Pivotal Phase 3 Trial of Neridronate in Complex Regional Pain Syndrome Type-1: CRPS-RISE Study Design and Methodology

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Background

- Complex Regional Pain Syndrome Type-1 (CRPS-1) is a rare, chronic, and often disabling condition. There are no FDA-approved medicines, and few therapies demonstrate efficacy in rigorous clinical trials.[1]
- Neridronate, approved for treatment of CRPS in Italy,[2-4] is an alkyl-aminobisphosphonate believed to impact CRPS-1 via multiple mechanisms, including bone-targeting and immunomodulatory actions as well as anti-inflammatory effects.[5-7]
- In the Italian phase 3 registrational trial, a significant improvement in pain intensity was observed within the first 20 days of treatment with intravenous (IV) neridronate 400 mg vs placebo (p=0.043).[3]
- The intended population for the planned Phase 3 trial of neridronate for CRPS-1, CRPS-RISE, leverages a precision medicine approach believed to improve the odds of identifying patients with CRPS-1 most likely to respond to neridronate based on its proposed mechanisms of action and analysis of prior trials. Specifically, patients with the warm CRPS-1 subtype (edema, red/warm skin) and a positive triple phase bone scan may be most likely to respond.

Objective

- To present the study design and methods of CRPS-RISE, which aims to evaluate the efficacy, safety, and tolerability of IV neridronate for the treatment of CRPS-1.

Methods

Design & Eligibility

- CRPS-RISE (NCT07210515) is a phase 3, multicenter, randomized, triple-blind, placebo-controlled trial evaluating the efficacy, safety, and tolerability of IV neridronate for the treatment of CRPS-1.
- ~270 participants who satisfy all eligibility criteria (key criteria in Table 1) will be enrolled in the trial across ~60 sites in the US.
- The trial includes a screening, treatment, and follow-up period (Figure 1).
- Eligible participants will be randomized to receive either neridronate or matching placebo in a 1:1 ratio.

Concomitant Treatments and Therapies

- All participants will take supplemental calcium and vitamin D (standard of care for participants treated with bisphosphonates).
- Stable doses of many medicines and therapies are allowed to continue during the trial. For example:
  - Analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs, opioids ≤ 45 morphine equivalents/day, and neuropathic therapies (e.g., gabapentinoids)
  - Physical therapy, occupational therapy, rehabilitation modalities, psychological or psychiatric modalities

Methods (cont'd)

Rescue Treatment

- Rescue medications are permitted to treat pain and include:
  - 1st line: Acetaminophen, with a total daily dose ≤ 4 grams/day
  - 2nd line: For moderate to severe pain (e.g., > 4 on 0-10 scale) that persist 30 min after acetaminophen was taken as rescue, oxycodone 5 mg immediate release may be taken (up to 4 times/day)

Prophylaxis of Acute Phase Reaction

- Short-term use of IV bisphosphonates, as in the case of this trial, is generally well-tolerated, with the most common adverse event expected to be acute phase reaction.
- Acute phase reaction typically presents with the first infusion as 'flu like' illness; mostly self-limiting with resolution within 24 to 72 hours.
- Participants will be prophylactically treated with oral acetaminophen 1 hour prior to the first infusion.

Endpoints & Assessments

- The trial is well-powered for the primary endpoint (> 90%) and key secondary efficacy endpoints (> 80%).
- The primary objective is to assess the efficacy of neridronate vs placebo based on change from baseline to Week 12 in pain intensity per 7-day diary averages (11-point NRS) (Figure 2).
- Key secondary endpoints (analyzed in a hierarchical manner) include:
  - ≥ 50% pain reduction from baseline to Week 12 in pain intensity using the 7-day dairy averages on the 11-point NRS
  - Change from baseline to Week 12 in CRPS Severity Score (CSS)
  - Patient Global Impression of Change in CRPS-related health at Week 12
  - Change from baseline to Week 12 in the Short Form Health Survey (SF-36), Physical Functioning domain
- Other secondary endpoints include assessments of percent reduction in average pain intensity from baseline to various time points (e.g., ≥ 30% reduction at Day 10), sleep disturbance, time to onset of analgesia, range of motion, pain with active motion, SF-36, McGill Pain Questionnaire, use of rescue medications, and warm CRPS clinical features.
- Safety and tolerability will be evaluated by incidence, seriousness, and severity of treatment-emergent adverse events; treatment emergent adverse events leading to discontinuation; values and changes from baseline in physical exams, vital signs, labs, and cardiac monitoring.

Site Selection & Enrollment Considerations

- Site selection across the US is ongoing, and enrollment is expected to begin in the first quarter of 2026.
- For participants who are not close to an investigative site, transportation and accommodation will be offered.
- Participants may have low vitamin D levels at screening, which is common in the U.S. There will be an opportunity to supplement and increase vitamin D levels during screening, as needed.

Table 1. Key Eligibility Criteria

Key Inclusion Criteria
≥ 18 years old
Diagnosed with CRPS-1 in a single affected limb based on clinical Budapest Criteria
A known inciting event (e.g., sprain, fracture, contusion)
CRPS-1 duration ≤ 6 months
Average weekly pain that is moderate-severe (> 4 on an 11-point "pain now" NRS, based on eDiary data)
Precision Medicine Inclusion Criteria
Positive triple-phase bone scan, demonstrating increased uptake in the affected limb compared to the contralateral limb (phase 2 and/or phase 3) during Screening ▪ A recent historic scan may be acceptable
Warm CRPS-1 subtype features in the affected limb defined as edema present and: ▪ ≥ 2 of the following: redness, warmth, moderate-to-severe edema severity
Key Exclusion Criteria
Score of ≥ 40 on the Pain Catastrophizing Scale
Prior use of neridronate or use of other protocol-restricted medicines or treatments
Significant underlying health conditions (e.g., severely impaired renal function, significant liver disease, excessive alcohol consumption, recent significant malignancy) ▪ Basal cell or squamous cell skin carcinoma, Stage 0 cervical carcinoma in situ, and treated ductal carcinoma in situ of the breast are ok within the last 5 years
Safety-related exclusions related to usage of an IV bisphosphonate, neridronate: ▪ Hypocalcemia ▪ Vitamin D deficiency ▪ Evidence of select dental findings ▪ Presence of ocular inflammation

Figure 1. Trial Schematic

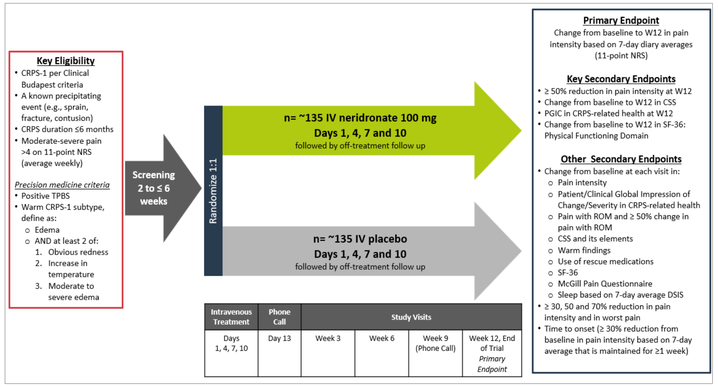

Figure 2. Pain Assessment

The participants will be asked to record their CRPS-related pain intensity using the following question:

Please rate your CRPS pain by selecting the one number that best describes your pain.

0 1 2 3 4 5 6 7 8 9 10

No pain — Worst possible pain

Discussion

- Neridronate's efficacy and safety in patients with early CRPS are supported by over 10 years of research and real-world clinical use in Italy.
- Pain specialists are uniquely positioned to identify CRPS-1 patients, who may be eligible to enroll in this pivotal clinical trial evaluating the efficacy and safety of neridronate, which has the potential to be the first FDA-approved medicine for CRPS-1.

Key Takeaways

- CRPS-RISE is a pivotal trial evaluating the bisphosphonate, neridronate, as an investigational treatment for CRPS-1, a rare disease that carries substantial burden for CRPS-1 patients, healthcare professionals, and the healthcare system.
- A key element of this trial's design is the precision medicine approach, an approach intended to improve the odds of identifying participants who are most likely to respond to neridronate: those with early, warm CRPS-1 and a positive triple phase bone scan.
- Given the progressive nature of CRPS and the different subtypes, it is important to consider a precision medicine approach that targets the right treatments to the right patients at the right time.
- There is a critical need for innovation and research to find safe and effective treatments that not only manage CRPS symptoms but also help prevent disease progression.

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Disclosures
SB: Consultant for Ambros Therapeutics, Inc. and Akigai; **SNR**: Consultant for Ambros Therapeutics, Inc. and Vertex Pharmaceuticals; **MR**: Consultant for Ambros Therapeutics, Inc.; **GC, ASR, MS**: Employee of Ambros Therapeutics, Inc.

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