Beyond Averages: Informing Clinical Decision Making in the Pharmacologic Treatment of CRPS-1 using Bayesian Network Meta-Analysis

Brian Cuffel, PhD[1], Amarita S. Randhawa, PharmD[1], Gail Cawkwell, MD, PhD[1]
[1]Ambros Therapeutics, Inc.
Corresponding Author: Brian Cuffel, PhD| bcuffel@ambrostx.com

24th Annual Pain Medicine Meeting
November 13-15, 2025 | Austin, TX

Background

- Complex Regional Pain Syndrome Type 1 (CRPS-1) is a rare, chronic condition with no FDA-approved medicines and no clear pharmacological standard of care.[1]
- Few therapies demonstrate efficacy in rigorous clinical trials, and while randomized controlled trials (RCTs) report average treatment effects, these have not led to clinical consensus in the management of CRPS-1.[1]
- Prior evidence-syntheses have focused on detecting average differences from placebo, but this approach does not estimate how likely the population-average treatment effect is to deliver benefit of a magnitude that is meaningful to patients or clinicians.

Objective

- To identify which pharmacologic treatments are most likely to deliver a clinically meaningful reduction, for adults with CRPS-1, using Bayesian network meta-analysis

Methods

- **Data Source:** Eligible randomized controlled trials were derived from a published meta-analysis of pharmacologic treatments available in the US or in development for CRPS-1 in the US that reported mean difference in VAS pain score between treatment and placebo arms.[2] The study question and eligibility criteria were prespecified using a PICO framework (Table 1).
- **Statistical Approach:** A Bayesian network meta-analysis (NMA) was conducted using a random-effects model, implemented in the gemtc package in R. A normal likelihood and identity link function were specified. Posterior distributions were estimated via Markov Chain Monte Carlo sampling with four chains, 5,000 adaptation iterations, and 20,000 sampling iterations. Mean treatment effects were estimated relative to placebo and reported with 95% credible intervals (CrI). Between-study heterogeneity was quantified by the estimated posterior standard deviation of random effects (SD_d = 6.03), corresponding to an I² of 11%. This indicates modest statistical heterogeneity and supports indirect comparisons across the network.
- **Threshold for Clinically Meaningful Benefit:** A clinically meaningful benefit was defined as a placebo-adjusted reduction in VAS pain score of ≥20 mm. Greater than a 10 mm difference on a 100 mm pain VAS has been defined as the minimum of clinically relevant difference in several chronic pain conditions. Therefore, in this study, we prespecified a higher threshold to reflect a magnitude truly meaningful to patients.[3] Posterior probabilities were used to estimate the likelihood that the true (population-average) treatment effect exceeded this threshold.

Table 1. PICO framework for the Bayesian network meta-analysis of pharmacologic treatments for CRPS-1 (placebo-controlled RCTs)

| Element	Definition
Population	Adults with Complex Regional Pain Syndrome Type 1 (CRPS-1) enrolled in randomized controlled trials
Intervention	Pharmacologic treatments available in the US or in development for CRPS-1 in the U.S. (e.g., neridronate, alendronate, ketamine, gabapentin)
Comparator	Placebo (common comparator across all included trials)
Outcome	Clinically meaningful reduction in pain, defined as a ≥20 mm decrease in pain on the 100 mm VAS

Results

Across 17 trials, a total of 375 subjects were randomized to active treatment arms, and 379 to placebo. The evidence network was a placebo-anchored star (Figure 1), with edge thickness proportional to the number of trials per comparison. Treatments included:

- **Neridronate:** n=160
- **Ketamine:** n=79
- **Alendronate:** n=59
- **Pamidronate:** n=48
- **Gabapentin:** n=46
- **Corticosteroids:** n=41
- **Mannitol:** n=41
- **IVIG:** n=13
- **Scavengers / Magnesium Sulfate:** n=257

Ranked posterior probabilities of achieving a ≥20 mm VAS pain reduction, alongside average placebo-adjusted effects and 95% credible intervals, are summarized in Table 2.

- **Neridronate** demonstrated the largest placebo-adjusted treatment effect (–24.4 mm, 95% CrI: –35.1 to –13.2) and the highest probability (83.2%) of the average effect exceeding the clinically meaningful threshold (≥20 mm).
- **Alendronate** followed with a placebo-adjusted effect of –21.5 mm (95% CrI: –31.8 to –8.6) and a probability of 65.3%.
- **Other treatments** — including pamidronate, gabapentin, ketamine, and scavengers/magnesium sulfate—had lower magnitudes of effect and lower posterior probabilities of achieving clinical benefit. 95% CrI exceeded 0 for these treatments, reflecting a chance of worsening.

Figure 1. Evidence Network: CRPS-1 Pharmacological Treatments vs Placebo*
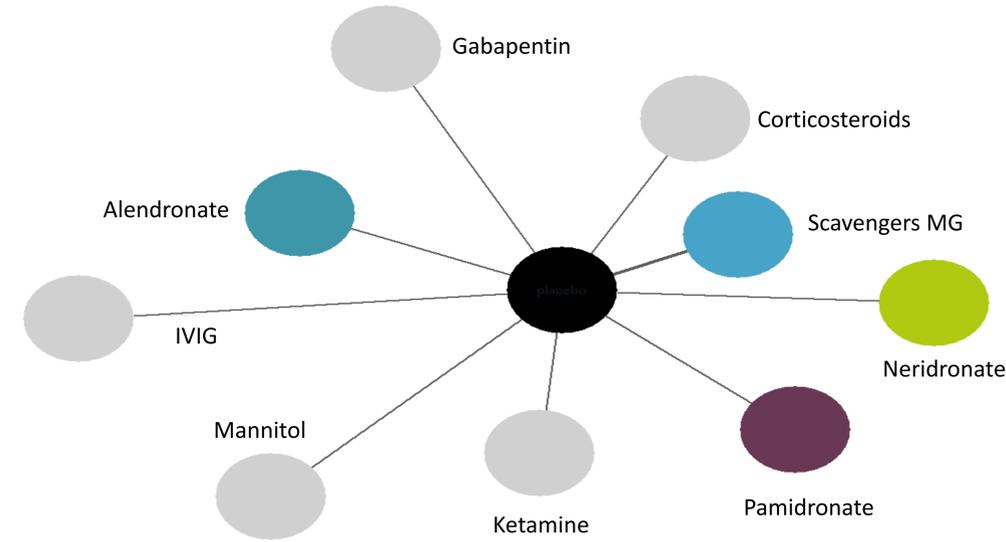
*Placebo node shown in black. Bisphosphonates use distinct colors (neridronate in green, pamidronate in purple, alendronate in teal); Scavengers/Mg in light blue; other pharmacological treatments in light gray. The thickness of the connector lines reflect the number of trials comparing each treatment with placebo.

Neridronate (investigational), followed by alendronate, most likely to meet the ≥20 mm clinically meaningful benefit threshold for reduction in pain

Table 2. Probability of a Clinically Meaningful Benefit in Pain Reduction*†

Rank	Treatment	Probability ≥20 mm	Mean Difference vs Placebo (mm)	95% Credible Interval (CrI, mm)
1	**Neridronate**	**83.18%**	**-24.4**	**-35.3 to -13.2**
2	**Alendronate**	**65.31%**	**-21.5**	**-31.9 to -8.6**
3	Pamidronate	19.17%	-13.9	-29 to 0.3
4	IVIG	15.18%	-11.1	-29.2 to 7.3
5	Mannitol	3.25%	-0.4	-21.4 to 20.6
6	Ketamine	2.58%	-9.1	-20.1 to 1.9
7	Corticosteroids	0.98%	-4.3	-16.9 to 9.4
8	Gabapentin	0.29%	8.1	-8.9 to 25
9	Scavengers MG	0.04%	0.9	-7.5 to 8.9

*All trials from the Fassio et al[2] meta-analysis were included except 3 trials related to treatments (i) not available in the US or (ii) not in development for a potential FDA-approved indication. Clinically meaningful benefit defined as a ≥20 mm VAS pain reduction.

† Probabilities represent the posterior probability that the true (population-average) treatment effect versus placebo is at least a 20-mm reduction on the 100-mm VAS.. Negative values indicate greater pain reduction relative to placebo.

Discussion

- This analysis demonstrates the value of moving beyond average treatment effects to inform clinical decision making and guideline development. Focusing on the probability of achieving a clinically meaningful pain reduction sharpened separation among treatments and provides decision-useful numbers for shared decision-making, guideline panels, and HTA decision making.
- Clear distinctions across pharmacologic treatments were evident by focusing analyses on clinically meaningful magnitude of benefit.[1]
- Within the bisphosphonate class, meaningful differences in both effect magnitudes and certainty of effects were observed with neridronate over alendronate and pamidronate.
  - Some of these trials included participants with CRPS-1 who were early in their disease course and/or presented with a specific clinical phenotype. If treatment effects are influenced by the disease timeframe (e.g., early) and/or phenotype (e.g., warm subtype), then early diagnosis and prompt initiation of treatment may be important.
- CRPS-1 subtypes and mechanisms of action varied across these studies, and it will be important to evaluate these influences in future research.

Limitations

- Network meta-analysis is widely used to synthesize comparative effectiveness for health technology assessment and clinical guideline development. It relies on indirect comparisons versus a common comparator, and results should be treated as supportive, not definitive.
- Indirect comparisons assume trials would have shown the same relative effects if they had compared the same treatments. Differences in effect modifiers (e.g., diagnostic criteria, timing of pain assessments, disease duration/subtype, dosing, geography, etc.) may affect trial outcomes and were not explored in this analysis.
- Existing CRPS-1 trials are small and vary in design and risk of bias. RCTs included in this meta-analysis were assessed by Fassio et al. as having low risk of bias using the Cochrane tool with independent assessors.[2]

Key Takeaways

- This Bayesian network meta-analysis demonstrates neridronate treatment has the highest probability of achieving a clinically meaningful pain reduction (≥20 mm VAS pain reduction) in CRPS-1.
- Evidence synthesis based on the probability of achieving ≥20 mm VAS improvement as a clinically meaningful benefit (rather than treatment averages alone) offers clearer guidance for patients, clinicians, and guideline developers.[4]
- Future studies in CRPS-1 should consider the use of responder outcomes and those evaluating bisphosphonates as potential treatments should compare or rank bisphosphonates vs. alternatives pharmacologic treatments.