

RELAX-AHF Study Backgrounder

Overview

RELAX-AHF is a Phase III study assessing the effects of RLX030 (serelaxin), a recombinant form of the human hormone relaxin-2, on symptom relief and clinical outcomes in patients with acute heart failure (AHF)¹. The study builds on the dose-finding Phase II study with RLX030 in AHF called Pre-RELAX-AHF². The main findings of RELAX-AHF were:

- The study met one of its two primary efficacy endpoints in reducing dyspnea (shortness of breath)³, the most common symptom of AHF⁴, and was therefore positive⁵
- The study did not meet its secondary efficacy endpoints, namely days alive and out of hospital up to day 60, and cardiovascular death or re-hospitalization due to heart or kidney failure up to day 60³
- The study showed that RLX030 significantly reduced all-cause and cardiovascular mortality at day 180³
- The study met a number of additional efficacy endpoints³
- The study showed that RLX030 was well tolerated³

Study design

The RELAX-AHF study was an international, multi-center, randomized, double-blind, placebo-controlled Phase III study in patients who met the following eligibility criteria³:

- Hospitalized for AHF
- Dyspnea at rest or with minimal exertion
- Congestion in the lungs
- Normal or elevated blood pressure (systolic blood pressure [SBP] >125 mm Hg)
- Elevated levels of brain natriuretic peptide (BNP) or its pre-active form (NT-proBNP) (≥ 350 pg/mL or ≥ 1400 pg/mL, respectively)
- Impaired kidney function (defined as an estimated glomerular filtration rate or eGFR of 30-75 mL/min/1.73m²)
- Received intravenous loop diuretics of at least 40 mg

A total of 1,161 patients were randomized (1:1) to receive placebo or RLX030 30 mcg/kg/day on top of standard heart failure therapy throughout the study³.

Study endpoints

The primary efficacy endpoints of the study were³:

- Change from baseline in patient-reported dyspnea measured by visual analog scale (VAS) scores through day five
- Change in patient-reported dyspnea on the Likert scale at 6, 12 and 24 hours

These efficacy endpoints are patient-reported outcomes that quantify patients' subjective assessments of their dyspnea, which cannot be readily measured by the physician^{6,7}. The VAS provided an absolute assessment of dyspnea relief, asking patients to evaluate their breathing at a given moment relative to the best and the worst their breathing had ever felt³. The Likert scale provided a baseline-related short-term assessment of dyspnea relief, asking patients to rank how much better or worse their breathing was at a given moment compared to when they first started the study³.

The study protocol specified that if either of the two primary endpoints was positive, then the study itself was positive⁵.

Secondary efficacy endpoints of the study included³:

- Number of days alive and out of the hospital from baseline to day 60
- Proportion of patients who experienced cardiovascular death or re-hospitalization due to heart failure or kidney failure from baseline to day 60

Additional efficacy endpoints included worsening signs and symptoms of heart failure and average length of hospital stay up to day 14 and cardiovascular mortality through day 180³.

Efficacy data were assessed up to day 60. In addition, patients were followed up to day 180 to collect longer-term survival data, which was designated as a safety endpoint³.

Results^{3,5}

- The study met one of the two primary endpoints, and therefore was positive
 - Compared to placebo, treatment with RLX030 improved dyspnea by about 19%, as measured by the VAS area under the curve (AUC) from baseline through day 5 (placebo: 2308 mm-hours, RLX030: 2756 mm-hours, which is 19% greater, $p=0.0075$)
 - Compared to placebo, RLX030 was not associated with an increased proportion of patients with moderately or markedly improved dyspnea on the Likert scale at the combined time points of 6, 12, and 24 hours (placebo: 25.9%, RLX030: 26.9%; $p=0.702$)
- The study did not meet its secondary efficacy endpoints, namely days alive and out of hospital up to day 60 ($p=0.37$) and cardiovascular death or re-hospitalization due to heart or kidney failure up to day 60 ($p=0.89$)
- RLX030 reduced all-cause and cardiovascular mortality by more than one-third
 - By 180 days, 7.3% of patients died from all causes in the RLX030 group compared to 11.3% in the placebo group ($p=0.02$). All-cause mortality up to day 180 was a safety endpoint of the study
 - Cardiovascular deaths up to day 180 (an additional efficacy endpoint) was also reduced with RLX030 compared to placebo: 6.1% vs. 9.6% ($p=0.028$)
- The study met a number of additional efficacy endpoints: RLX030 significantly reduced the worsening signs and symptoms of heart failure up to day 14 ($p=0.024$) and reduced the mean length of stay in hospital ($p=0.039$) and in the intensive/cardiac care unit ($p=0.029$)
- RLX030 was well tolerated and adverse events (AEs) were generally comparable for RLX030 and placebo
 - No clinically significant differences in the incidence of serious adverse events were seen between treatment groups
 - Discontinuations due to adverse events were similar for patients given RLX030 (4.6%) and placebo (3.9%)
 - The most common AEs by system organ class in both treatment groups were cardiac disorders, metabolism and nutrition disorders and gastrointestinal disorders

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