2. SYNOPSIS

Title Of Study:
A randomized, double-blind, placebo controlled study to assess the safety and the efficacy of neridronate 100 mg – 4 i.v. infusions in a course of 10 days treatment – in patients with algodystrophic syndrome
Protocol number: NERI-AS001-07
EudraCT number 2007-003372-18

Investigator(s): Coordinating Investigator Prof. Silvano Adami – Verona, Italy

List of Investigators: see Appendix 16.1.4

Study Center(s): 6 centres in Italy
List of sites see Appendix 16.1.3

Publication(s):

Studied Period:	First patient enrolled: 22.01.2008 Last patient completed: 23.07.2010	**Clinical Phase:** III

Objective(s):
Primary:

- To assess the efficacy in terms of proportion of patients with a 50% reduction of pain intensity compared to baseline measured by VAS 100 mm scale recorded at the last visit of the double-blind phase (day 40)

Secondary:

- To assess improvement in pain graded on a VAS and on a verbal scale
- To assess improvement in clinical signs and symptoms
- To assess quality of life through generic and specific questionnaires
- To assess rescue analgesic consumption
- To assess the effect of neridronate on body mass index
- To assess the effect of neridronate on markers of bone turnover
- To evaluate the safety of neridronate 100 mg in a total treatment course of 400 mg i.v. infusion.

Methodology: a superiority trial with a randomized, double-blind, parallel group, placebo controlled design. After screening, patients were randomized to receive in double-blind conditions either neridronate at a total dose of 400 mg i.v., four 100 mg infusions (one every third day) in a 10-day treatment cycle, or placebo i.v. with the same administration regimen, over a 40-day study duration. After the first 40 days of study patients were unblinded: those receiving neridronate ended the study; those receiving placebo, after a 10-days wash-out period were treated with neridronate with the same regimen.

Number of Subjects:
Planned: 80 randomised patients

Screened: 84 patients
Randomized: 82 patients (41 to neridronate and 41 to placebo).
Completed at visit 7: 76 patients (neridronate 40; placebo 36)
Open phase
Entered: 36 patients
Completed: 34

Analyzed
- Safety: 82 patients (neridronate 41; placebo 41)
- Efficacy (FAS): 81 patients (neridronate 41; placebo 40)
- Efficacy (PP): 78 patients (neridronate 40; placebo 38)
- Efficacy (PP Completers): 77 patients (neridronate 40; placebo 37)

Diagnosis and Criteria for Inclusion:
Patients meeting the following criteria were included:

- Male or female patients aged 18 years or greater
- Patients with confirmed diagnosis of AS according to IASP modified criteria and as evidenced by a bone scintigraphy performed within 4 months before study entry.

- Disease duration ≤ 4 months
- Patients with spontaneous pain (100 mm VAS scale) > 50 mm in the affected limb (or in the selected limb)
- Opioid analgesics, non-opioid analgesics, NSAIDs, anticonvulsants, antidepressant drugs and other non-drug therapies may be continued provided the dose is stable for at least 4 weeks before treatment start.
- Women of childbearing potential must have a negative pregnancy test (urine) before entering the study
- Women of childbearing potential must agree not to become pregnant and to breastfeed throughout the study period.
- Signature of written Inform Consent Form before any screening procedures

Test Product, Dose, Mode of Administration, Batch No(s):
Neridronate ampoules 100 mg / 8 mL i.v. infusion
Batch N: 0207SGA

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Placebo ampoules 8 mL i.v. infusion
Batch N: 0107SGA

Rescue Therapy, Dose, Mode of Administration, Batch No(s):
Paracetamol 500 mg, oral route
Batches: 01107; 01708

Duration of Treatment:
For the individual patient:
Screening: up to 14 days Double-blind phase: 40 days Wash-out: 10 days Open phase: 40 days
Global study duration:
Total recruitment period (first patient in to last patient in): 27 months
Study conduct (first patient in to last patient completed): 30 months

Criteria for Evaluation:
Main efficacy criteria

Primary efficacy parameter:
- Pain score (as recorded by the patients on a 100 mm VAS) difference between visit 2 and visit 7

Secondary parameters:
- Spontaneous pain graded on a 100 mm VAS scale recorded at the intermediate visits;
- Pain reduction evaluated by patient on a verbal scale (pain reduction: none, mild, moderate, complete reduction)
- Clinical score based on an arbitrary score (0-3) for objective signs : swelling (none, mild, moderate, severe), pain evoked by passive motion (none, mild, moderate, severe) active ROM, assessed by goniometric measurement compared to the unaffected limb
- Tenderness evaluated on a categorical score (0-3: absent, mild, moderate, severe)
- Allodynia present or absent
- Hyperalgesia, present or absent
- Sweating, present or absent
- Quality of life: SF-36 questionnaire
- Mc Gill Pain Questionnaire Short Form
- Rescue medication consumption
- BMI
- Fasting urinary CTx compared to baseline (expressed as ratio with creatinine excretion).

Safety criteria
- Monitoring and recording all adverse events (AE) and serious adverse event (SAE)
- Monitoring of hematology, blood chemistry and urinalysis
- Measurements of vital signs
- Performance of physical examinations

Statistical Methods:
The primary analysis was to be the statistical evaluation of the primary end-point: i.e. the proportion of patients with a 50% decrease from baseline in the Pain evaluation on a 100 mm VAS scale (0= no pain; 100= unbearable pain) recorded at the last visit. At this purpose treatments were to be compared with Fisher's Exact Test whilst results was to be reported as Risk Difference together with associated exact two-sided 95% Confidence Limits. Analysis was to be performed both on FAS and per-protocol sets. Being a superiority trial, the results obtained from the analysis on the FAS (intention-to-treat population) was to be considered as the primary analysis, whilst the per-protocol set was to be analyzed with the aim of ensuring that protocol violations/deviations and dropouts or withdrawals did not affect the

results. The Worst Rank approach was to be used for missing data imputation.
The secondary efficacy analyses had to include the following variables:
• Pain graded on a 100 mm Vas scale (0= no pain; 100= unbearable pain) recorded at the intermediate visits. Treatment groups were to be compared at each visit using an ANCOVA model using the change from baseline as dependent variable and baseline, treatment, and centre as covariates. Differences between treatments were to be reported as Least-Square mean estimates together with associated two-sided 95% CL.
• Pain reduction evaluation (by patient) on a verbal scale (pain reduction: none, mild, moderate, complete reduction). Treatment groups were to be compared at each visit using the Wilcoxon Rank Sum Test. Results were to be summarized using the nonparametric Hodges-Lehmann estimate together with the non-parametric Moses two-sided 95% CL.
• Clinical scale:
  a) based on an arbitrary score (0-3) for objective signs swelling (none, mild, moderate, severe); pain evoked by passive motion (none, mild, moderate, severe). Treatment groups were to be compared at each visit using the Wilcoxon Rank Sum Test. Results were to be reported using the nonparametric Hodges-Lehmann estimate of the treatment difference together with the corresponding non-parametric Moses two-sided 95% CL.
  b) Active range of motion (ROM) assessed by goniometric measurement for both affected and unaffected limb: treatment groups were to be compared at each visit using the Wilcoxon Rank Sum Test.
• Sweating, allodynia and hyperalgesia: based on a dichotomous (present/absent) evaluation. Treatments were to be compared with Fisher's Exact Test whilst results were to be reported as Risk Difference together with associated two-sided 95% Exact Confidence Limits
• Quality of life: SF 36 questionnaire. Data were to be analyzed using proper repeated measures ANOVA models in order to detect clinically and statistically significant trends.
• Mc Gill Pain Questionnaire Short Form: Data were to be analyzed using proper repeated measures ANOVA models in order to detect clinically and statistically significant trends.
• Rescue medication consumption, i.e. number of paracetamol 500 mg tablets taken were to be summarized using nonparametric methods. Additionally, rescue medication consumption was to be included as a continuous covariate in exploratory analyses of the primary end-point: using a logistic regression model to analyse the proportion of patients with a decrease ≥ 50% from baseline and in the ANCOVA model on the ranked data.
• Body Mass Index data was to be analyzed using a repeated measure mixed model similar to the model described for pain assessment by VAS; however a post-treatment bodyweight was only to be assessed on visit 7, an ANCOVA for change from baseline was performed instead.
Analyses of the open-label extension phase were to be only descriptive.

SUMMARY – CONCLUSIONS

RESULTS:

Baseline characteristics

The patient population recruited in this study consisted in patients of both sexes, with a prevalence of females (61.0% in the neridronate group and 68.3% in the placebo group) and with a broad range of ages (26-78 years) with a mean age similar in the two groups (58 years versus 57 years). On average the patients were slightly overweight with a mean BMI of 26 in both treatment groups. Most of them (66% in the Neridronate group and 56% in the placebo group) had at least one concomitant disease and was taking at least one concomitant medication (68% in the Neridronate group and 66% in the placebo group).

The proportion of patients suffering from at least one concomitant disease was slightly higher in the Neridronate group: 27/41 patients (66%) vs 23/41 patients (56%) in the placebo group.

The most common concomitant diseases were: vascular disorders (29%), metabolism and nutrition disorders (27%), including hypercholesterolemia (13%), hypothyroidism (9%) diabetes mellitus (6%) and dyslipidaemia (4%); musculoskeletal and connective tissue disorders (12%); gastrointestinal disorders (12%) and psychiatric disorders (7%).

There were no important differences between the two treatment groups.

The proportion of patients who were taking concomitant medications was similar in the two treatment groups: 28/41 patients (68%) in the Neridronate treatment group vs 27/41 patients (66%) in the placebo group.

The most common concomitant medications were analgesics and antipyretics (15%), cholesterol and triglyceride reducers (13%) and drugs for treatment of peptic ulcer (12%).

Nineteen patients (46%) in the Neridronate group and fifteen (37%) on placebo group had a previous treatment for algodystrophic syndrome and the most commonly used treatments were the same in the two treatment groups: non steroidal anti-inflammatory/antirheumatic drugs (22% in the Neridronate group and 32% in the placebo group) and analgesics and antipyretics (15% in the Neridronate group and 12% in the placebo group) except for corticosteroid for systemic use (10% in the Neridronate group vs 2% in the placebo group)

Efficacy

Primary endpoint

In the FAS, the 50% decrease cut-off was obtained in 30 Neridronate treated patients (73.2%) versus 13 placebo treated ones (32.5%): this leads to a treatment difference (Neridronate-placebo) of 40.7% [95% CI: 18.7%; 59.5%],

highly significant in favour of Neridronate (p=0.0003).

Considering that the size of the 2 efficacy analysis sets is very similar, it is not surprising to obtain very similar results in the PP set, i.e. a difference between treatments of 40.8% [95% CI: 18.5%; 59.8%], again highly significant in favour of Neridronate (p=0.0005).

The analysis performed on the 77 PP completers provides very similar results with a treatment difference of 40.0% [95% CI: 17.5%; 59.0%], highly significant in favour of Neridronate (p=0.0005).

Additional analysis of covariance on ranked changes from baseline to end of treatment, taking into account the unranked baseline value, confirms the highly significant difference between treatment groups (p<0.0001) in FAS, PP and PP completers analysis sets.

Secondary endpoints:

Pain graded on a 100 mm VAS (0= no pain; 100= unbearable pain)

Mixed model including assessments at all visits performed on changes from baseline, until visit 7 shows a significant treatment-by-visit interaction (p<0.0001) indicating a different pattern of decrease between treatment groups: pain decreases significantly from visit 3 in the Neridronate group and visit 4 in the placebo one, but always at a greater extent in Neridronate group. At the end of double-blind phase, estimates for changes form baseline were respectively -47.0 mm [95% CI: -53.7; -40.3] for Neridronate and -22.6 mm [95% CI: -29.5; -15.6] for placebo and treatment difference was estimated as -24.5 mm [95% CI: -32.6; -16.3]. VAS values in Neridronate group exhibit a slightly better improvement than placebo until visit 6, when difference becomes significant (p=0.043), but, whereas with Neridronate improvement goes on until visit 7, VAS values remain unchanged (or worsened) between visits 6 and 7 in the placebo group, leading finally to a highly significant difference between groups (p<0.0001).

Pain reduction

Results of the analysis performed on the FAS, for pain reduction assessed by patient on a verbal scale (none, mild, moderate, complete reduction) show again a highly significant difference between treatments at the end of double blind phase: p<0.0001 (2-sided Wilcoxon Two-Sample Test): median for the difference Neridronate - placebo is estimated to 1 point (location shift) toward better score, with a 95% confidence interval between 1 and 2, as estimated by the Hodges-Lehmann method.

Clinical scores

- Swelling
- Pain evoked by passive motion

scored on a 4-point scale (0-3 : none, mild, moderate, severe) were analysed on the FAS.

Swelling as well as pain evoked by passive motion both show a highly significantly better improvement in the Neridronate group compared to the placebo one at the end of the double-blind phase, with median for the difference Neridronate - placebo estimated to -1 point (location shift) toward better score, [95% CI: -1; 0] p=0.0009 for swelling, and -1 point [95% CI: -1;-1] p<0.0001 for pain,as estimated by the Hodges-Lehmann method.

Active ROM improves in both groups for affected limb from 49.6 ± 26.3 to 68.2 ± 28.5 (change 18.6 ± 15.1) in the Neridronate group versus 45.0 ± 24.0 to 53.1 ± 27.8 (change 8.1 ± 12.2) in the placebo one: difference between treatments at visit 7 is very significant (p=0.0011).

Active ROM remains almost unchanged when measured on unaffected limb from baseline to visit 7: 1.2 ± 3.4 for Neridronate versus 0.2 ± 2.7 for placebo, even if this difference appears statistically significant (p=0.011).

Clinical signs / clinical symptoms

A significant difference between treatment groups is obtained for Allodynia and Hyperalgesia at the end of the double-blind treatment, whereas for sweating, symptom present in half of the patients on visit 2 seems to disappear in almost all patients of both groups on visit 7, even with a slightly but non significantly better advantage for Neridronate.

Tenderness, assessed a 4-point scale score (0-3 : none, mild, moderate, severe) shows a highly significant difference between treatment at the end of double blind phase, p<0.0001 (2-sided Wilcoxon Two-Sample Test): median for the difference Neridronate - placebo is estimated to -1 point (location shift) toward better disappearance of symptom, with a 95% confidence interval of [-1; -1] ,as estimated by the Hodges-Lehmann method.

Quality of life: SF 36 questionnaire

A significant increase from baseline value, both at visits 6 and 7, is obtained for all items except for social functioning in the placebo group (the increase is significant only at visit 7 for Neridronate) and general health in both arms.

However a significant difference between treatments is obtained at visit 7 for all items except for role limitations due to emotional problems, vitality and general health.

Mc Gill Pain Questionnaire Short Form

A significant decrease from baseline value is observed for both sensory and affective items in both groups, but the difference between treatment arms is highly significant at visit 7. Affective items even show a significant difference in improvement from visit 6 (p=0.0044).

Rescue medication consumption

The average and median medication consumption of paracetamol appears greater in the Neridronate group, difference doesn't reach statistical significance (p=0.17 for between groups comparison at visit 7). When primary endpoint is re-analysed including rescue medication consumption as continuous covariate in a logistic regression model, it appears not to significantly influence pain response (odds ratio (OR): 0.99 [0.98; 1.01] p=0.34), whereas difference between

treatment groups remains highly significant [OR: 5.79 [2.14; 15.69] p=0.0006]; in the same way when included in the analysis of covariance on ranked changes from baseline to end of treatment, rescue medication consumption doesn't significantly influence treatment effect (p value for rescue medication consumption: 0.62, for treatment effect: p<0.0001).

Body Mass Index

BMI did not change significantly within each treatment group during double-blind phase.

Results for urinary CTx showed a statistical significant decrease in the active group versus placebo

Open-label phase

Pain assessed on VAS, for which an impairment was noted between the 2 last double-blind visits in the placebo group, decreased from 55.4 mm to 13.9 mm at the end of the open phase; 28 out of the 35 patients assessed at visit 13 (80%) decreased by at least 50% their VAS pain value compared to baseline (visit 8). Four patients classified as responders at the end of the double-blind phase were classified as not responders at the end of the open one, even if their pain score continued to improve (between 35% and 44%), without however reaching the 50% cut-off value respect visit 8. 57% of patients had a complete disappearance of pain assessed on a verbal scale, whereas swelling completely disappeared in almost all patients. An improvement was observed in affected limb for active ROM. The same improvement was noted on clinical signs and symptoms assessments. All quality of life indexes, as well as Mc Gill Pain Questionnaire scores, in particular sensory items, were also improved during the open treatment phase.

Safety:

A total of 21 patients (51%) in the Neridronate group and of 12 patients (29%) in the placebo group reported at least one treatment-emergent adverse event during the double-blind phase.
Seventeen (41%) in the Neridronate group and 6 patients (15%) in the placebo group reported at least one adverse event related to study medication (i.e. classified by the investigator as certainly, probably or possibly related).
Fourteen (14) patients (39%) out of the 36 patients participating to the open label phase reported at least one TEAE (mainly polyarthralgia (14%) and fever (11%)).

Three (3) patients (7 %) reported at least one serious adverse event (SAE) during the double blind phase with 4 events reported, all in the placebo group and all unrelated to study medication; no serious AE was reported during the open label phase.
Finally, one patient (2%) in each group withdrew due to safety reasons.

CONCLUSIONS:

The analysis of the primary endpoints of this study has demonstrated that Neridronate administered at the dosage of 100 mg – 4 i.v. infusions in a course of 10 days treatment is much more effective than placebo in reducing pain in patients with algodystrophic syndrome.
The same result was obtained both on FAS and PPS and was also confirmed when pain-related secondary endpoints, pain decrease graded on a VAS and pain reduction assessed on a verbal scale, were considered.
Neridronate showed a clinical and statistical significant difference respect to placebo for the other secondary endpoints and an improvement was also demonstrated in almost all items of SF-36 quality of life questionnaire and McGill Pain questionnaire.
Finally, when patients assigned to placebo group during the double-blind phase of the study were treated with Neridronate during the open-label extension phase, all signs and symptoms and in particular those related to pain improved.
Efficacy results obtained in this study are similar to those previously obtained in other studies with Neridronate and with a different biphosphonate, clodronate, at a dosage equivalent to 400 mg Neridronate. In effect all these studies showed a significant reduction of pain VAS and differences in all clinical variables when neridronate or clodronate were compared to placebo, while when neridronate was compared to clodronate a significant reduction of pain VAS was obtained with both drugs, but Neridronate showed a faster improvement of symptomatic pain.
Finally similar results were obtained with a third biphosphonate, alendronate, in the treatment of patients with reflex symphatetic dystrophy syndrome of foot and hand.
All these data, including those obtained in this study, suggest that biphosphonates can be considered an adequate therapy for algodystrophic syndrome.

The safety data collected in this study showed that Neridronate is well tolerated in patients with algodystrophic syndrome. The number of patients who reported at least one related treatment-emergent adverse event was equal to 41% in Neridronate group. Treatment with Neridronate was associated with a flu-like syndrome, characterised by polyarthralgia (the most common treatment related emergent adverse event occurred) and fever, well known and expected adverse reactions already reported in the drug's summary of product characteristics.
Only two patients treated with Neridronate withdrew because of an adverse event: one during the double-blind and one during the open-label phase of the study
Four serious adverse events were reported during the double-blind phase of the study all in the placebo group and not related to the treatment.

In conclusion, this study confirms the preliminary data already obtained and demonstrates that Neridronate is safe, well tolerated and effective in reducing the pain in patients with algodystrophic syndrome.