Published in final edited form as:

Pain. 2014 January ; 155(1): 108–117. doi:10.1016/j.pain.2013.09.016.

A Pilot Trial of Intravenous Pamidronate for Chronic Low Back Pain

Marco Pappagallo, MD^{1,3,*}, Brenda Breuer, PhD, MPH¹, Hung-Mo Lin, ScD², James B. Moberly, PhD⁴, Julia Tai, MA⁵, Christopher Noto, MD³, Angela Sanchez, BS³, and Paolo L. Manfredi, MD⁶

¹Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY

²Department of Health Evidence and Policy, The Mount Sinai Medical Center, New York, NY

³Department of Anesthesiology, The Mount Sinai Medical Center, New York, NY

⁴Grünenthal USA, Bedminster, NJ

⁵The Feinstein Institute for Medical Research at The North Shore - LIJ Health System, Long Island, NY

⁶Patrician Medical, West Chester, PA

Abstract

Intravenous (IV) bisphosphonates relieve pain in conditions such as Paget's disease of bone, metastatic bone disease and multiple myeloma. Based on positive findings from a prior case series, we conducted a randomized, placebo-controlled study to assess the analgesic effect of IV pamidronate in subjects with chronic low back pain (CLBP) and evidence of degenerative disease of the spine. Four groups of 11 subjects (7 active, 4 placebo) were enrolled at escalating dose levels of 30, 60, 90, and 180 mg pamidronate (the latter administered as two 90 mg infusions). Primary outcomes were safety and change from baseline in average daily pain scores, recorded at 1, 2, 3, and 6 months post-infusion using electronic diaries. Secondary outcomes included responder rate, daily worst pain, and pain-related interference of daily function. There were no pamidronate-related serious adverse events or other significant safety findings. A statistically significant overall treatment difference in pain scores was observed, with clinically meaningful effects persisting for 6 months in the 180 mg pamidronate group. Least square mean changes in daily average pain score were -1.39 (SE=0.43) for placebo, and -1.53 (0.71), -1.26 (0.81), -1.42 (0.65), and -4.13 (0.65) for pamidronate 30, 60, 90 and 180 mg, respectively ($p=0.012$ for pamidronate 180 mg versus placebo). The proportion of responders, changes in worst pain and pain interference of daily function were also significantly improved for pamidronate 180 mg compared to placebo. In conclusion, IV pamidronate, administered as two 90 mg infusions, decreased pain intensity for 6 months in subjects with CLBP.

© 2013 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

*Current address for corresponding author: Marco Pappagallo, Grünenthal USA, Inc., One Pluckemin Way, Bedminster, NJ 07921
Tel: 908-306-0024; marco.pappagallo@grunenthal.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

CLBP; musculoskeletal pain; non-specific low back pain; bisphosphonate; analgesia

1 Introduction

Chronic low back pain (CLBP) is a widespread disorder affecting men and women of nearly all ages [3,10]. The lifetime prevalence of CLBP is reported to be between 54% and 80%, with an annual prevalence between 15% and 45% and a point prevalence ranging from 12% to 30% [20,34]. The prevalence of CLBP appears to be increasing: a survey of North Carolina households found an increase in disabling CLBP from 3.9% in 1992 to 10.2% in 2006, distributed across all adult ages and races [20]. Persistent pain and disability due to CLBP contribute to significant social and economic health burdens; CLBP is the number one cause of disability in persons under the age of 45 and one of the most expensive nonfatal medical conditions in industrialized countries [3,34].

Based on imaging studies, the majority of patients with CLBP present with variable evidence of spondylotic disease, degenerative disc disease or facet joint arthritis. However, imaging studies are mechanistically non-specific and findings correlate poorly with both the occurrence and severity of low back pain. Therefore, in the absence of findings of a specific spinal or extra-spinal pathology, the term “non-specific” is sometimes added to the diagnosis of low back pain [12]. A number of pharmacologic, interventional, surgical, and rehabilitative treatment approaches are currently available for CLBP; however, despite the variety of treatments, most patients experience only short term or unsatisfactory pain relief [12].

Bisphosphonates are known to have significant analgesic activity in addition to their well-characterized role in inhibiting bone resorption. For example, pamidronate (Aredia®, Novartis), an aminobisphosphonate, demonstrates clinically significant pain relief when administered intravenously for treatment of Paget’s disease, metastatic breast cancer and osteolytic lesions of multiple myeloma [6,25,51]. In addition, IV pamidronate has been shown to have analgesic activity in a wide variety of painful conditions, including complex regional pain syndrome (CRPS) [13,44,53], fibrous dysplasia [11], recurrent multifocal osteomyelitis [23,35], ankylosing spondylitis [33], rheumatoid arthritis [31], and others (for review, see [49]). The mechanism(s) of this analgesic effect is not fully known, but antinociceptive effects of pamidronate and other bisphosphonates have been reported in animal models of pain [5,8,9,52]. Inhibition of osteoclast proton secretion and other cellular and molecular mechanisms may contribute to the analgesic effect [37,54].

IV pamidronate has been shown to produce clinically significant pain relief in patients with osteoporotic vertebral fractures [1,4,22,26] as well as in patients with refractory degenerative lumbar spinal stenosis and erosive degenerative disk disease [19,41]. We previously explored the relationship between pamidronate infusions and pain relief in a retrospective review of medical records from 25 patients with disabling spinal mechanical pain [40]. Results of this review indicated an association between monthly pamidronate infusions and relief of intractable chronic back pain in the absence of spinal stenosis, suggesting pamidronate may have therapeutic potential in treatment of CLBP. We therefore undertook the present study to assess the safety and efficacy of IV pamidronate in patients with CLBP and MRI evidence of degenerative disc disease or spondylotic disease of the spine.

2 Methods

2.1 Study Administration

This was a randomized, double-blind, placebo-controlled, escalating-dose, pilot study of IV pamidronate in subjects with CLBP. The trial was initiated at Beth Israel Medical Center, New York, NY, where subjects in the first 2 dose levels were enrolled, and was completed at Mount Sinai Medical Center, New York, NY, where the last 2 dose levels were enrolled. The primary objective was to determine the optimal dose regimen for subsequent investigation of IV pamidronate for treatment of CLBP.

The study was registered at clinicaltrials.gov (NCT00101790) and was approved by the institutional review boards of Beth Israel Medical Center and Mount Sinai Medical Center prior to subject screening and enrollment at each institution. Written informed consent was obtained from each subject prior to his or her participation in any study procedures. An investigational new drug application (IND # 67,071), including the study protocol, was submitted to the US Food and Drug Administration (FDA) prior to study initiation.

An ad-hoc safety medical officer and a National Institutes of Health (NIH)-appointed Data and Safety Monitoring Board (DSMB) performed independent evaluation of safety data and provided authorization for escalation to the next dose level. DSMB members were not directly involved in the study, had no ties to study investigators, and were not financially or otherwise vested in the study outcome. As planned in the protocol, data from the first 3 dose levels were unmasked and reviewed by the DSMB prior to the decision to proceed to the highest dose level.

2.2 Participants

Study participants were men or women, at least 21 years of age, with predominantly axial back pain persisting for at least three months. Requirements for enrolment included MRI evidence of disc degeneration and/or vertebral changes consistent with the diagnosis of degenerative disc disease or spondylotic disease of the lumbar spine, an average pain score of 4 or higher on a 0–10 numeric rating scale (NRS), and evidence of reading skills at a sixth-grade level or above.

Subjects were excluded if they had prior back surgery; a compression vertebral fracture; cancer as a possible cause of back pain; MRI evidence of frank disk herniation or any other spinal or extraspinal structural pathology (other than disc degeneration or spondylotic disease of the spine) as a probable cause of the back pain; a defect or fracture of a pars interarticularis; a clinical diagnosis of radiculopathic or neuropathic leg pain; back pain in the presence of neurological deficits consistent with lumbosacral radiculopathy (upon examination) or presumptive compression of a spinal nerve root; or spondylolisthesis with a greater than 4 mm misalignment. Subjects were also excluded if they had a history of hypocalcemia; an estimated glomerular filtration rate (GFR) less than 60 ml/min; a history of clinically significant cardiac, hematological, renal, hepatic, metabolic, endocrinological, psychiatric, or neurological disease; a known allergy to bisphosphonates; were pregnant or nursing; weighed less than 45 kg; abused alcohol abuse or illicit drugs; were receiving worker's compensation, or had a pending legal or worker's compensation claim; were blind, deaf, or mute, or had a physical or mental handicap that would impede administration of outcome tool instruments; had a Beck Depression Inventory score of 26 or above; had received prior IV pamidronate treatment; had a tooth extraction or any invasive dental procedure within three months prior to study enrollment; had poor oral hygiene or inadequate dental care, in the opinion of the investigator; were currently receiving treatment for cancer; had received systemic steroid therapy or spinal steroid injections within four

months of study enrollment; or were anticipated to need injections of steroids within six months following enrollment.

2.3 Study Procedures

Eleven subjects were enrolled in each of 4 sequentially ascending dose levels of pamidronate: 30, 60, 90 and 180 mg. Within each dose level, subjects were randomized (4:7) to receive placebo (normal saline) or disodium pamidronate (Aredia®), diluted in 250 mL of normal saline, administered by 4-hour intravenous infusion (see Aredia® Prescribing Information [38]). The 180 mg dose was selected as the top dose following a planned interim analysis. The 180 mg dose was administered in two 90 mg infusions separated by an interval of 4 weeks, in accordance with the recommended administration schedule for use in multiple myeloma and breast cancer (once monthly or every 3–4 weeks) [38]. All study staff, except for an independent pharmacist and a secondary statistician, remained blinded throughout the study. The placebo and pamidronate solutions for infusion were prepared by the independent pharmacist and were identical in appearance. Infusions of placebo and placebo were performed in an identical manner and schedule in order to maintain subject and investigator blinding.

At screening, all subjects underwent a physical examination, oral/dental health review, electrocardiogram (ECG), Beck Depression Inventory (BDI), Brief Pain Inventory (BPI), laboratory blood tests, including complete blood count (CBC) with differential, and serum chemistry, and urinalysis. Serum chemistry measurements included vitamin D, calcium, magnesium, phosphorus, alkaline phosphatase, creatinine, albumin, and serum-specific alkaline phosphatase activity. Urinalysis included measurement of urinary cross-linked N-terminal telopeptides of type I collagen (NTX).

Subjects who were considered eligible for randomization were enrolled in a 2-week baseline period and scheduled to undergo imaging studies, including x-rays of the lumbosacral (LS) spine with flexion, extension and oblique views; MRI of the LS spine; dual-energy X-ray absorptiometry (DXA) (for assessment of bone density); and a bone scan using technetium-99m methylene diphosphonate (MDP) as a tracer.

The subject's analgesic regimen was optimized and stabilized during the 2-week baseline period, and subjects were asked to follow guidelines provided for the use of both short acting and long acting analgesic medications throughout the study. Subjects were asked to continue all other prescribed medications or over-the-counter preparations at a stable dosage throughout the study. These included daily supplements of calcium (600 mg) and low-dose vitamin D (400 IU), starting from the baseline period and throughout the study, to reduce risks of hypocalcemia and to optimize healthy bone formation. Subjects with vitamin D deficiency/insufficiency at screening (< 20 ng/ml) could be prescribed higher dose vitamin D (50,000 IU capsules) for up to five days to qualify for enrollment. Normal vitamin D levels were to be confirmed by laboratory testing prior to infusion of study drug.

During the 2-week baseline period, subjects recorded the following information, once daily in the evening, using an electronic diary (LogPad Systems, PHT Corporation, Boston, MA). All daily diary information was to apply to the previous 24-hour period.

- Average overall pain intensity and worst pain intensity (both on a scale of 0 to 10, where 0 means “no pain” and 10 means the “worst possible” pain)
- Pain interference with sleep (on a scale of 0 to 10, where 0 means “not at all” and 10 means “the most interference”)

- Any side effects and changes in health status, including whether the side effect or change was mild, moderate or severe,
- Any analgesic medication use, including the number of pills and how many times the medication(s) was taken. A reference checklist of pain medications was provided to guide subjects using PRN medications. Subjects also indicated whether they had taken their calcium and vitamin D supplements.

Subjects who completed the baseline period, screening laboratory assessments and imaging evaluations, and who continued to meet all entry criteria, including an acceptable vitamin D level, returned to the research unit for randomization and infusion of study drug. Prior to infusion of study drug, women of child-bearing potential underwent a urine pregnancy test, and all subjects underwent baseline ECG and BPI assessments and completed a physical performance test battery [48], a modified Oswestry Disability Index Questionnaire [15], and quality of life outcomes questionnaires (including the EuroQol). During the infusion period, subjects were monitored closely for changes in vital signs and for any systemic and local infusion site reactions. Subjects were permitted to ambulate, sit, or lie down during the 4-hour infusion. After the infusion, blood was drawn and results were obtained for immediate determination of calcium, phosphorus, magnesium, general chemistry, and CBC with differential. Prior to discharge from the research unit, subjects were prescribed 650 mg acetaminophen to be taken at once and 3 times daily for 3 days post-infusion.

Acetaminophen has been shown to reduce the incidence and severity of post-dose flu-like symptoms (known as an acute-phase response) associated with other aminobisphosphonates such as zoledronate [43,47].

Subjects returned to the research unit 2 and 4 weeks post-infusion and then monthly for 6 months for safety and efficacy assessments. For subjects in the highest dose level (pamidronate 180 mg or placebo), efficacy assessments were scheduled from the time of the second infusion, and final follow-up was 6 months from the time of the second infusion. The total duration of study participation, including the baseline period, was approximately 29 weeks for the first 3 dose levels and approximately 37 weeks for the highest dose level.

Subjects were instructed to self-report adverse events using the electronic diary; diary entries were to be screened within ~24 hours by the study coordinator. In addition, the study coordinator made telephone calls on days 1, 2 and 3 after infusion to inquire about subjects' well-being and document any adverse events. Subjects received a pamphlet listing possible health changes, including flu-like symptoms, muscle or joint pain, increased temperature, diarrhea, nausea/vomiting, blurred vision, and headache. Any serious adverse events were to be reported immediately to the principal investigator and medical safety officer. Concomitant medications or other treatments administered for an adverse event were recorded.

Physical examinations were performed monthly and included a brief oral hygiene assessment; if any dental abnormalities were observed, the subject was to be referred to a dentist. Laboratory testing, including serum chemistry, hematology and urinalysis, was performed at 2 weeks after each infusion and at each monthly follow-up visit. Glomerular filtration rate was calculated from serum creatinine using the Cockcroft-Gault equation.

BPI was performed weekly (by telephone at weeks for which no visit was scheduled). The physical performance battery, Oswestry Disability Index and quality of life questionnaires (including EuroQol) were administered at monthly visits. Subjects continued use of the electronic diary to record daily average pain intensity, worst pain intensity, side effects and analgesic medication use throughout the study. Information collected on the diaries was submitted electronically via a secure modem to Studyworks™ (a data site managed by PHT

Corporation, Boston, MA). Study coordinators were able to access subjects' responses on a daily basis. Subjects were provided with paper diaries in the event of failure of the electronic system. At the final study visit, subjects in the two highest dose levels (90 and 180 mg pamidronate) were asked to assess overall satisfaction with study treatment and whether they believed they had received placebo or active study drug. Study coordinators were also asked whether they felt these subjects had received placebo or active study drug.

2.4 Statistical methods

The primary efficacy variable was change from baseline in daily average pain intensity, obtained from electronic diaries, at 24 hours and 1, 2, 3, and 6 months post-infusion (for the 180 mg dose level, time points were measured from the time of the second infusion). Baseline average pain intensity was calculated from daily average pain scores obtained from diary entries during the 7 days prior to the first infusion. For all post-infusion time points except 24 hours, the daily average pain score was calculated from diary entries obtained over the previous 7 days. Secondary efficacy variables included the proportion of subjects who were classified as responders (defined as a decrease of 2 or more points on the NRS pain scale or at least a 30% decrease from baseline), change in daily worst pain, pain interference with sleep, BPI scores, use of 'rescue' medications, changes in the physical performance test battery, Oswestry Disability Index and EuroQol questionnaires, and subject's overall satisfaction with study treatment.

The primary efficacy analysis assessed whether changes from baseline in daily average pain intensity were the same across the 4 active dose levels and placebo, while adjusting for baseline average pain, bone scan results, and time effect. Box and whisker plots were constructed to depict change from baseline in daily average pain score at 24 hours and 1, 2, 3, and 6 months post-infusion. A mixed model was fit for repeated measures of the changes in daily average pain intensity, assuming autoregressive covariance structure. As planned in the protocol, an analysis was first performed to determine whether placebo subjects from different dose levels could be combined. Since no statistical difference was observed for mean change from baseline in daily average pain scores between the 4 groups of placebo subjects ($p=0.550$), all placebo subjects ($n=16$) were combined for subsequent analyses. Interactions between time and study phases were then tested to see if the treatment effect was a function of time. Since no significant interaction was observed between time and treatment group, least square mean changes across all assessment times were contrasted between treatments. As this was a pilot study, the sample size was determined based on practical considerations. Assuming previous clinical observations to be generalizable to the target population [40], and that placebo subjects at different dose levels could be combined for the analysis, a total of 7 pamidronate subjects and 4 placebo subjects at each dose level was anticipated to provide at least 80% power to detect at least a 30% reduction or a 2 point decrease from baseline in the overall average daily pain intensity score [16,17].

For secondary efficacy analysis, a responder was defined as a subject whose daily average pain score decreased from baseline by at least 30% or at least 2 points, consistent with proposed definitions of a clinically meaningful response [16,17]. Mean responder rates (proportions of responders) were calculated for each treatment group at 24 hours and at 1, 2, 3, and 6 months post-infusion, as defined above. A Generalized Estimating Equations (GEE) model was used to compare response rates across treatment groups. In the presence of 100% response rates, only Fisher's exact test was performed for cross-sectional analysis. A graph of the cumulative proportion of responders (continuous responder analysis) was generated to depict the likelihood of response over the full range of potential response cut-off points (0% to 100%). Continuous responder analysis allows comparison between groups over a variety of response levels, thereby alleviating concern over selection of an arbitrary cut-off point [18].

Change from baseline in worst pain intensity, pain interference (of sleep and other functions, obtained from the BPI), and changes in performance test battery measures were analyzed using the mixed model, following the same analytic steps as for primary outcomes described above. Oswestry Disability Index and EuroQol scores were compared across groups at 3 and 6 months post-infusion using Fisher's exact tests. The proportions of subjects who required opioids (including tramadol) and non-opioid pain medications (eg, acetaminophen, NSAIDs, muscle relaxants, etc), determined from electronic diary entries from the 7 days preceding the 3- and 6-month follow-up visits, were contrasted between responders and non-responders using chi-square tests. Additional exploratory analyses evaluated whether baseline bone density and the bone scan results (positive/negative) were potential predictors for reduction of pain relief based on daily average pain scores. Interaction between treatment groups and bone-related imaging results were analyzed to determine if these baseline covariates were modifiers of treatment efficacy. For analysis of urinary NTX and alkaline phosphatase, logistic regression models were fitted at 3 and 6 months post-infusion to see if changes in these variables were associated with response to treatment. For interaction with baseline vitamin D status, subjects were categorized into 3 groups (no requirement for high-dose vitamin D supplementation, vitamin D supplementation with PTH < 70 pg/mL, and vitamin D supplementation with PTH > 70 pg/mL) and the GEE model was used to compare response rates (responders versus non-responders) at 1, 2, 3 and 6 months post-infusion.

Analysis of safety was performed by tabulation of all adverse events, including abnormal laboratory tests and clinically important changes in physical exams or other safety assessments. Adverse events occurring during the 7 days after each infusion were tabulated in order to better assess the acute-phase, flu-like reactions that commonly occur following infusions of aminobisphosphonates. As for efficacy endpoints, placebo-treated subjects from each dose level were combined for tabulation of adverse events.

All analyses were performed on an intention-to-treat basis. Any changes in the analysis plan or post-hoc analyses were discussed with and approved by the DSMB. Subject baseline and disease characteristics were reported as percentage, median (range) or means (standard deviation). Chi-square (Fisher's exact) tests or ANOVA (Kruskal-Wallis) tests were performed for cross-sectional group comparisons, including baseline. Analyses were carried out using SAS 9.1 (SAS Institute, Inc., Cary, NC), and the level of statistical significance for hypothesis testing was set at 0.05.

3 Results

3.1 Subject characteristics

A total of 882 subjects underwent telephone screening between April, 2004 and December, 2009; 129 subjects were invited to report to the research unit to provide consent to undergo screening evaluation. Forty-four subjects who met all eligibility criteria and completed all laboratory and imaging assessments were enrolled in the study. All 44 subjects were randomized and received at least one infusion of study drug; these subjects comprise the full safety and efficacy analysis sets. Twelve subjects discontinued the study, and 32 subjects completed the 6-month follow up visit (Figure 1). Reasons for discontinuation were voluntary withdrawal (7 subjects), lost to follow-up (4 subjects) and non-compliance with the electronic diary (1 subject).

Baseline demographics and pain scores for combined the placebo group and each pamidronate dose level are shown in Table 1. Except for age, no significant differences in baseline variables were observed between subjects receiving placebo or pamidronate. The majority (>90%) of enrolled subjects had tried alone or in combination physical therapy, NSAIDs, or muscle relaxants. About 50% were taking other drugs, including anti-

depressants, tramadol, or gabapentin, and 20% or less received low-doses opioid. About 40% of enrolled subjects had tried interventional approaches, eg, trigger point injections, facet blocks or epidurals.

3.2 Efficacy results

3.2.1 Primary efficacy endpoint—Box and whisker plots depicting mean change from baseline in daily average pain intensity and interquartile ranges (25th and 75th percentiles, corresponding to the top and bottom of each box) are presented for the combined placebo group and each pamidronate dose level in Figure 2. Mean pain scores for the pamidronate 180 mg dose level were lower than those for other treatment groups at all efficacy assessments, including 24 hours post-infusion.

In the primary efficacy analysis, a statistically significant overall treatment effect ($p=0.02$) was observed using repeated measures analysis, after adjustment for baseline pain intensity, bone scan and bone density results, and time effect. The time and treatment group interaction was not statistically significant ($p=0.32$), indicating that observed group differences did not change over time. Analyzing across all time points, least square mean changes from baseline in daily average pain score were -1.39 ($SE=0.43$) for the placebo group and -1.53 (0.71), -1.26 (0.81), -1.42 (0.65), and -4.13 (0.65) for pamidronate 30, 60, 90 and 180 mg, respectively. Least square mean contrasts were statistically significant for comparisons between the pamidronate 180 mg dose level and all other treatments ($p=0.012$, 0.013 , 0.009 and 0.009 for pamidronate 180 mg versus placebo and pamidronate 30, 60 and 90 mg, respectively). No other pairwise comparison was statistically significant.

3.2.2 Secondary efficacy endpoints—Fisher's exact tests for group differences in the proportion of responders were statistically significant for the pamidronate 180 mg group when compared to all other groups at 1, 2, 3 and 6 months post-infusion ($p = 0.026$, 0.008 , 0.043 and 0.047 , respectively) (Supplemental Figure 1). The responder rate for pamidronate 180 mg increased from 50% at 24 hours after the second infusion to 100% at month 2; the 100% responder rate was maintained at all subsequent time points. In comparison, responder rates did not exceed 67% during the follow-up period for the other pamidronate dose levels and did not exceed 43% for the placebo group. Continuous responder analysis (Figure 3) illustrates that all subjects receiving 180 mg pamidronate had at least 50% pain relief at both 3 and 6 months post-infusion, and nearly 85% of subjects receiving 180 mg pamidronate had 100% pain relief at 6 months. Although the pamidronate 60 mg dose group also showed a high proportion of responders, there was no clear dose-response, as there were no meaningful differences in the proportion of subjects meeting response thresholds for other pamidronate dose levels relative to placebo.

Similar to changes for daily average pain, changes in worst pain, pain interference in general activity (from the BPI), and the 'reaching' and 'distance' components from the physical performance test battery were also statistically significantly different for the pamidronate 180 mg group compared to placebo and to some of the other pamidronate dose levels (Table 2). The Oswestry Disability Index and EuroQol scores, in general, showed no significant differences among the treatment groups at 3 and 6 months post-infusion (Table 2). The only exception was the EuroQol question on "Usual Activities", for which 0% of subjects in the pamidronate 180 mg group reported "some problem" or "unable", compared to 60%, 67%, 100%, and 43% of subjects in the placebo, 30, 60 and 90 mg pamidronate groups, respectively ($p<0.01$).

Opioid pain medications were used less frequently in subjects classified as responders: Among 20 subjects classified as responders, none took opioid medications during the week prior to the 3-month post-infusion assessments, and 0 of 11 responders took opioids prior to

the 6-month assessment. In contrast, 4 of 18 (22.2%) subjects classified as non-responders took opioids at 3 months and 4 of 14 (28.6%) took opioids at 6 months ($p=0.04$ and $p=0.11$ at 3 and 6 months, respectively). No significant difference was found between responders and non-responders for use of non-opioid analgesic medications at 3 months (40.0% of responders versus 55.6% of non-responders, $p=0.34$). However, at 6 months, the proportion of subjects using non-opioid analgesics was numerically lower for responders than non-responders (27.3% versus 64.3%, $p=0.07$).

Information on overall satisfaction with study treatment at 6 months post-infusion was available for 4 subjects receiving pamidronate 180 mg, 7 subjects receiving pamidronate 90 mg, and 5 subjects receiving placebo. All 4 subjects receiving pamidronate 180 mg were either somewhat or greatly satisfied with study treatment, compared to 42.9% of subjects meeting these criteria in the pamidronate 90 mg group and 60.0% in the placebo group ($p=0.05$).

Based on end of study assessments performed at the two higher dose levels, most subjects were unable to correctly guess their treatment assignment: 5 of 18 (27.8%) subjects guessed correctly, 10 (55.6%) were unsure; and 3 (16.7%) guessed incorrectly. Study coordinators correctly guessed treatment assignments for 9 of 21 (42.9%) subjects, were unsure for 5 subjects (23.8%), and guessed incorrectly for the remaining 7 (33.3%).

3.2.3 Exploratory efficacy endpoints—Of the 44 subjects enrolled, 30 subjects had a normal DXA scan of the LS spine at baseline, and 14 subjects had evidence of mild decrease in spinal bone mineral density (osteopenia); no subject had osteoporosis. There was no significant correlation between baseline bone mineral density and the analgesic response to pamidronate treatment. For baseline bone scans using the MDP tracer, 27 subjects exhibited abnormal uptake in the LS spine, and the remainder (17 subjects) had normal uptake. Baseline bone scan status did not appear to influence response to treatment with pamidronate; however, subjects with a negative baseline bone scan of the LS spine appeared to have a greater decrease in average daily pain intensity compared to subjects with a positive scan ($p=0.02$). In the logistic regression analysis of urinary NTX and alkaline phosphatase, changes in these parameters showed no significant association with response to pamidronate treatment at 6 months.

Prior to study entry, 25 (57%) of the enrolled subjects had vitamin D deficiency/insufficiency, and, of these, 8 subjects were found to have secondary hyperparathyroidism ($PTH > 70$ pg/mL). Post-infusion levels of vitamin D remained above 20 ng/mL in all subjects. There was no meaningful difference in the proportion of responders according to pre-study vitamin D status (deficiency versus no deficiency); however, the proportion of responders among subjects with secondary hyperparathyroidism (73.7%) was greater than that for subjects without vitamin D deficiency (41.1%, $p=0.03$) and those with vitamin D deficiency without secondary hyperparathyroidism (32.3%, $p=0.10$).

3.3 Safety

There were no deaths or serious adverse events (SAEs). One subject randomized to placebo treatment underwent an elective total hip replacement surgery that was classified by the investigator as unrelated to treatment. This event was not classified as an SAE because hospitalization for surgery was scheduled in advance. No subject discontinued the study due to an adverse event.

Adverse events related to the acute-phase response were more frequent in the pamidronate treatment groups, particularly during the first week following infusion (Table 3). Headache and flu-like symptoms were statistically significantly more frequent for subjects receiving

pamidronate (headache: 57% of subjects in the combined pamidronate treatment group versus 12.5% of subjects receiving placebo; $p<0.01$; flu-like symptoms: 46.4% in the combined pamidronate group versus 6.7% for placebo; $p<0.01$). The frequency of these events appeared somewhat higher following infusion of 90 mg pamidronate relative to the pamidronate 30 and 60 mg infusions. Most pamidronate-related symptoms were mild to moderate in severity and resolved within two weeks post-infusion. The frequency of acute-phase symptoms following the second infusion of pamidronate 90 mg in the pamidronate 180 mg group appeared lower than that in the pamidronate 90 mg group.

There were no dental, maxillary, or mandibular complaints among pamidronate treated subjects. No subject had osteonecrosis of the jaw, or necrosis of any other bone, and there were no bone fractures during the study.

There were no clinically meaningful changes in ECG or clinically significant abnormal laboratory findings among pamidronate-treated subjects. There were no clinically significant changes in calcium or phosphorus levels in any treatment group.

4 DISCUSSION

Results of this pilot study provide evidence for the analgesic efficacy of IV pamidronate in patients with CLBP and degenerative disease of the spine. To our knowledge, this is the first controlled clinical study assessing the analgesic effects of a bisphosphonate in CLBP. The cumulative pamidronate dose of 180 mg showed clinically significant and sustainable decreases in daily average pain intensity, recorded by subjects using electronic diaries. The magnitude of this effect was clinically meaningful, with an overall least square mean decrease from baseline of over 4 points on the 11-point NRS versus a decrease of ~1.5 points for placebo. The analgesic response increased over the duration of the study, with the greatest response observed at the 6 month follow-up visit (ie, at the conclusion of the trial). The cumulative proportion of responders at 6 months post-infusion for the pamidronate 180 mg group was 100% for the cutoff of 50% pain relief and nearly 85% at a cut-off of 100% pain relief. Secondary endpoints of daily average pain, changes in worst pain, pain interference (from the BPI), and components of the physical performance test battery were also significant for the high dose group, consistent with the primary analysis.

A cumulative 180 mg dose was efficacious while single infusions of 90 mg or lower were ineffective. Multiple IV infusions of pamidronate are generally indicated for palliative treatment of painful bone metastasis and in certain painful bone-related conditions such as Paget's disease and fibrous dysplasia [11,25,30,51]; however, a single infusion of pamidronate has been reported to relieve pain in patients with complex regional pain syndrome, hypertrophic osteoarthropathy and Charcot arthropathy [44,49]. Efficacy and duration of response probably relate to both dose and pharmacokinetic properties of bisphosphonates, which can persist in bone for months [24,27]. In animal studies, the amount of bisphosphonate deposited in bone is greater when administered in divided doses compared to the amount that can be absorbed following a single infusion at the same cumulative dose [29], suggesting a pharmacokinetic rationale for multiple infusions. In addition, a divided dose of pamidronate is recommended to limit potential risks of renal toxicity [38]. Further investigation is needed to optimize the dose and dosing interval for use of pamidronate in treatment of CLBP.

The molecular mechanisms of pamidronate's analgesic effects are not fully understood. Bisphosphonates are known to inhibit activity and/or cause apoptosis of osteoclasts [21,46], which remodel bone by creating an acidic micro-environment via the release of protons through vacuolar H^+ -ATPase [7,45]. Osteoclast-induced high concentrations of protons may activate acid-sensing ion channels (ASICs) and transient receptor potential vanilloid type 1

channel (TRPV1) expressed by small nerve fibers involved in pain signal transmission [37,42,54]. Osteoclasts appear to have a role in inflammatory pain adjacent to bone and in the hyperalgesia observed in type IX collagen deficient mice [2,37]. Of interest, inhibition of osteoclasts by bisphosphonates in a rat model of degenerative joint disease has recently been found to prevent subchondral bone resorption, cartilage loss, and decrease pain [50]. Clinical findings also may suggest a role for subchondral bone changes in the early development of painful osteoarthritis [14,36]. Furthermore, the anatomical core structure of the spine is made of bone tissue, and immunohistochemical studies have revealed the presence of a widespread network of peptidergic small sensory fibers throughout the bone marrow, mineralized bone, and periosteum [28,32]. Thus it is conceivable that: a) nonspecific low back pain (associated with degenerative disc disease or spondylotic disease as in our study population) may be related to sensitization of bone nociceptors, plausibly in the context of subchondral bone resorption (for example, at the vertebral endplates and/or facet joints); and b) inhibition of subchondral osteoclasts (and possibly of other phagocytic or inflammatory bone resident cells) by IV pamidronate might be clinically relevant to the treatment of CLBP.

In exploratory analyses of covariates of treatment response, we were unable to detect any relationship between analgesic response and baseline bone density as assessed by DXA. Moreover, there was no relationship between treatment-related changes in bone metabolism biomarkers such as NTX or alkaline phosphatase and analgesic response. However, a relationship between baseline vitamin D and PTH status and treatment response was observed, meriting investigation of the potential role of secondary hyperparathyroidism as prognostic indicator of treatment response in subsequent trials. The reason for the inverse relationship between tracer uptake in baseline bone scans and improvement in back pain is unclear. It is conceivable that patients with a positive bone scan might suffer from more advanced symptomatic changes that would require higher doses of IV pamidronate for analgesia.

IV pamidronate administered up to 180 mg appeared safe and well tolerated in this study. No serious adverse events related to administration of study drug occurred during the infusions or 6-month follow-up, and no subject withdrew from the study due to an adverse event. Most adverse events were mild or moderate in severity. Acute phase reactions, including flu-like symptoms (fever and body ache), myalgia, arthralgia, fatigue and headache, were reported frequently by pamidronate-treated subjects in this study. For example, approximately half of pamidronate-treated subjects reported fever and body ache (versus 7% placebo-treated subjects). Myalgia and arthralgia were also frequently reported, although the frequency of these events was also high in the placebo group. Acute phase reactions are common following IV infusion of pamidronate and other aminobisphosphonates [39,43], and the high frequency of events reported in this study was not unexpected, as subjects were instructed to self-report adverse events using an electronic diary. Furthermore, study coordinators made telephone calls on days 1, 2 and 3 after infusion to inquire about subjects' well-being and to document any adverse events. Symptoms related to the acute-phase response resolved within 2 weeks post-infusion and appeared to be less prominent following the second infusion in the pamidronate 180 mg group, consistent with prior clinical experience [39]. In contrast to prior studies [47], use of acetaminophen (650 mg TID) did not appear to prevent flu-like symptoms associated with IV pamidronate, although some lessening of symptoms may have occurred. Ocular side effects have been reported as part of the acute-phase reaction following pamidronate administration; there were no significant ocular complaints in this study.

Bisphosphonates have potential for renal toxicity and pamidronate carries warnings for renal deterioration and progression to renal failure and dialysis [38]. However, renal safety risks

of pamidronate are mitigated by restricting use in patients with renal impairment, limiting any single administration to 90 mg, slow infusion over at least 2 hours, and an interval of at least 3–4 weeks between doses. We used 4 hour infusions up to a maximum of 90 mg, separated doses by 4 weeks for the 180 mg dose level, and did not observe any clinically significant changes in renal function. Hypocalcemia and other electrolyte changes, usually asymptomatic, can be observed following bisphosphonate treatment due to suppression of bone turnover. We ensured all subjects had normal vitamin D levels before initiating treatment and supplemented subjects with calcium and vitamin D throughout the study. We did not observe any changes in calcium or other electrolytes during the study. Osteonecrosis of the jaw (ONJ) has been reported in cancer patients treated with frequent, high doses of pamidronate and other IV bisphosphonates. Consistent with guidelines, we required subjects to maintain good oral hygiene and avoided invasive dental procedures during treatment; no signs of ONJ were observed in any subject during the study.

This pilot study has some limitations. A large number of exclusion criteria were employed to identify eligible subjects and to ensure a diagnosis of CLBP, including MRI evidence of degenerative disease of the spine; this could affect the generalizability of our findings. Subjects in the first two dose levels were recruited at a different institution than the last two dose levels; although the same inclusion and exclusion criteria were used, this may have unpredictably affected the efficacy findings. Subjects who developed flu-like symptoms could have interpreted these symptoms as induced by the study drug and developed expectations of benefit of treatment. However, only about 30% of subjects in the highest two dose levels correctly guessed their treatment assignment (pamidronate or placebo), and the remaining subjects were unsure or guessed incorrectly. Finally, our pilot, dose-finding study consisted of small groups of subjects at each dose level and combined placebo-treated subjects for the statistical analysis. Nevertheless, the magnitude of the effect observed at the highest dose level strongly suggests there may a clinically meaningful benefit of IV pamidronate for treatment of CLBP.

In conclusion, IV pamidronate, administered as two 90 mg infusions, produced a sustained and clinically significant decrease in pain intensity in subjects with CLBP and MRI evidence of degenerative disc disease or spondylotic disease of the spine. While these results are promising, we emphasize this was a pilot study with limited numbers of highly selected subjects, and results should not be generalized. Further studies are needed to confirm these findings and assess the overall risks/benefits in this population before any medical recommendation can be made for use of pamidronate in the medical therapy of CLBP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank the study participants and support staff of Beth Israel and Mount Sinai Medical Centers, including Janet Auger, Dionne Bobb, Carol Bodian, and Marina Korkmazsky, for their suggestions, technical assistance, time and talent in support of the conduct and completion of the study. We also wish to thank our consultants (Mone Zaidi, MD; Socrates Papapoulos, MD; Sol Epstein, MD; and Russell Portenoy, MD) and members of the data and safety monitoring board: Nathaniel Katz, MD (DSMB Chairman); Robert Dworkin, PhD; Christine Sang, MD; and Li Ming Dong, PhD (DSMB Statistician).

The study was funded by the US National Institutes of Health grant R01 NS44845-01A1 and supported by M01RR000071 (GCRC) and UL1RR029887 (CTSA) from the National Center for Research Resources. Marco Pappagallo, MD, is inventor on a patent for treating chronic spinal mechanical pain by intravenous administration of bisphosphonate, and he and James Moberly are current employees of Grünenthal USA, Inc. No other conflicts of interest were reported.

References

1. Abdulla AJ. Use of pamidronate for acute pain relief following osteoporotic vertebral fractures. *Rheumatology*. 2000; 39(5):567–8. [PubMed: 10852994]
2. Allen KD, Griffin TM, Rodriguiz RM, Wetsel WC, Kraus VB, Huebner JL, Boyd LM, Setton LA. Decreased physical function and increased pain sensitivity in mice deficient for type IX collagen. *Arthritis Rheum*. 2009; 60(9):2684–93. [PubMed: 19714629]
3. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999; 354(9178):581–5. [PubMed: 10470716]
4. Armingeat T, Brondino R, Pham T, Legré V, Lafforgue P. Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. *Osteoporos Int*. 2006; 17(11):1659–65. [PubMed: 16896508]
5. Kawabata A, Kawao N, Hironaka Y, Ishiki T, Matsunami M, Sekiguchi F. Antiallodynic effect of etidronate, a bisphosphonate, in rats with adjuvant-induced arthritis: Involvement of ATP-sensitive K⁺ channels. *Neuropharmacology*. 2006; 51(2):182–190. [PubMed: 16678221]
6. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, Lipton A, Keller A, Ballester O, Kovacs MJ, Blacklock HA, Bell R, Simeone J, Reitsma DJ, Heffernan M, Seaman J, Knight RD. for the Myeloma Aredia Study Group. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med*. 1996; 334(8):488–93. [PubMed: 8559201]
7. Bianchi M, Franchi S, Ferrario P, Sotgiu ML, Sacerdote P. Effects of the bisphosphonate ibandronate on hyperalgesia, substance P, and cytokine levels in a rat model of persistent inflammatory pain. *Eur J Pain*. 2008; 12(3):284–92. [PubMed: 17664076]
8. Bonabello A, Galmozzi MR, Bruzzese T, Zara GP. Analgesic effect of bisphosphonates in mice. *Pain*. 2001; 91(3):269–75. [PubMed: 11275384]
9. Bonabello A, Galmozzi MR, Canaparo R, Serpe L, Zara GP. Long-term analgesic effect of clodronate in rodents. *Bone*. 2003; 33(4):567–74. [PubMed: 14555260]
10. Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults—United States, 1999. *JAMA*. 2001; 285(12):1571–72. [PubMed: 11302137]
11. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *J Bone Miner Res*. 1997; 12(10):1746–52. [PubMed: 9333137]
12. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK. Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007; 147(7):478–91. [PubMed: 17909209]
13. Cortet B, Flipo RM, Coquerelle P, Duquesnoy B, Delcambre B. Treatment of severe, recalcitrant reflex sympathetic dystrophy: assessment of efficacy and safety of the second generation bisphosphonate pamidronate. *Clin Rheumatol*. 1997; 16(1):51–6. [PubMed: 9132326]
14. Crema MD, Roemer FW, Zhu Y, Marra MD, Niu J, Zhang Y, Lynch JA, Javaid MK, Lewis CE, El-Khoury GY, Felson DT, Guermazi A. Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema-like lesions in patients with or at risk for knee osteoarthritis: detection with MR imaging--the MOST study. *Radiology*. 2010; 256(3):855–62. [PubMed: 20530753]
15. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine*. 2000; 25(22):2940–52. [PubMed: 11074683]
16. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*. 2000; 88(3):287–94. [PubMed: 11068116]
17. Farrar JT, Pritchett YL, Robinson M, Prakash A, Chappell A. The clinical importance of changes in the 0 to 10 numeric rating scale for worst, least, and average pain intensity: analyses of data from clinical trials of duloxetine in pain disorders. *J Pain*. 2010; 11(2):109–18. [PubMed: 19665938]

18. Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: Making clinical trial data more understandable. *J Pain Symptom Manage*. 2006; 31(4):369–77. [PubMed: 16632085]
19. Feld J, Rosner I, Avshovich N, Boulman N, Slobodin G, Rozenbaum M. An open study of pamidronate in the treatment of refractory degenerative lumbar spinal stenosis. *Clin Rheumatol*. 2009; 28(6):715–7. [PubMed: 19219479]
20. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med*. 2009; 169(3): 251–58. [PubMed: 19204216]
21. Frith JC, Mönkkönen J, Auriola S, Mönkkönen H, Rogers MJ. The molecular mechanism of action of the antiresorptive and anti-inflammatory drug clodronate: evidence for the formation in vivo of a metabolite that inhibits bone resorption and causes osteoclast and macrophage apoptosis. *Arthritis Rheum*. 2001; 44(9):2201–10. [PubMed: 11592386]
22. Gangji V, Appelboom T. Analgesic effect of intravenous pamidronate on chronic back pain due to osteoporotic vertebral fractures. *Clin Rheumatol*. 1999; 18(3):266–7. [PubMed: 11206358]
23. Gleeson H, Wiltshire E, Briody J, Hall J, Chaitow J, Sillence D, Cowell C, Munns C. Childhood chronic recurrent multifocal osteomyelitis: pamidronate therapy decreases pain and improves vertebral shape. *J Rheumatol*. 2008; 35(4):707–12. [PubMed: 18381777]
24. Hoffman A, Stepensky D, Ezra A, Van Gelder JM, Golomb G. Mode of administration- dependent pharmacokinetics of bisphosphonates and bioavailability determination. *Int J Pharm*. 2001; 220(1–2):1–11. [PubMed: 11376962]
25. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C, Wheeler H, Simeone JF, Seaman J, Knight RD. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med*. 1996; 335(24):1785–91. [PubMed: 8965890]
26. Laroche M, Cantogrel S, Jamard B, Constantin A, Zabranieski L, Cantagrel A, Mazières B. Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. *Clin Rheumatol*. 2006; 25(5): 683–86. [PubMed: 16391891]
27. Lasseter KC, Porras AG, Denker A, Santhanagopal A, Daifotis A. Pharmacokinetic considerations in determining the terminal elimination half-lives of bisphosphonates. *Clin Drug Investig*. 2005; 25(2):107–14.
28. Lerner UH. Neuropeptidergic regulation of bone resorption and bone formation. *J Musculoskelet Neuronal Interact*. 2002; 2:440–7. [PubMed: 15758412]
29. Lin JH. Bisphosphonates: A review of their pharmacokinetic properties. *Bone*. 1996; 18(2):75–85. [PubMed: 8833200]
30. Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K, Reitsma DJ, Heffernan M, Seaman JJ. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer*. 2000; 88(5):1082–90. [PubMed: 10699899]
31. Maccagno A, Di Giorgio E, Roldan EJ, Caballero LE, Perez Lloret A. Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol*. 1994; 23(4):211–14. [PubMed: 8091148]
32. Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, Keyser CP, Clohisey DR, Adams DJ, O’Leary P, Mantyh PW. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience*. 2002; 113(1):155–66. [PubMed: 12123694]
33. Maksymowych WP, Jhangri GS, Fitzgerald AA, Leclercq S, Chiu P, Yan A, Skeith KJ, Aaron SL, Homik J, Davis P, Sholter D, Russell AS. A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal anti-inflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum*. 2002; 46(3):766–73. [PubMed: 11920413]
34. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician*. 2009; 12(4):E35–70. [PubMed: 19668291]

35. Miettunen PMH, Wei X, Kaura D, Reslan WA, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO). *Pediatr Rheumatol Online J*. 2009; 7(1–14):2. [PubMed: 19138427]
36. Moisio K, Eckstein F, Chmiel JS, Guermazi A, Prasad P, Almagor O, Song J, Dunlop D, Hudelmaier M, Kothari A, Sharma L. Denuded subchondral bone and knee pain in persons with knee osteoarthritis. *Arthritis Rheum*. 2009; 60(12):3703–10. [PubMed: 19950284]
37. Nagae M, Hiraga T, Wakabayashi H, Wang L, Iwata K, Yoneda T. Osteoclasts play a part in pain due to the inflammation adjacent to bone. *Bone*. 2006; 39(5):1107–15. [PubMed: 16769263]
38. Novartis prescribing information for Aredia® (pamidronate disodium) for intravenous infusion. Accessed on-line at: <http://www.pharma.us.novartis.com/product/pi/pdf/aredia.pdf>
39. Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *J Oncol Pharm Pract*. 2007; 13(4):223–29. [PubMed: 18045781]
40. Pappagallo M, Breuer B, Schneider A, Sperber K. Treatment of chronic mechanical spinal pain with intravenous pamidronate: a review of medical records. *J Pain Symptom Manage*. 2003; 26(1):678–83. [PubMed: 12850650]
41. Poujol D, Ristori JM, Dubost JJ, Soubrier M. Efficacy of pamidronate in erosive degenerative disk disease: a pilot study. *Joint Bone Spine*. 2007; 74(6):663–4. [PubMed: 17913553]
42. Reeh PW, Steen KH. Tissue acidosis in nociception and pain. *Prog Brain Res*. 1996; 113:143–51. [PubMed: 9009732]
43. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab*. 2010; 95(9):4380–87. [PubMed: 20554708]
44. Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. *Pain Med*. 2004; 5(3):276–280. [PubMed: 15367305]
45. Rousselle AV, Heymann D. Osteoclastic acidification pathways during bone resorption. *Bone*. 2002; 30(4):533–540. [PubMed: 11934642]
46. Selander KS, Mönkkönen J, Karhukorpi E-K, Härkönen P, Hannuniemi R, Väänänen HK. Characteristics of clodronate-induced apoptosis in osteoclasts and macrophages. *Mol Pharmacol*. 1996; 50(5):1127–38. [PubMed: 8913344]
47. Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E. Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. *Osteoporos Int*. 2011; 22(8):2337–45. [PubMed: 21116816]
48. Simmonds MJ, Olson SL, Jones S, Hussein T, Lee CE, Novy D, Radwan H. Psychometric characteristics and clinical usefulness of physical performance tests in patients with low back pain. *Spine*. 1998; 23(22):2412–21. [PubMed: 9836355]
49. Slobodin G, Rosner I, Feld J, Rimar D, Rozenbaum M, Boulman N, Odeh M. Pamidronate treatment in rheumatology practice: a comprehensive review. *Clin Rheumatol*. 2009; 28(12):1359–64. [PubMed: 19690938]
50. Strassle BW, Mark L, Leventhal L, Piesla MJ, Jian Li X, Kennedy JD, Glasson SS, Whiteside GT. Inhibition of osteoclasts prevents cartilage loss and pain in a rat model of degenerative joint disease. *Osteoarthritis Cartilage*. 2010; 18(10):1319–28. [PubMed: 20633675]
51. Vasireddy S, Talwalkar A, Miller H, Mehan R, Swinson DR. Patterns of pain in Paget's disease of bone and their outcomes on treatment with pamidronate. *Clin Rheumatol*. 2003; 22(6):376–80. [PubMed: 14677009]
52. Walker K, Medhurst SJ, Kidd BL, Glatt M, Bowes M, Patel S, McNair K, Kesingland A, Green J, Chan O, Fox AJ, Urban LA. Disease modifying and anti-nociceptive effects of the bisphosphonate, zoledronic acid in a model of bone cancer pain. *Pain*. 2002; 100(3):219–29. [PubMed: 12467993]
53. Yanow J, Pappagallo M, Pillai L. Complex regional pain syndrome (CRPS/RSD) and neuropathic pain: role of intravenous bisphosphonates as analgesics. *ScientificWorldJournal*. 2008; 8:229–36. [PubMed: 18661047]

54. Yoneda T, Hata K, Nakanishi M, Nagae M, Nagayama T, Wakabayashi H, Nishisho T, Sakurai T, Hiraga T. Involvement of acidic microenvironment in the pathophysiology of cancer-associated bone pain. *Bone*. 2011; 48(1):100–5. [PubMed: 20637323]

Figure 1. CONSORT (patient flow) diagram

All subjects randomized to treatment (n=44) were included in the intent-to-treat analysis. The number of days (d) from infusion is listed for subjects who withdrew consent, were withdrawn due to non-compliance, or were lost to follow-up.

Figure 2. Box and whisker plot of change from baseline in daily average pain score
 Bottom and top edges of each box represent the 25th and 75th percentiles (interquartile range [IQR]). Within each box, the median (50th percentile) is displayed as a line and the mean as a diamond. Whiskers extending from each box indicate the range of values outside of the IQR. Points at a distance of more than 1.5 x the IQR from the box are considered outliers.

Figure 3. Continuous Responder Analysis

Blue solid line, placebo; red dashed line, 30 mg pamidronate; green dashed/dotted line, 60 mg pamidronate; brown dashed line, 90 mg pamidronate; purple dashed/dotted line, 180 mg pamidronate.

Table 1

Subject Demographics and Baseline Characteristics

	Placebo (N=16)	Pamidronate 30 mg (N=7)	Pamidronate 60 mg (N=7)	Pamidronate 90 mg (N=7)	Pamidronate 180 mg (N=7)	P value
Age (years)	42.3 ± 13.1	59.7 ± 9.1	51.9 ± 15.0	44.0 ± 14.6	54.0 ± 12.2	0.010
Weight (kg)	85.1 ± 17.7	79.6 ± 12.3	74.2 ± 15.5	95.6 ± 30.8	76.2 ± 13.3	0.340
Male gender	9 (56.3%)	3 (42.9%)	3 (42.9%)	4 (57.1%)	5 (71.4%)	0.830
Race						0.571
White	10 (62.5%)	5 (71.4%)	3 (42.9%)	3 (42.9%)	3 (42.9%)	--
Black	5 (31.3%)	1 (14.3%)	4 (57.1%)	2 (28.6%)	9 (56.3%)	--
Other	1 (6.3%)	1 (14.3%)	0	2 (28.6%)	2 (28.6%)	--
Hispanic ethnicity	3 (18.8)	0	0	1	3 (42.9)	0.093
Pain intensity (0 – 10)	6.1 ± 1.4	5.6 ± 1.4	6.6 ± 2.2	5.2 ± 1.6	6.7 ± 1.1	0.277
Duration of CLBP (years)	5 (0.5, 58)	15 (3.3, 20)	8 (0.5, 25)	3 (1, 50)	5 (1, 27)	0.429
BDI score	7 (0, 25)	3 (0, 11)	6 (0, 13)	5 (3, 10)	5 (0, 15)	0.656

Age, weight and pain intensity score are shown as mean ± standard deviation. Duration of pain and Beck Depression Inventory (BDI) scores are presented as median (range). All others are shown as number (percent). Placebo subjects from each dose level were combined. P-value for between group comparisons was determined using Chi-square (Fisher's exact) tests or ANOVA (Kruskal-Wallis). NRS=numeric rating scale

Table 2

Secondary Efficacy Measures and Health Outcomes

Placebo (N = 16)		Pamidronate (N = 28)				
		(30mg) n = 7	(60mg) n = 7	(90mg) n = 7	(180mg) n = 7	
Measure	Mean Change (SE)	Mean Change (SE)	Mean Change (SE)	Mean Change (SE)	Mean Change (SE)	p- value
Log Pad – Pain Severity						
Worst Pain	-1.4 (0.5)	-1.2 (0.8)	-0.5 (0.9)	-1.9 (0.7)	-4.4 (0.7)	0.008 ¹
BPI – Interference with:						
General Activity	-0.8 (0.5)	0.4 (0.7)	-0.4 (0.8)	-1.8 (0.7)	-3.1 (0.7)	0.012 ²
Mood	-1.5 (0.8)	0.0 (0.8)	-0.3 (0.8)	-2.3 (0.8)	-2.6 (0.8)	0.120
Walking	-1.0 (0.6)	0.4 (0.9)	-0.8 (0.8)	-1.6 (0.8)	-2.7 (0.8)	0.120
Ability						
Normal Work	-1.4 (0.6)	-0.1 (0.9)	-0.9 (0.9)	-2.1 (0.9)	-3.2 (0.8)	0.145
Relations with Other People	-1.0 (0.5)	0.4 (0.8)	-0.0 (0.7)	-1.8 (0.7)	-2.4 (0.7)	0.061
Sleep	-1.7 (0.6)	-0.6 (0.9)	-1.3 (0.9)	-0.6 (0.9)	-2.6 (0.8)	0.424
Enjoyment of Life	-1.9 (0.5)	-0.7 (0.8)	-1.2 (0.9)	-2.7 (0.8)	-3.5 (0.8)	0.137
PGIC – Improvement #						
Overall Activity	60%	n/a	n/a	43%	100%	
Overall Satisfaction	60%	n/a	n/a	57%	100%	
SIMMONDS PHYSICAL PERFORMANCE BATTERY						
Average time to perform 20 repetitions of rising from chair, standing and returning to sit (seconds)	-1.2 (1.5)	-2.1 (2.1)	-2.3 (2.2)	0.1 (2.1)	-1.2 (2.1)	0.936
Average time to perform 20 repetitions of bending forward to the limit of patient's range and returning to upright (seconds)	-1.7 (1.3)	-2.1 (1.8)	-3.7 (1.9)	-0.2 (1.8)	-6.4 (1.9)	0.181
Maximum distance patient reaches with trunk leaning forward holding 4.45kg weight (inches)	-1.6 (0.8)	1.5 (1.3)	0.8 (1.2)	0.7 (1.0)	2.2 (1.0)	0.025 ³
Time taken to walk 50 feet (seconds)	1.0 (1.8)	4.0 (2.5)	-0.2 (2.5)	0.3 (2.4)	-1.6 (2.5)	0.596
Distance walked in five minutes (Log) (feet)	-0.0 (0.4)	-0.1 (0.5)	0.1 (0.5)	-0.0 (0.5)	0.1 (0.5)	0.010 ⁴
Time to complete a 360° roll-over (seconds)	-2.4 (1.6)	2.7 (2.4)	-3.0 (2.4)	-3.5 (1.9)	-4.7 (2.0)	0.218

Table 3

Frequency of Treatment Emergent Adverse Events

	Placebo (N=16) n (%)	30 mg (N=7) n (%)	60 mg (N=7) n (%)	90 mg (N=7) n (%)	180 mg [#] (N=7) n (%)	Total (N=28) n (%)
Any TEAEs	16 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	7 (100.0)	28 (100.0)
Any SAE	0	0	0	0	0	0
Any TEAE resulting in discontinuation	0	0	0	0	0	0
TEAEs reported in >5% of subjects during the first 7 days post-infusion						
	N=15	N=7	N=7	N=7	N=7	N=28
Muscle pain	10 (66.7)	7 (100.0)	5 (71.4)	5 (71.4)	5 (71.4)	22 (78.6)
Fatigue	7 (46.7)	6 (85.7)	4 (57.1)	5 (71.4)	4 (57.1)	19 (67.9)
Joint pain	7 (46.7)	5 (71.4)	4 (57.1)	5 (71.4)	0	16 (57.1)
Headache	2 (13.3)	4 (57.1)	4 (57.1)	5 (71.4)	3 (42.9)	16 (57.1)
Flu-like symptoms	1 (6.7)	2 (28.6)	3 (42.9)	5 (71.4)	3 (42.9)	13 (46.4)
Nausea/vomiting	1 (6.7)	0	0	1 (14.3)	1 (14.3)	2 (7.1)
ENT and mouth	4 (26.7)	1 (14.3)	1 (14.3)	2 (28.6)	1 (14.3)	5 (17.6)
Eye discomfort	1 (6.7)	0	1 (14.3)	0	1 (14.3)	2 (7.1)

Treatment-emergent adverse events were defined as adverse events that emerged during treatment, having been absent pre-treatment, or worsened relative to the pre-treatment state.

* Only events occurring in at least 5% of subjects are reported in this table.

Only AEs after the second infusion are reported

TEAE = treatment-emergent adverse event; SAE = serious adverse event; ENT = ear, nose and throat