A Precision Medicine Approach to Identifying Patients with Complex Regional Pain Syndrome Type 1 who may Benefit from Neridronate

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Background

- Complex Regional Pain Syndrome Type 1 (CRPS-1) is a rare, chronic, and often disabling condition with no FDA-approved medicines.[1]
- Per the FDA, precision medicine targets the right treatments to the right patients at the right time.[2]
- With this goal in mind, we explored clinical phenotype factors that might identify patients who would respond better to treatment with neridronate, an alkyl-aminobisphosphonate.
- Given that neridronate is believed to have inhibitory effects on activated mononuclear cells that produce inflammatory mediators, we hypothesized that inflammation-relevant clinical features of the warm CRPS-1 subtype (i.e., warmth, redness, edema), all generally present early in disease, might be associated with greater clinical efficacy of neridronate.[3,4]

Objective

Evaluate neridronate's efficacy in a subgroup of participants who presented with key features of the warm CRPS-1 subgroup.

Methods

- Three phase 3, randomized, double-blind, placebo-controlled trials (KF7013-02 [NCT03530345], NERIAS[5], NAIMES[6]; Table 1) achieved their primary efficacy endpoint.
  - These trials evaluated the efficacy and safety of high-dose intravenous (IV) (NERIAS; KF7013-02) or intramuscular (NAIMES) neridronate 400 mg vs placebo for CRPS.
  - Following IRB/Ethics Committee approval, participants provided informed consent prior to any trial procedures.
  - NERIAS and NAIMES were completed trials and the basis of regulatory filings in Italy; KF7013-02 combined with a second phase 3 trial terminated early due to futility. Despite this, KF7013-02 still achieved its primary endpoint while the second phase 3 trial did not.
- In all three trials, participants diagnosed with CRPS-1 who exhibited features of the warm CRPS subtype in the affected limb at screening or baseline prior to initial dosing (hereafter, collectively referred to as "baseline") were identified as a subgroup. For comparison, a corresponding subgroup of participants without these features was also identified in each trial, and the two groups were evaluated in this post-hoc analysis.
- Features of the warm subtype included redness, warmth, and/or edema.
  - In the KF7013-02 trial, redness and/or warmth in the affected limb were scored as Yes or No by the investigator, and edema was scored as either present (+) or absent (-) by the investigator.
  - In NERIAS and NAIMES trials, edema in the affected limb was scored on a 4-point NRS, defined as 0=none, 1=mild, 2=moderate, 3=severe.
- Change from baseline in average pain intensity was analyzed using a linear mixed effects for repeated measures model (MMRM) with fixed effect terms for treatment, visit and the treatment by visit interaction. Baseline was included in the model as a covariate with subject as a random effect.
- Least squares mean changes from baseline (LS mean change) in average pain intensity to the time of each study's primary endpoint (KF7013-02: LS mean change_{12week}, NERIAS: LS mean change_{6week}, NAIMES: LS mean change_{4week}) and corresponding LS mean differences between neridronate and placebo were estimated from the MMRM model.
  - LS mean difference values indicate the placebo adjusted change in average pain from baseline; larger negative numbers indicate greater pain relief with neridronate.
  - P-values for testing if the LS mean differences between neridronate and placebo were significantly difference from zero were not adjusted for multiple comparisons.

Results

- Overall, 206 participants across 3 trials had CRPS-1 at baseline (Table 1).
- Trial KF7013-02

Red and/or warm affected limb subgroup (scored as yes/no)

- The analysis included participants with CRPS-1 and available Week 12 pain intensity scores with (n=12) and without (n=19) physical exam findings of affected limb redness and/or warmth prior to receiving study treatment.
- Treatment with neridronate in participants with a red and/or warm affected limb at baseline showed a greater LS mean $\text{difference}_{12week}$ in average pain intensity of -2.11 (95% CI: -3.99, -0.23; nominal p=0.03; Table 2) compared to those without these inflammatory signs at baseline (-1.14; 95% CI: -1.92, -0.36; nominal p=0.004; Table 2).

Edema in the affected limb subgroup (scored as present (+)/absent (–)

- The analysis included participants with CRPS-1 and available Week 12 pain intensity scores with (n=17) and without (n=14) edema prior to receiving study treatment.
- Treatment with neridronate in participants with baseline edema resulted in an LS mean $\text{difference}_{12week}$ in average pain intensity of -2.11 (95% CI: -3.32, -0.90; nominal p=0.001; Figure 1), which was greater than that observed in participants without baseline edema (-0.91; 95% CI: -1.99, 0.17; nominal p=0.096; Figure 1).

- NERIAS

Edema in the affected limb subgroup (scored on a 4-point NRS: none, mild, moderate, severe)

- The analysis included participants with CRPS-1 and available Week 6 pain intensity scores with moderate (n=27) and mild (n=26) edema prior to receiving study treatment.
- Treatment with neridronate in participants with moderate edema prior to receiving treatment resulted in a LS mean $\text{difference}_{6week}$ in pain intensity of -28.6 (95% CI: -47.1, -10.1; nominal p=0.004; Figure 1), which was notably greater than that observed in participants with mild edema (-15.4; 95% CI: -32.0, 1.22; nominal p=0.068; Figure 1).

- NAIMES

Edema in the affected limb subgroup (scored on a 4-point NRS: none, mild, moderate, severe)

- The analysis included participants with CRPS-1 and available Week 4 pain intensity scores with severe (n=18), moderate (n=25) and mild (n=24) edema prior to receiving study treatment.
- Treatment with neridronate in participants with severe edema at baseline resulted in the greatest LS mean $\text{difference}_{4week}$ in pain intensity of -37.6 (95% CI: -61.9, -13.3; nominal p=0.005; Figure 1) vs those with moderate (-24.3 [95%CI: -39.7, -8.79; p=0.003]) and mild edema (-6.71 [95%CI: -31.5, 18.11; p=0.576]).

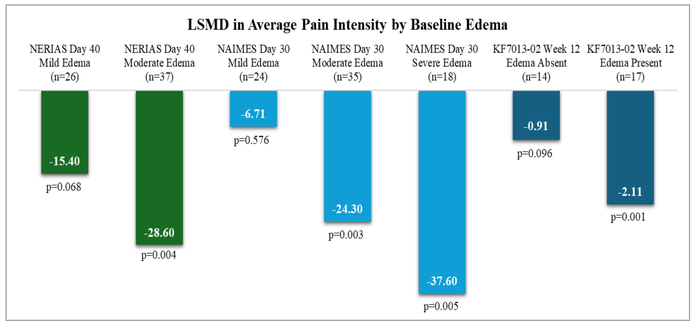
Table 1. Brief Overview of Phase 3 Trials that Achieved Primary Efficacy Endpoint

Trial Name	Select Baseline Characteristics	Treatment Arms	Primary Endpoint
KF7013-02	▪ CRPS Type-1 & Type-2, N=57 at time of early termination due to futility*; Type-1, n=46 ▪ Pain intensity (11-point NRS) at baseline, mean: neridronate: 6.9; placebo: 7.0 ▪ Time since CRPS-1 diagnosis, mean: 10.7 months	▪ IV 100mg neridronate x 4 doses over 10 days (total dose: 400 mg) ▪ placebo	Change from baseline to Week 12 in pain intensity (pain now averaged over 7 days) on an 11-point NRS: neridronate, -1.23 (SE: 0.310) vs placebo, -0.16 (SE: 0.305); p=0.011
NERIAS[5]	▪ CRPS Type-1, N=82 ▪ Positive triple-phase bone scan required ▪ Pain intensity (100 mm VAS) at baseline, mean ± SD: neridronate: 71.6 ± 11.8; placebo: 70.4 ± 8.3 ▪ Time since CRPS-1 diagnosis, mean ± SD in weeks: neridronate: 4.7 ± 4.1; placebo: 5.0 ± 4.6	▪ IV 100mg neridronate x 4 doses over 10 days (total dose: 400 mg) ▪ placebo	Proportion of population with ≥50% improvement in pain intensity from baseline to Day 40 (~6 weeks) in pain intensity on 100 -mm VAS: neridronate, n=30 (73.2%) vs placebo, n=13 (32.5%); p=0.0003
NAIMES[6]	▪ CRPS Type-1, N=78 ▪ Positive triple-phase bone scan required ▪ Pain intensity (100 mm VAS) at baseline, mean ± SD: neridronate: 73.4 ± 12.5; placebo: 74.6 ± 11.2 ▪ Time since CRPS-1 diagnosis, mean ± SD weeks: neridronate: 4.8 ± 4.9; placebo: 4.3 ± 5.5	▪ IM 25 mg neridronate once daily for 16 days (total dose: 400 mg) ▪ placebo	Proportion of population with ≥50% improvement in pain intensity from baseline to Day 30 (~4 weeks) in pain intensity on 100 -mm VAS: neridronate, n=27 (65.9%) vs placebo: n=11 (29.7%); p=0.0017

Table 2. Summary of Changes in Average Pain Intensity by Features of the Warm CRPS-1 Subtype Prior to Study Treatment†‡§

Trial KF7013-02 (11-point NRS)					
Subgroup	**Treatment Arm**	**LS mean change_{12week}**	**LS mean difference**	**95% CI**	**p-value**
(+) Red and/or warm affected limb at baseline	Neridronate (n=7)	-1.75	-2.11	-3.99, -0.23	p=0.03
	Placebo (n=5)	+0.36			
(–) Red and/or warm affected limb at baseline	Neridronate (n=8)	-1.21	-1.14	-1.92, -0.36	p=0.004
	Placebo (n=11)	-0.07			
(+) Edema in the affected limb at baseline	Neridronate (n=10)	-1.37	-2.11	-3.32, -0.90	p=0.001
	Placebo (n=7)	+0.74			
(–) Edema in the affected limb at baseline	Neridronate (n=5)	-1.10	-0.91	-1.99, 0.17	p=0.096
	Placebo (n=9)	-0.19			
NERIAS (100-mm VAS)					
Subgroup	**Treatment Arm**	**LS mean change_{6week}**	**LS mean difference**	**95% CI**	**p-value**
Moderate edema in the affected limb at baseline	Neridronate (n=18)	-51.73	-28.6	-47.1, -10.1	0.004
	Placebo (n=19)	-23.12			
Mild edema in the affected limb at baseline	Neridronate n=12)	-38.65	-15.4	-32.0, 1.22	0.068
	Placebo (n=14)	-23.27			
NAIMES (100-mm VAS)					
Subgroup	**Treatment Arm**	**LS mean change_{4week}**	**LS mean difference**	**95% CI**	**p-value**
Severe edema in the affected limb at baseline	Neridronate (n=10)	-42.71	-37.6	-61.9, -13.3	0.005
	Placebo (n=8)	-5.10			
Moderate edema in the affected limb at baseline	Neridronate (n=18)	-47.56	-24.3	-39.7, -8.79	0.003
	Placebo (n=17)	-23.29			
Mild edema in the affected limb at baseline	Neridronate (n=13)	-33.86	-6.71	-31.5, 18.11	0.576
	Placebo (n=11)	-27.16			

Figure 1. Change in Average Pain Intensity with Neridronate vs Placebo in Participants with CRPS-1 based on Baseline Edema†‡§



Discussion

- This post-hoc analysis reinforces neridronate's established efficacy in early CRPS-1, highlighting its particular clinical benefit in patients with characteristic features of the warm CRPS-1 subtype.
- Greater improvements in average pain intensity were observed with neridronate treatment vs placebo in subgroups of patients with features of warm CRPS-1 (i.e., redness, warmth, and/or edema in the affected limb) across multiple phase 3 clinical trials.
- This benefit may stem from neridronate's bone specific immunomodulatory actions, including inhibitor effects on macrophages and gamma-delta T cells, which are particularly relevant in the early, inflammatory phase of CRPS-1.
- Additional research evaluating neridronate's efficacy and safety in patients with warm CRPS-1 and other relevant precision medicine features, such as a positive triple phase bone scan (given neridronate's possible bone mechanisms) is warranted.

Limitations

- Other patient features may also be associated with neridronate response and contribute to a precision medicine approach, ie, neridronate preserves and improves bone architecture, thus increased tracer uptake in the affected limb on triple phase bone scan may also be an important attribute.[7]
- These post-hoc analyses were not pre-specified and should be considered hypothesis-generating rather than confirmatory.
- The sample sizes within subgroups may limit the ability to detect true differences and increase the risk of false negatives.
- Subgroups may differ in other baseline characteristics, introducing bias or confounding effects.
- Findings may not be generalizable beyond the studied subgroups.

Key Takeaways

- In CRPS, given the progressive nature of the disease and its different subtypes, it is important to consider a precision medicine approach that targets the right treatments to the right patients at the right time.
- This post-hoc subgroup analysis suggests neridronate shows meaningful benefit in CRPS-1, particularly in patients with features of the warm CRPS-1 subtype.
- Further research is needed to confirm the efficacy and safety of neridronate in this focused patient population.

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*KF7013-02 combined with a second pivotal phase 3 trial terminated early due to anticipated futility; despite this, KF7013-02 achieved its primary endpoint at completion following early termination. †NERIAS assessed change in pain intensity from baseline to Day 40 (~6 weeks) on 100 mm VAS; NAIMES assessed change in pain intensity from baseline to Day 30 (~4 weeks) on 100-mm VAS; KF7013-02 study assessed change in pain intensity from baseline to Week 12 on 11-point NRS. ‡Baseline defined as prior to dosing, either at screening or first visit. §In the NERIAS study, n=5 with no swelling at baseline, of which 1 was a placebo-treated participant and thus, comparison between treatment arms would not be appropriate; in the NAIMES study, n=1 with no swelling at baseline (no comparator available).

References
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Disclosures
GA: Consultant for Ambros Therapeutics, Inc., Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen, Abbvie, Alfa Sigma, Pfizer; **SB:** Consultant for Ambros Therapeutics, Inc. and Akigai; **GC, ASR, JB**: Employee/Consultant of Ambros Therapeutics, Inc.

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