Synopsis

Name of sponsor/company:	Cardiorentis AG, Churerstrasse 77, CH-8808 Pfäffikon
Name of product:	Ularitide-2.5 mg for injection
Name of active ingredient:	Ularitide acetate

Title of the study:

Randomized, double-blind, placebo-controlled dose escalation study of ularitide followed by a 42-hour infusion for the treatment of acute kidney injury (AKI) in patients post cardiac surgery

Study acronym:	TRUST
Study registry:	EudraCT No.: 2018-004871-11
Protocol number:	ULA02

Studied period:

19-Nov-2019 (the only treated subject in) to 21-Nov-2019 (the only treated subject out)

Study and reporting period:

The study included a screening period, a treatment period in 2 parts (Part A and Part B), and a follow-up period.

The study was on hold since 12-Feb-2020 due to a lower-than-expected recruitment rate and was prematurely terminated by the sponsor on 26-Sep-2022. At study termination, 1 patient had been enrolled and had already terminated the trial prematurely.

Reason for early study termination:

Based on a review of current literature on acute kidney injury following cardiac surgery and recently published real-world data from the German Heart Center, the sponsor concluded that the ULA02 study was underpowered to demonstrate statistically significant differences between the study arms. To achieve statistically significant differences, the sample size would need to be many times larger with the study itself to be conducted in multiple centers, rather than in a single center.

Clinical phase: 2

Objectives and endpoints:

Objectives Part A: To investigate the safety, tolerability, and dose-effect-relationship of 3 different doses of ularitide on renal and central hemodynamics and on renal excretory function in patients post cardiac surgery, who have developed AKI (as defined in the protocol), and to identify the individual maximum tolerated dose of ularitide in these patients.

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Objectives Part B: To investigate the safety, tolerability, and effect of the individual maximum tolerated ularitide dose identified in Part A for up to an additional 42 hours.

Primary endpoint: Change (absolute and percentage) of GFR-1h-Crea at the end of the dose escalation phase (6 hours post infusion start) versus (vs) Baseline (mean value from 2 post-surgery screening measurements).

Other endpoints included safety endpoints and performance endpoints, e.g. a variety of renal parameters, length of intensive care unit stay, number of patients requiring renal replacement therapy and further exploratory endpoints.

Methodology:

This was a randomized, double-blind, placebo-controlled dose escalation study with an adjacent continued treatment period at the individual maximum tolerated dose and a 30-day follow-up.

Patients planned to undergo cardiac surgery were routinely assessed for their risk of developing postoperative AKI using a predictive score for cardiac surgery-associated AKI on the day before surgery. This scoring was a routine procedure and unrelated to this study. Those patients identified to be at a medium to high risk to develop post-surgery AKI (score ≥3) were asked to participate in the study.

Patients who have provided written informed consent were screened for their pre-surgery renal status. Only patients meeting the pre-surgery eligibility criterion of an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 could transition into the post-surgery screening phase.

During the first 3 hours post-surgery, the patients' GFR-1h-Crea was determined twice approximately 1 hour apart. Post-surgery AKI was defined as a ≥50% decrease in each GFR-1h-Crea measurement compared to the pre-surgery eGFR value. If all other eligibility criteria including hemodynamic stability within the first 2 hours post-surgery were met, patients were randomized to receive either ularitide or placebo.

Baseline assessments had to be completed within 1 hour after randomization. Intravenous (IV) infusion of the investigational medicinal product (IMP) (ularitide or placebo) was started immediately after randomization and completion of baseline assessments.

In Part A, patients received a continuous IV infusion of either ularitide at a starting dose of 20 ng/kg/min or matching placebo at the same infusion rate. After 2 hours, the ularitide dose was increased to 40 ng/kg/min, and after another 2 hours to 80 ng/kg/min by adjusting the infusion rate. The highest dose was administered for a further 2 hours. Patients in the placebo arm received matching placebo at the same infusion rates. The planned total duration of the dose escalation phase was 6 hours.

After Part A, patients entered Part B at their maximum tolerated dose in Part A, i.e. where stopping criteria were absent, and were continuously infused at that dose for another 42 hours.

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During study treatment, patients received all appropriate post-surgery therapy as clinically indicated. However, use of sacubitril-valsartan from the day before surgery until 12 hours after end of the IMP infusion was not permitted.

Over the entire treatment period, the patients were assessed for safety, tolerability, and efficacy parameters. The primary efficacy endpoint was assessed at the end of the dose escalation phase at 6 hours post infusion start (Part A).

Follow-up assessments were performed 12 hours after end of treatment and on Day 30 after end of study treatment to monitor the patients' safety and record clinical outcome parameters.

Number of subjects (total and for each treatment) planned and analyzed:

- A sample size of 45 patients was planned, 30 in the ularitide and 15 in the placebo arm.
- The study was temporarily discontinued and subsequently terminated early, and only 1 patient was treated and analyzed.

Diagnosis and main criteria for inclusion and exclusion:

Patients were eligible for inclusion into the study, if each of the following inclusion criteria applied:

Inclusion criteria

1. Male and post-menopausal female patients of ≥ 18 years. Post-menopause was defined as ≥12 months after the last menstruation without an alternative medical cause
2. Body mass index ≤ 35 kg/m^2
3. Decrease of post-surgery GFR-1h-Crea measured twice approximately 1 hour apart within the first 3 hours post-surgery ≥50% compared to pre-surgery eGFR (CKD-EPI)
4. Index hospitalization for planned cardiac surgery via open sternotomy on cardiopulmonary bypass namely coronary artery bypass graft, valve surgery, thoracic aortic surgery, repair of ventricular septal defect or a combination thereof
5. Preoperative predictive score for cardiac surgery-associated AKI of 3 or higher according to Jiang et al., 2016[1]
6. Hemodynamic stability defined as:
    a. Systolic blood pressure >90 mmHg in at least 2 consecutive non-invasive measurements that were at least 60 minutes apart in a 2-hour time window immediately post-surgery

[1] Jiang W, Teng J, Xu J, Shen B, Wang Y, Fang Y, Zou Z, Jin J, Zhuang Y, Liu L, Luo Z, Wang C, Ding X. Dynamic Predictive Scores for Cardiac Surgery-Associated Acute Kidney Injury. J Am Heart Assoc. 2016 Aug 4; 5(8). pii: e003754. doi: 10.1161/JAHA.116.003754.

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   b. No increase in vasopressor and/or inotropic support at the end of a 2-hour time window immediately post-surgery compared to its start

7. Signed written informed consent

Patients were not eligible for inclusion into the study, if any of the following exclusion criteria applied:

Exclusion criteria

1. Documented medical history of renal artery stenosis (≥70%), nephrotic syndrome, renal sclerosis
2. Clinical diagnosis of
   a. Severe cardiogenic shock (INTERMACS level I) or extracorporal membrane oxygenation, or any other short-term pre-surgery mechanical circulatory support other than intra-aortal balloon pump
   b. Right ventricular infarction
3. Body temperature >38.0°C on the day before surgery
4. Patients started on dialysis prior to surgery or immediately thereafter
5. Pre-surgery eGFR (CKD-EPI) <60 mL/min/1.73 m^2 based on serum concentrations of creatinine and cystatin C
6. Treatment with sacubitril-valsartan from the day before surgery until 60 hours post infusion start
7. Advanced cancer or any other acute or chronic consuming disease which could relevantly interfere with the surgery outcome (survival) or success of test treatments
8. Known hypersensitivity to the active substance or to any of the excipients of each investigational medicinal product (verum and placebo) or other natriuretic peptides
9. Known Hepatitis B or C or Human Immunodeficiency Virus infection
10. Participation in an interventional clinical drug trial within 1 month prior to randomization
11. Legal incapacity or limited legal capacity
12. Breastfeeding or pregnancy
13. Employees of the sponsor or patients who were employees or relatives of the investigator
14. Patient has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

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Test product, dose, mode of administration:
Test product: Ularitide-2.5 mg for injection, containing 2.5 mg of the active ingredient ularitide (free base) and mannitol; continuous IV infusion.

Dose: Part A: escalating doses of 20, 40 and 80 ng/kg/min; Part B: individual maximum tolerated dose as identified in Part A.

Reference product, dose, mode of administration,:
Matching placebo, containing mannitol; continuous IV infusion.

Dose: Part A: volumes corresponding to the escalating doses of ularitide; Part B: individual maximum tolerated dose as identified in Part A

Duration of treatment: 48 hours, i.e. 6 hours during the dose escalation phase (Part A; 2 hours for each dose), and 42 hours for continued treatment at the maximum individual tolerated dose (Part B).

Statistical methods:
As only 1 patient was randomized no statistical analysis was performed.

Summary and Conclusions:
Overall, 40 patients were screened, and 1 patient was randomized and treated. Not meeting the post-surgery GFR-1h-Crea criterion (inclusion criterion 3) was the most common reason for screening failure (25 patients).

The patient randomized was a white, female patient (age range 65 to 84 years), who received 3 doses of placebo within a total treatment duration of 5.0 hours.

The patient experienced 1 treatment-emergent serious adverse event (SAE), which was not related to the IMP. This SAE was evaluated to be related to the surgical procedure and led to withdrawal of the IMP. The patient prematurely terminated the treatment due to the SAE.

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