

Ularitide Clinical Trial Factsheet

Ularitide has been studied for the treatment of acute heart failure (AHF) in two double-blind, placebo-controlled Phase Iⁱ and Phase IIⁱⁱ studies (Safety and efficacy of an Intravenous placebo controlled Randomised Infusion of Ularitide in a prospective double – blind Study in patients with symptomatic, decompensated chronic heart failure - SIRIUS I and SIRIUS II).

Cardiorentis is now recruiting for patients in a Phase III trial – TRUE-AHF (TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure).

Phase II trial summaries

SIRIUS I (Phase IIa)

Study design

SIRIUS I was designed to examine the effects of ularitide in patients with AHF. It was a randomised, double-blind, ascending-dose study. 24 patients with AHF received 24 hour intravenous (IV) infusion of placebo or ularitide at 7.5, 15, or 30 ng/kg/min in addition to standard therapy.

Key findings

- In general, a meaningful number of patients in each ularitide group had marked or moderate improvement over baseline in self-assessed dyspnea (breathlessness) at six hours, whereas minimal improvement was observed in the placebo group
- The proportion of subjects with marked or moderate improvement was greater in the 15 and 30 ng/kg/min groups compared with the 7.5 ng/kg/min group
- Mortality at Day 30 was 5.6% (1 of 18 patients) across the three ularitide groups and 16.7% (1 of 6 patients) in the placebo group
- The most frequently reported adverse events (AEs) were hypotension, a confusional state, restlessness and dyspnea

SIRIUS II (Phase IIb)

Study design

The SIRIUS II study was a placebo controlled, double-blind, parallel-group study, which randomised 221 patients with ADHF to one of three different ularitide doses of 7.5 ng/kg/min (n=60), 15 ng/kg/min (n=53) and 30 ng/kg/min (n=55) or to placebo (N=53), which were administered in addition to standard therapy.

Key findings

- At six hours:
 - All three infusion rates of ularitide produced greater decrease in pulmonary capillary wedge pressure, a key indicator of cardiac function, compared with the placebo group
 - 34.0% of subjects in the placebo group reported no change in dyspnea as compared to 10.3% to 17.6% in the three ularitide groups
 - A greater proportion of subjects in the 7.5, 15, and 30 ng/kg/min dose (39.7%, 47.1% and 45.5%, respectively) reported a marked or moderate improvement over baseline in self-assessed dyspnea compared with subjects in the placebo group (24.5%), $p < 0.05$ for each dose versus placebo
- The median time of hospitalisation was shorter for the 15 ng/kg/min and 30 ng/kg/min groups (122 and 158 hours, respectively) compared with the placebo and the 7.5 ng/kg/min groups (201 and 192 hours, respectively)
- Mortality at Day 30 was 3% across the three ularitide dose groups compared to 13.2% for the placebo group
- The most frequent drug-related AEs across the three ularitide groups were hypotension and dose-dependent decreases in blood pressure (BP)
 - Decreases in BP were seen between four to 12 hours after start of dosing and about half were asymptomatic
- Other frequent ularitide-related AEs included:
 - Sweating (4.2%)
 - Dizziness (3.0%)
 - Asthenia (2.4%)
 - Headache (1.2%)
 - Decreased heart rate or bradycardia (1.2%)

Phase III Trial summary - TRUE-AHF

Study design

TRUE-AHF is a Phase III, multicentre, randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of ularitide as an IV infusion in addition to conventional therapy in patients suffering from AHF.

The study is currently in the process of recruiting participants from 190 centres in North America, Europe and Latin America and intends to recruit approximately 2,116 patients with AHF.

Patients will be randomised within 12 hours after clinical assessment at the emergency room. Following randomisation, patients will receive a 48 hour infusion of either ularitide 15 ng/kg/min or matching placebo (1:1 ratio) in a double-blind manner. In addition, patients will receive all appropriate

therapy, that may include: vasodilatory, inotropic and diuretic support as clinically indicated. However, nesiritide, levosimendan, milrone, or any other phosphodiesterase will not be administered.

Clinical data for the primary efficacy endpoints will be assessed at six, 24 and 48 hours from the start of the infusion.

Safety parameters will be assessed during hospitalisation and AEs and serious adverse events (SAEs) will be evaluated until 30 days after the start of therapy.

Primary efficacy endpoints

Assessment of the clinical composite will be performed at six, 24 and 48 hours after the start of ularitide IV infusion. Patients will be classified as 'improved' if the patients are:

- Moderately or markedly improved at all three time points (at six, 24 and 48 hours) and do not fulfil criteria for 'worse' during the first 48 hours following the start of the study drug infusion
 - Patients will be classified as 'worse' if (during the 48 hours) they:
 - Die
 - Experience worsening heart failure requiring a pre-specified intervention at any time during the first 48 hours
 - Experience moderate or marked worsening of their global assessment at any of the three time points (at six, 24 or 48 hours)

Primary safety endpoint

The Primary Safety Endpoint for the TRUE-AHF trial is:

- All-cause mortality and cardiovascular re-hospitalisation at 30 days after start of study drug infusion

Secondary Endpoints

The secondary endpoints are:

- Changes of levels of NT-pro BNP in the blood at 48 hours of treatment from baseline
- All-cause mortality and cardiovascular rehospitalisation at Day 90 after start of study drug infusion
- Cardiovascular mortality rate at Day 90

Exploratory Endpoints

The exploratory endpoints are:

- Components of primary efficacy endpoint:
 - Proportions improved/not improved and worse/not worse
 - Proportions of patients alive

- Proportions of patients requiring an intervention for persistent or worsening heart failure
- Proportions of patients who are 'moderately or markedly improved'
- Combined risk of all-cause mortality or cardiovascular rehospitalisation at Day 60 and Day 180 after start of study drug infusion
- Changes in BP and heart rate during the first 72 hours from the start of the study drug infusion or hospital discharge, whatever comes first
- Length of stay of index hospitalisation in hours after start of study drug infusion
- Change in glomerular filtration rate (GFR) from baseline, as assessed by change in Modification of Diet in Renal Disease (MDRD) at 48 hours after start of the study infusion as compared to baseline

ⁱ Mitrovic V, Lüss H, Nitsche K, et al. Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: A double-blind, placebo-controlled, ascending-dose trial. *Am Heart J*. 2005;150:1239.e1-1239.e8.

ⁱⁱ Mitrovic V, Seferovic P, Simeunovic D, et al. Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Euro Heart J* 2006; 27, 2823–2832.