred term more than once then the subject will be calculated only once and under the worst case for relationship and the worst case for intensity
MedDRA version 18.0
Source: Appendix 16.2.7

## Table 14.3.1.4 Adverse Events: Number of Subjects by Treatment, System Organ Class, Preferred Term and Intensity (safety population)

## Treatment: Placebo

| | | Mild | | Moderate | | Severe | | Total | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | | R | NR | R | NR | R | NR | R | NR | R+NR |
| Infections and infestations | Postoperative wound infection | | 2 (3%) | | | | | | 2 (3%) | 2 (3%) |
| | Infection | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| | Mediastinitis | | | | | 1 (1%) | | 1 (1%) | | 1 (1%) |
| | Pneumonia | 1 (1%) | | | | | | 1 (1%) | | 1 (1%) |
| | Urinary tract infection | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| Nervous system disorders | Cerebrovascular accident | | | | | | 2 (3%) | | 2 (3%) | 2 (3%) |
| Psychiatric disorders | Delirium | | | | 2 (3%) | | | | 2 (3%) | 2 (3%) |
| Respiratory, thoracic and mediastinal disorders | Pleural effusion | | 2 (3%) | | | | | | 2 (3%) | 2 (3%) |
| | Cough | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |
| Cardiac disorders | Angina pectoris | | 1 (1%) | | | | | | 1 (1%) | 1 (1%) |
| | Cardiac disorder | | | | | | 1 (1%) | | 1 (1%) | 1 (1%) |
| | Pericardial effusion | | | | 1 (1%) | | | | 1 (1%) | 1 (1%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Ventricular arrhythmia | | 1 (1%) | | 1 (1%) | 1 (1%) |
| Cardiac disorders, Cardiac disorders, Respiratory, thoracic and mediastinal disorders | Cardiac arrest, Myocardial infarction, Pulmonary oedema | | | 1 (1%) | 1 (1%) | 1 (1%) |
| Gastrointestinal disorders | Diarrhoea | | 1 (1%) | | 1 (1%) | 1 (1%) |
| | Gastrointestinal haemorrhage | | | 1 (1%) | 1 (1%) | 1 (1%) |
| General disorders and administration site conditions | Non-cardiac chest pain | | 1 (1%) | | 1 (1%) | 1 (1%) |
| General disorders and administration site conditions, Gastrointestinal disorders, Gastrointestinal disorders | Chest pain, Nausea, Vomiting | | 1 (1%) | | 1 (1%) | 1 (1%) |
| General disorders and administration site conditions, Investigations | Pyrexia, C-reactive protein increased | 1 (1%) | | | 1 (1%) | 1 (1%) |
| Injury, poisoning and procedural complications | Postpericardiotomy syndrome | | 1 (1%) | | 1 (1%) | 1 (1%) |
| Investigations | Hepatic enzyme increased | 1 (1%) | | | 1 (1%) | 1 (1%) |
| | Liver function test abnormal | 1 (1%) | | | 1 (1%) | 1 (1%) |
| Renal and urinary disorders | Urinary retention | 1 (1%) | | | 1 (1%) | 1 (1%) |
| Renal and urinary disorders, Renal and urinary disorders | Hydronephrosis, Ureteral stenosis | | | 1 (1%) | 1 (1%) | 1 (1%) |
| Vascular disorders | Deep vein thrombosis | | 1 (1%) | | 1 (1%) | 1 (1%) |

R=Related (Possibly), NR=Not Related (Unlikely)
If a subject had the same preferred term more than once then the subject will be calculated only once and under the worst case for relationship and the worst case for intensity
MedDRA version 18.0
Source: Appendix 16.2.7

### 14.3.2 Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events

All AEs including deaths, SAEs and clinically meaningful AEs are listed in Appendix 16.2.7.

### 14.3.3 Narratives of Deaths, Other Serious and Certain Other Clinically Meaningful Adverse Events

Narratives of all 26 SAEs, including one fatal SAE in the placebo group, are located in a separate document.

### 14.3.4 Data Listings (Each Subject) for Abnormal Clinically Meaningful Laboratory Values, Vital Signs, Physical Examinations and Other Observations Related to Safety

All such observations were to be reported as AEs and are included in Appendix 16.2.7.

## 14.4 Other Data

Not applicable.

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## LIST OF APPENDICES

### 16.1 Study Information

#### 16.1.1 Protocol and protocol amendments

Enclosed.

#### 16.1.2 Sample of case report form (unique pages only)

Enclosed.

#### 16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms

Enclosed.

#### 16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Enclosed.

#### 16.1.5 Signatures of principal or co-ordinating investigator(s) or sponsor's responsible medical officer

Enclosed.

#### 16.1.6 Listing of patients receiving test drug(s)/ investigational product(s) from specific batches, where more than one batch was used

Available on request.

#### 16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

Enclosed.

#### 16.1.8 Audit certificates

N.A. since no audit was performed.

#### 16.1.9 Documentation of statistical methods

Enclosed.

#### 16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Available on request.

#### 16.1.11 Publications based on the study

Not applicable.

#### 16.1.12 Important publications referenced in the report

Available on request.

### 16.2 Patient Data Listings

#### 16.2.1 Discontinued patients

One patient was discontinued after study drug administration in accordance with pre-defined withdrawal criteria, see Section 10.1.

#### 16.2.2 Protocol deviations

Not applicable as no major protocol deviations were reported.

#### 16.2.3 Patients excluded from the efficacy analysis

One patient was excluded from the efficacy analysis in accordance with pre-defined withdrawal criteria, see Section 10.3.

#### 16.2.4 Demographic data

Enclosed.

#### 16.2.5 Drug concentration data

Enclosed.

#### 16.2.6 Individual efficacy response data

Enclosed.

#### 16.2.7 Adverse event listings (each patient)

Enclosed.

#### 16.2.8 Listing of individual laboratory measurements by patient

Enclosed.

### 16.3 Case Report Forms

#### 16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

Available on request.

#### 16.3.2 Other CRFs submitted

Not applicable.

### 16.4 Individual Patient Data Listings

Not included.

**Annex I (Appendix 16.1.5)**

## PRINCIPAL INVESTIGATOR SIGNATURE AND STATISTICIAN'S SIGNATURE

**Study Title:** Ciclosporin to Protect Renal function In Cardiac Surgery. CiPRICS. A Phase II Double Blind Randomized Placebo Controlled Study.

**Study Number:** 2014.001.

**Report Version:** Final 12-May-2017

**Study Authors:**

I have read this report and confirm that it to the best of my knowledge accurately describes the conduct and results of the study.

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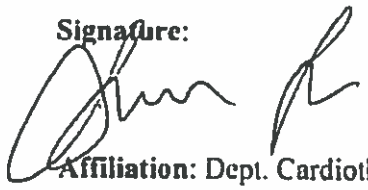
**Principal Investigator:** Henrik Bjursten, MD, PhD

**Signature:**



**Affiliation:** Dept. Cardiothoracic Surgery, Skåne University Hospital, SE-221 85 Lund, Sweden

**Date:** 12/5 -2017

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**Sponsor's Responsible Medical Officer:** Not applicable since this was an investigator-initiated study.

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**Statistician:** Helene Jacobsson, MSc

**Signature:**

**Affiliation:** Clinical Studies Sweden – Forum South, Unit for Medical Statistics and Epidemiology, Skåne University Hospital, Lund

**Date:**

30/5 - 2017