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: Open-label, dose escalation study of ularitide for the investigation of hemodynamic effects in patients with pulmonary arterial hypertension

Study acronym: UPAH

Study registry: EudraCT No.: 2020-004815-29

Protocol number: ULA03

Studied period: 24-May-2022 to 09-Dec-2022

Study and reporting period: The study included a screening period, a treatment period in 2 parts separated by a dose-escalation step, and a follow-up period.

The study was on hold since 19-Jan-2023 due to a substantially lower-than-expected recruitment rate and was prematurely terminated by the sponsor on 15-Jul-2024. At trial termination, three (3) patients had been enrolled, who had already finished the trial according to the study protocol.

Reason for early study termination: Based on a review of the data obtained from the two enrolled patients and from the current literature on PAH on the one hand side, and of the underlying assumptions for the design of this clinical study on the other hand side, the sponsor concluded that the clinical study was underpowered to demonstrate a statistically significant effect in treated patients. To achieve such effect, a many times larger sample size would be required

Clinical phase: 2

Objectives and endpoints: The objectives of the clinical trial were the investigation of the hemodynamic effects induced by stepwise increased doses of the IV administered ularitide in patients suffering from PAH, and the investigation of the safety and tolerability of ularitide in this patient population.

Primary efficacy endpoint: Maximum absolute change of pulmonary vascular resistance (PVR) from baseline at the individual maximum tolerated ularitide dose.

Other endpoints included safety endpoints, secondary efficacy endpoints such as dose-related hemodynamic parameters, and further exploratory endpoints.

Methodology:

This was a prospective, open-label, dose escalation, multi-center, phase II proof-of-concept clinical study in patients with PAH.

Patients suffering from PAH and who were scheduled for a control visit at the respective study centre, which included right heart catheterization as part of their medical surveillance, were asked for participation in the clinical study prior to their admission to the study centre. Eligible patients who have provided informed consent were enrolled into the clinical study.

The study involved two treatment groups: Group 1 was to receive ularitide doses of 5 and 10 ng/kg/min and Group 2 ularitide doses of 20 and 40 ng/kg/min, respectively (see Figure 1). On Day 1 (treatment day) a right heart catheter (RHC) was inserted (as part of routine clinical control practice), and hemodynamic measurements performed via the RHC were started immediately thereafter and before study drug infusion. SBP and heart rate were continuously monitored during treatment. The specified dose escalation scheme was used to collect data allowing the evaluation of the ularitide-induced hemodynamic response in PAH patients in a dose-dependent manner.

Treatment duration per dose was up to three hours. Treatment duration could be reduced to less than three hours, if the hemodynamic effect of ularitide on PVR had reached a plateau. A plateau is defined as any two consecutively measured PVR values at least 30 min apart with a variability ≤10%. However, the initial dose of 5 ng/kg/min must have been administered at least for 90 min.

After the end-of-treatment (EOT) assessment following the end of the second dosing sequence in each group, the RHC was removed. Patients were followed up for safety one hour after RHC removal (±15 min) and at hospital discharge or 24 ±4 hours after treatment start, whatever came first. A follow-up call was performed 30 ±2 days after the day of treatment.

After the last patient of Group 1 had finished the examination at hospital discharge, an interim analysis of safety data was planned before treatment of patients in Group 2 would have started. However, since the clinical study was terminated before all patients of Group 1 had been enrolled, the planned interim analysis of safety data was not performed.

Safety and tolerability of the ularitide-treatment was assessed for the entire treatment period.

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

- A sample size of 10 patients was planned, 5 in each of the two treatment groups.
- The study was temporarily discontinued in Jan 2023 and then prematurely terminated in Jul 2024. At that time a total of three patients had been treated.

Diagnosis and main criteria for inclusion and exclusion:

Patients were eligible for inclusion into the clinical study, if they met each of the following inclusion criteria:

Inclusion criteria

1. Male and female patients 18 to 75 years of age
2. Known diagnosis of PAH (idiopathic, hereditary, drug-associated, due to connective tissue disease, simple congenital heart defects closed >1 year) as evidenced by
   a. PVR >3 WU (determined at last right heart catheterization), and
   b. Mean pulmonary arterial pressure (mPAP) ≥25 mmHg (determined at last right heart catheterization), and
   c. Pulmonary arterial wedge pressure (PAWP) ≤15 mmHg (determined at last right heart catheterization)
3. Stable PAH background therapy for ≥3 months including endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE5) inhibitors, soluble guanylate cyclase (sGC) stimulators, prostacyclin analogues, prostacyclin-receptor agonists or any combination thereof
4. Scheduled for a control visit including right heart catherization
5. No morning intake of PAH background medication at the day of ularitide treatment
6. Negative pregnancy test (β-human chorionic gonadotropin) at screening in women of childbearing age
7. Ability to understand the purpose and risks of the study and to provide signed and dated written informed consent

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

Exclusion criteria

1. Known diagnosis of
   a. medium- or high-grade left-sided valvular disease
   b. hypertrophic obstructive cardiomyopathy
   c. chronic heart failure
   d. diastolic heart failure with preserved ejection fraction (HFpEF)
   e. state post pulmonary embolism
   f. clinically relevant parenchymal lung diseases as evidenced by
      - Ratio of forced expiratory volume in one second to forced vital capacity (FEV1/ FVC ratio) of <55% of predicted
      - Forced vital capacity (FVC) <60% of predicted, and
      - Diffusion capacity of the lung for carbon dioxide (DLCO) <50% of predicted.

      All respiratory values must not be older than 12 months at the time of screening and documented in the medical history of the patient. If documented values were older than 12 months from screening, the patient must undergo spirometry during screening to determine these values.
2. Contraindications for right heart catheterization such as uncontrolled coagulation disorders, uncontrolled disorders of cardiac excitation generation and conduction, permanent pacemaker, implanted defibrillator
3. Documented left ventricular ejection fraction <40%

4. Documented partial pressure of pulmonary arterial oxygen <50 mmHg (despite oxygen supplementation) and/or partial pressure of carbon dioxide >50 mmHg
5. Uncontrolled severe systemic hypertension at screening, i.e. arterial hypertension >200 mmHg (systolic) or >120 mmHg (diastolic)
6. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening
7. Severe hepatic impairment or porphyria characterized by elevations of one or both serum transaminases (alanine-aminotransferase, aspartate-aminotransferase) >3 x upper limit of normal (ULN) or bilirubin >3 x ULN at screening
8. Use of sGC stimulators within three days prior to start of ularitide treatment
9. Use of nitric oxide donors or sacubitril-valsartan within three days prior to start of ularitide treatment
10. Known hypersensitivity to the active substance or to any of the excipients of the study drug or other natriuretic peptides
11. Known Hepatitis B or C or human immunodeficiency virus infection
12. Participation in an interventional clinical trial within one month prior to screening or 5 half-lives of the corresponding investigational medicinal product, whichever is longer
13. Active substance abuse
14. Legal incapacity or limited legal capacity
15. Breastfeeding or pregnancy
16. Employees of the sponsor or patients who are employees or relatives of the investigators
17. Patients committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

Test product, dose, mode of administration, batch no.:

Ularitide-2.5 mg for injection, containing 2.5 mg of the active ingredient ularitide and mannitol; continuous IV infusion.

Dose-group 1: escalating doses of 5 and 10 ng/kg/min ularitide

Dose-group 2: escalating doses of 20 and 40 ng/kg/min ularitide

Duration of treatment: Maximum 360 min.

Statistical methods:

As only three patients were enrolled and treated, no statistical analysis was performed.

Summary and Conclusion:

Three patients were enrolled and treated. There were no screening failures. The patients had signed the informed consent form and met all eligibility criteria. All patients had stable PAH background therapy at the time of screening and completed the clinical study. All patients were female with an age range of 47 to 74.

One patient experienced one AE, tachycardia, which was rated to be mild and treatment-related. This AE led to withdrawal of the IMP after 105 min of treatment.

Vital signs, laboratory data (hematology, coagulation, blood chemistry; peripheral oxygen saturation) and ECG data did not indicate IMP-related safety issues.

The patients received doses of 5 and 10 ng/kg/min during the first and second dosing sequence, respectively. The primary endpoint was the maximum absolute change in PVR at the individual maximum tolerated dose versus baseline. None of the patients showed a meaningful reduction in PVR at their individual maximum tolerated dose versus baseline. Since the study employed a dose escalation design in order to identify doses with an effect on hemodynamic parameters in PAH patients, the doses of the first dosing sequence in Group 1 have to be considered non-efficacious.

No conclusion can be drawn on a possible treatment effect of ularitide on hemodynamic parameters in PAH patients.