2.SYNOPSIS

Study Title:
Randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of treatment with neridronate 100 mg (four infusions over a period of 10 days) in patients with transient osteoporosis of the hip.
Study Number: TOHNER/31
EudraCT Number: 2018-003505-26
Study Phase: III
Sponsor: Abiogen Pharma S.p.A., Pisa, Italy
CRO: Phidealive S.r.l., Milano, Italy
Investigational Intervention: neridronate 100 mg i.v. (four infusions in 10 days)
Control: placebo (eight mL vials)
Study Design: Randomized, double-blind, placebo-controlled, parallel-group; open-label extension for placebo patients.
Study Duration:

- First Patient In: Q3 2019;
- Planned Last Patient Last Visit: Q3 2023;
- Total planned duration per patient: four-six months (depending on assignment);
- Total estimated period: 57 months (Q3 2024).

The TOHNER/31 study was designed to address a relevant unmet medical need in the management of transient osteoporosis of the hip, a condition characterized by acute pain, functional impairment, and a highly variable natural history. The unpredictable duration of symptoms and the lack of standardized therapeutic interventions often result in prolonged disability and reduced quality of life.
The present trial was therefore conceived to rigorously evaluate whether an early pharmacological intervention with intravenous neridronate could provide a clinically meaningful acceleration of pain resolution compared with placebo, while maintaining an acceptable safety profile.

2.1. Background and Rationale

Transient osteoporosis of the hip (TOH) is a rare, self-limiting condition characterized by acute spontaneous hip pain, functional limitation, and magnetic resonance imaging (MRI) evidence of diffuse bone marrow edema affecting the femoral head and frequently extending to the femoral neck and intertrochanteric region [1,3]. Conservative measures, including reduction of weight bearing, joint unloading, avoidance of prolonged standing, and use of analgesics, represent the standard of care but do not consistently shorten recovery time [1].
Small uncontrolled studies have suggested that bisphosphonates—particularly intravenous amino-bisphosphonates—may accelerate symptomatic improvement and the reduction or resolution of bone marrow edema on MRI in patients with TOH and related bone marrow edema syndromes [2,3]. However, robust placebo-controlled evidence has been lacking.
The clinical course of TOH is highly variable, with symptom duration ranging from a few weeks to several months, often resulting in prolonged pain, impaired mobility, and reduced quality of life.

The absence of validated predictors of disease duration further complicates clinical management and may expose patients to extended periods of functional disability. In this context, interventions capable of accelerating symptom resolution, rather than providing symptomatic relief alone, represent a relevant unmet medical need.
Neridronate has established efficacy and safety in bone and pain-related conditions characterized by altered bone turnover and acute bone pain. Its anti-resorptive and anti-edema effects, together with its documented impact on bone marrow edema–associated pain, provide a strong biological rationale for its evaluation in TOH [2,3].
The TOHNER study is the first placebo-controlled phase III trial designed to confirm the efficacy and safety of intravenous neridronate in this condition. By adopting a randomized, double-blind design, the study aimed to overcome the methodological limitations of previous uncontrolled reports and to generate robust clinical evidence on the potential role of neridronate in modifying the symptomatic course of TOH beyond the expected spontaneous resolution.

2.2. Objectives and Endpoints

Primary Objective
To evaluate the superiority of neridronate 100 mg (administered as four intravenous infusions over a 10-day period on days one, four, seven, and 10, for a total dose of 400 mg) compared to placebo in achieving remission of spontaneous pain symptoms associated with transient osteoporosis of the hip.

Primary Endpoint
A reduction ≥50% in spontaneous pain on the Huskisson Visual Analogue Scale (VAS) of 100 mm (0 = no pain; 100 = severe pain), from baseline (V2) to the end of the double-blind randomized phase (V6), will be assessed.

Secondary Objectives

- To estimate the difference in pain levels at Day 30 between the experimental and placebo groups;
- To evaluate the progression of pain intensity over time;
- To assess the improvement of quality of life;
- To assess the improvement of the functional state of the affected hip compared to baseline;
- To assess the rescue analgesic consumption (Paracetamol);
- To assess the effect of treatment on Body Mass Index (BMI);
- To assess the safety and tolerability of neridronate i.v. infusions;
- To assess imaging features and BMD over time.

Secondary Endpoints

- Post-treatment Huskisson Visual Analogue Scale (VAS) values of up to 100 mm (0 = no pain; 100 = severe pain) will be recorded at baseline (V2) and at the 30-day (V6) follow-up;

- Measurements of the intensity of the pain symptomatology on the VAS scale of 100 mm will be recorded at V2, V3, V4, V5, V7/V7A, V7B, V7C, V7D, V7E, V8/V8A;
- Measurements of the intensity of pain symptoms, expressed through the score, derived from the Short-Form McGill Pain questionnaire, will be evaluated at V2, V6, V7/V7A, V7E, V8/V8A, V9;
- Improvement of quality of life, by SF-36 questionnaire, will be evaluated at V2, V6, V7/V7A, V7E, V8/V8A, V9;
- Change of the functional state of the affected hip, by WOMAC questionnaire, will be evaluated at V2, V6, V7/V7A, V7E, V8/V8A, V9;
- Paracetamol use will be evaluated from V2 to V6 in double blind phase (for all patients) and from V6 to V7E in the open label phase (applicable only for patients who will take neridronate in open label phase); in case of discontinuation, until subject remains in the study;
- BMI will be evaluated at V1, V7/V7A, V8/V8A, V9;
- Incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs);
- Femoral DEXA measurements and MRI findings at baseline and follow-up visits.

2.3. Study Design and Methods

The study was conducted as a randomized, double-blind, placebo-controlled, parallel-group trial, designed to compare the efficacy and safety of intravenous neridronate versus placebo in patients with transient osteoporosis of the hip.
Randomization was performed in a 1:1 ratio.
The double-blind design was adopted to minimize bias in the assessment of pain-related outcomes, which represent the primary clinical manifestation of the disease and are known to be influenced by placebo response.
An open-label extension was included for patients initially assigned to placebo, allowing access to active treatment after completion of the double-blind phase while preserving the validity of the primary comparative analysis.
The overall study design was selected to ensure methodological rigor and ethical appropriateness in the context of a rare, self-limiting condition, while enabling a reliable evaluation of treatment effects within a limited sample size.

2.4. Patients

The study enrolled adult patients with a diagnosis of TOH, confirmed by clinical evaluation and magnetic resonance imaging findings consistent with diffuse bone marrow edema of the femoral head. At study entry, patients were required to present with spontaneous hip pain attributable to TOH.
Eligibility criteria were designed to ensure a homogeneous study population by excluding patients with alternative causes of hip pain, evidence of avascular necrosis or structural joint damage on

MRI, or relevant comorbid conditions that could interfere with the assessment of efficacy or safety outcomes. Patients with conditions or treatments potentially affecting bone metabolism or renal function were also excluded.
A total of 60 patients were planned for randomization. The enrolled population was considered representative of patients typically affected by TOH in clinical practice and appropriate for evaluating the therapeutic effects of neridronate in this indication.

Planned N: 60 randomized patients (approx. 54 evaluable).
Population: adults ≥18 years, MRI-confirmed TOH, VAS ≥50 mm for ≥3 weeks.

Inclusion criteria
Patients were eligible if they met all the following:

- Age of 18 years or older;
- Ability to understand study objectives and all required study procedures;
- Approval and signature of Informed Consent, prior to participating to the study;
- Women of child-bearing potential must have a negative pregnancy test prior to starting the study and use adequate contraceptive methods (for all women who already terminated pregnancy period, it's mandatory that they have interrupted breastfeeding time, before participation to the study); in order to ensure highly effective birth control methods, women will use one of the following measures: combined hormonal contraception (containing oestrogens and progestogen) associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence;
- The diagnosis of TOH will take place through the anamnestic data collection, the clinical examination, DEXA evaluation and hip bone MRI;
- MRI should indicate the typical pattern of TOH, which will show an extended and homogeneous area of reduced signal in T1 sequences, and of hyperintensity in T2 images at femoral head level, with possible extension to neck level and femoral intertrochanteric region;
- Presence of spontaneous pain longer than three weeks and expressed by the patient, on the VAS scale, as equal to or greater than 50 mm;

Exclusion criteria

- Subjects with age < 18 years;
- Severe inability to understand the study and to undergo to all necessary procedures;
- Refuse to provide written informed consent, prior to participating to the study;
- Women of childbearing potential who do not undergo pregnancy tests and do not use adequate contraceptive methods;

- Women of childbearing age with a positive pregnancy test, in a pregnant or breastfeeding status;
- Other causes of coxalgia related to inflammatory joint diseases (rheumatoid arthritis, psoriatic or septic arthritis) or linked to stress fractures, villonodular synovitis, synovial chondromatosis;
- Contemporary presence of osteometabolic diseases. The coexistence of initial coxarthrosis is not an exclusion criterium, for enrolment in the study;
- Presence at MRI examination, of compatible alterations with aseptic osteonecrosis, with a changed profile of the articular surfaces;
- Other diagnosis of osteonecrosis detected by instrumental examinations;
- Blood calcium values, below standard parameters, or a glomerular filtrate lower than 35 ml/min;
- Positive history and/or evocative signs or symptoms for relevant diseases, related to ongoing organ failures (hepatic, renal, endocrine, haematological, cardiac, pulmonary, or neurological failures);
- Recent tooth extraction (in the previous three months to Visit 1), unhealed or infected extraction site, significant dental/periodontal disease that may predispose to tooth extraction or other invasive dental procedures during the trial;
- Evidence of denture-related gum trauma or injury;
- Prior development of an allergic reaction/hypersensitivity to bisphosphonates;
- Current treatment with bisphosphonates in the previous 12 months;
- Patient who received any new investigational drug within the last 12 weeks;

2.5. Interventions

Patients randomized to the active treatment group received intravenous neridronate administered over a short treatment period, while patients assigned to the control group received matching placebo according to the same administration schedule.
The dosing regimen and route of administration were selected based on the established clinical use of neridronate in other bone-related conditions and were intended to achieve a rapid therapeutic effect during the acute phase of the disease.
During the double-blind phase, the intervention strategy allowed a clear comparison between treatment groups while ensuring consistency of exposure and patient safety.
The study protocol permitted the use of paracetamol as rescue medication. Following completion of the double-blind phase, patients initially assigned to placebo were eligible to receive open label neridronate treatment.

Neridronate:
100 mg/8 mL diluted in 500 mL NaCl 0.9%; infused over ≥ two hrs on Days 1, 4±1, 7±1, 10±1.
Placebo:
Eight mL vials diluted as above; identical administration schedule.
Open-label extension:
Placebo-arm patients may receive neridronate infusions on Days 57–60.

2.6. Statistical Methods

The primary efficacy analysis compared the proportion of responders, defined as patients achieving a ≥50% reduction in spontaneous pain on the 100-mm Visual Analog Scale (VAS) at Day 30 (V6), between treatment groups. The comparison was performed using Fisher's Exact Test.
Secondary efficacy endpoints were analyzed using appropriate statistical methods according to the nature of the variables. Changes from baseline in continuous outcomes were evaluated using analysis of covariance (ANCOVA), while longitudinal pain assessments over time were analyzed using mixed models for repeated measures. Use of rescue medication (paracetamol) was analyzed using non-parametric methods, including Wilcoxon tests with Hodges–Lehmann estimates.
Safety analyses were descriptive in nature and summarized by treatment group. Patients who discontinued due to lack of efficacy or adverse events were considered non-responders for the primary endpoint. Other missing data were handled using a last observation carried forward (LOCF) approach.
All analyses were conducted according to predefined analysis of populations and a prespecified statistical analysis plan. Given the limited sample size and the exploratory nature of secondary analyses, results were interpreted in a supportive and contextual framework.

2.7. Patient Disposition

A total of 40 patients were screened for eligibility. Thirty-six patients were randomized and entered the double-blind phase of the study, with 19 patients allocated to the neridronate group and 17 to the placebo group.
All randomized patients completed the double-blind treatment period. Following completion of the double-blind phase, 16 patients entered the open-label extension phase and 15 completed it as per protocol.
Overall, 34 patients completed the study, while two patients discontinued prematurely. Discontinuations were limited in number and occurred after randomization.
The distribution of patients across treatment groups and study phases was balanced and did not indicate differential attrition that could meaningfully affect the interpretation of efficacy or safety outcomes.

2.8. Baseline Characteristics

Baseline demographic and clinical characteristics were generally comparable between treatment groups. The mean age of the study population was 48 years, and the majority of patients were male (29 males and 7 females), consistent with the known epidemiology of TOH.
Baseline pain severity was high in both treatment groups. Mean baseline VAS scores were 70.89 mm (SD 16.08) in the neridronate group and 72.82 mm (SD 10.92) in the placebo group, indicating a comparable level of spontaneous hip pain at study entry.
Baseline BMI was also similar between groups, with mean BMI values of 27.79 kg/m² (SD 5.24) in the neridronate group and 27.13 kg/m² (SD 2.85) in the placebo group.
Overall, baseline characteristics did not reveal clinically relevant imbalances between treatment groups and were considered appropriate for comparative evaluation of efficacy and safety outcomes.

2.9. Efficacy Results

Efficacy analyses were conducted in the randomized population. The primary efficacy endpoint was the proportion of patients achieving a ≥50% reduction from baseline in spontaneous hip pain, as measured by the 100-mm Visual Analog Scale (VAS), at V6.

At V6, a higher proportion of responders was observed in the neridronate group compared with the placebo group. Specifically, 14 out of 19 patients (73.68%) treated with neridronate met the responder definition, compared with 10 out of 17 patients (58.82%) in the placebo group. The difference between treatment groups did not reach statistical significance (Fisher's Exact Test, p = 0.4826).

Secondary efficacy endpoints supported the primary analysis. Mean VAS pain scores decreased substantially from baseline to V6 in both treatment groups. In the neridronate group, mean VAS values decreased from 70.32 ± 15.90 mm at baseline to 18.42 ± 18.73 mm at V6, corresponding to a mean reduction of approximately 52 mm. In the placebo group, mean VAS values decreased from 69.82 ± 14.05 mm to 35.18 ± 32.44 mm, corresponding to a mean reduction of approximately 35 mm.

An ANCOVA analysis adjusting for baseline VAS showed an estimated 16.84-mm lower VAS score at V6 in the neridronate group compared with placebo; this difference was clinically meaningful but did not reach statistical significance (p = 0.0646).

Functional outcomes assessed by the WOMAC index improved in both groups. ANCOVA analyses at V6 consistently favoured neridronate across all WOMAC domains, including Pain (−70.98 points; p = 0.1074), Physical Functioning (−274.73 points; p = 0.0745), and Stiffness (−27.86 points; p = 0.1281), although none of these comparisons reached statistical significance.

Quality of life, assessed using the SF-36 questionnaire, showed improvements from baseline in both treatment groups. Analyses of physical health–related subscales demonstrated numerically greater improvements in the neridronate group, including Physical Functioning (+9.08 points; p = 0.2897), Bodily Pain (+5.15 points; p = 0.5047), and General Health (+3.59 points; p = 0.4203), without statistically significant between-group differences.

Use of paracetamol as rescue medication declined during the study in both groups. At V6, paracetamol use was reported in 0% of patients in the placebo group and in 10% of patients in the neridronate group.

Overall, secondary endpoint results were consistent with the primary efficacy analysis and showed a numerical trend in favour of neridronate, despite the absence of statistically significant differences between treatment groups.

2.10. Safety Results

Safety was evaluated in all patients who received at least one dose of study treatment. The overall incidence of adverse events was comparable between treatment groups. At least one adverse event was reported in 63.16% of patients in the neridronate group and in 52.9% of patients in the placebo group.

No serious adverse events were reported in either treatment group during the study. The most frequently reported adverse events were flu-like symptoms, transient fever, headache, back pain, and arthralgia, consistent with the known safety profile of intravenous amino-bisphosphonates.

Laboratory parameters were monitored throughout the study. No clinically relevant laboratory abnormalities or treatment-related safety signals were identified, as summarized in the laboratory safety tables.
Overall, neridronate was generally well tolerated in the study population, and no new or unexpected safety concerns emerged.

2.11. Conclusions

The TOHNER study provides the first placebo-controlled phase III data evaluating the efficacy and safety of intravenous neridronate in patients with TOH.
In this randomized, double-blind trial, neridronate was associated with a higher proportion of pain responders and greater reductions in pain intensity and functional impairment compared with placebo, although these differences did not reach statistical significance.
Secondary efficacy outcomes, including functional measures, quality-of-life assessments, and rescue medication use, were consistent with the primary analysis and showed a numerical trend in favour of neridronate.
The treatment was generally well tolerated, with a safety profile consistent with the known effects of intravenous amino-bisphosphonates and no new safety concerns identified.
Overall, the results support the feasibility and safety of neridronate treatment in TOH and provide controlled clinical evidence to inform future research and clinical decision-making in this condition.

2.12. Date and Version of Synopsis

Synopsis Version 1.0 Dated 30.03.2026. This synopsis corresponds to the CSR prepared on the basis of Protocol TOHNER/31 – Version 4.0 (05 July 2022).

2.13. References

[1] Hofmann S, Engel A, Neuhold A, Leder K, Plenk H Jr. Bone-marrow oedema syndrome and transient osteoporosis of the hip: an MRI-controlled study. *J Bone Joint Surg Br.* 2004; 86(5): 698–702.

[2] La Montagna G, Malesci D, Tirri R, Valentini G. Successful neridronate therapy in transient osteoporosis of the hip. Clin Rheumatol. 2005;24(1):67–69. doi:10.1007/s10067-004-0957-9.

[3] Plenk H Jr, Hofmann S, Eschberger J, Gstettner M, Kramer J, Schneider W, Engel A. Histomorphology and bone morphometry of the bone marrow edema syndrome of the hip. Clin Orthop Relat Res. 1997 Jan;(334):73-84. PMID: 9005898.