

Efficacy of Zoledronic Acid in the Treatment of Nonmalignant Painful Bone Marrow Lesions: A Triple-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial (ZoMARS)

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Abstract

Bone marrow lesions (BML) represent areas of deteriorated bone structure and metabolism characterized by pronounced water-equivalent signaling within the trabecular bone on magnetic resonance imaging (MRI). BML are associated with repair mechanisms subsequent to various clinical conditions associated with inflammatory and non-inflammatory injury to the bone. There is no approved treatment for this condition. Bisphosphonates are known to improve bone stability in osteoporosis and other bone disorders and have been used off-label to treat BML. A randomized, triple-blind, placebo-controlled phase III trial was conducted to assess efficacy and safety of single-dose zoledronic acid (ZOL) 5 mg iv with vitamin D 1000 IU/d as opposed to placebo with vitamin D 1000 IU/d in 48 patients (randomized 2:1) with BML. Primary efficacy endpoint was reduction of edema volume 6 weeks after treatment as assessed by MRI. After treatment, mean BML volume decreased by 64.53% ($\pm 41.92\%$) in patients receiving zoledronic acid and increased by 14.43% ($\pm 150.46\%$) in the placebo group ($p = 0.007$). A decrease in BML volume was observed in 76.5% of patients receiving ZOL and in 50% of the patients receiving placebo. Pain level (visual analogue scale [VAS]) and all categories of the pain disability index (PDI) improved with ZOL versus placebo after 6 weeks but reconciled after 6 additional weeks of follow-up. Six serious adverse events occurred in 5 patients, none of which were classified as related to the study drug. No cases of osteonecrosis or fractures occurred. Therefore, single-dose zoledronic acid 5 mg iv together with vitamin D may enhance resolution of bone marrow lesions over 6 weeks along with reduction of pain compared with vitamin D supplementation only. © 2021 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: BONE BIOLOGY; OSTEOPOROSIS; BONE MARROW LESION/EDEMA; BISPHOSPHONATES; ZOLEDRONIC ACID

Introduction

The term bone marrow lesion (BML, also called bone marrow edema) is a descriptive diagnosis referring to magnetic resonance imaging (MRI) findings associated with a deterioration of trabecular bone typically occurring in the lower extremities.⁽¹⁾ Lesions do not have a defined margin and can extend across the epi-/metaphysis toward the diaphyseal part of the bone and involvement of contiguous bones is not uncommon. The lesions must be distinguished from structurally different marrow abnormalities like osteonecrosis or intramedullary tumor

manifestation.⁽²⁾ BMLs can occur in association with a wide spectrum of clinical entities or their combination, including acute or chronic mechanical overload and conditions levering mechanical competence of bone, such as systemic inflammatory disorders, metabolic bone diseases, and osteoarthritis.⁽³⁾ Histologically, lesions are associated with fibrosis, lymphocytic infiltrates, recruitment of osteoclast precursors, and increased vascularization. Within the lesions, signs of microfractures have been described and bone mineralization can be reduced.^(4,5) Enhanced remodeling activity within these lesions with enrichment of angiogenic markers, increased numbers of

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preosteoclasts and bone formation, entailing elevated bone turnover, and putatively enhanced bone loss account for the reported finding of “transient” or “regional” osteoporosis in longstanding bone marrow lesions.^(1,6-9)

BMLs can best be detected on MRI using water-sensitive sequences, eg, fat suppressed T2-weighted, proton density-weighted, or intermediate-weighted fast spin echo or short tau inversion recovery sequences. Lesions are characterized by a largely homogenous distribution of hyperintense signal on T2-weighted sequences, while T1-weighted sequences show hypointense signaling regularly not having sharp margins.⁽¹⁰⁾

From a clinical perspective, painful lesions typically affecting the lower extremities are associated with severe disability. Because of increased turnover with high regenerative capacity, the condition is considered self-limiting. However, it can take more than 1 year until these areas of locally increased bone turnover resolve.⁽³⁾ There is no established treatment strategy. Treatment options comprise surgical core decompression and extracorporeal shock wave therapy as well as pharmaceutical approaches, most commonly bisphosphonates and iloprost, a prostacyclin analogue.⁽¹¹⁾ Although the latter aims at improving osseous microcirculation, bisphosphonates appear suitable to silence excessive remodeling by reducing bone resorption and consequently bone remodeling, thus stabilizing otherwise progressive deterioration within the trabecular bone environment.^(11,12)

Zoledronic acid (ZOL) is a third-generation, nitrogen-containing bisphosphonate with high affinity to calcium-hydroxyapatite (HA), approved for treatment of postmenopausal osteoporosis, male osteoporosis, Paget’s disease of bone, and glucocorticoid-induced osteoporosis. Upon intravenous application, 61% of ZOL is readily deposited at accessible HA-enriched surfaces of increased bone turnover, while unbound ZOL is rapidly excreted by the kidney.⁽¹³⁾ From the bone surface, ZOL is incorporated by active osteoclasts, thereby inhibiting osteoclast-mediated bone resorption and potentially improving mineral apposition by a mechanism detailed before.^(11,12,14-16) Known side effects of ZOL include acute-phase reactions, arthralgia, and myalgia, typically starting within 24 hours after infusion.⁽¹⁷⁾

We hypothesized that a single infusion of ZOL should improve BML healing by mitigating the presumed high-turnover state, enabling coordinated formation of appropriately mineralized and mechanically competent bone, and this appeasement of bone remodeling should be visible on MRI by reduction of edema signal volume as a surrogate marker for reconciled excessive repair activity. Along with that, pain and associated disabilities were hypothesized to improve upon ZOL treatment.

Materials and Methods

Trial design

This was a triple-blind, placebo-controlled, randomized (2:1) phase III clinical trial to evaluate efficacy and safety of single-dose zoledronic acid (5 mg iv) for the treatment of bone marrow lesions. The trial was initially set up at two neighboring trial sites. For practical reasons, all patients were enrolled at the Orthopedic Department of the University of Wuerzburg (site 02).

Objectives and endpoints

The primary objective of this trial was to evaluate the efficacy of a single dose of ZOL 5 mg iv in the treatment of painful bone

marrow lesions. Secondary objectives aimed at evaluating clinical improvement, safety, and tolerability.

The primary endpoint was defined as the change in volumetric size of the lesion on water-sensitive MRI sequences at 6 weeks’ follow-up compared with baseline upon single-dose ZOL 5 mg iv versus placebo (PBO). A statistically significant greater reduction of the edema volume was considered evidence for efficacy. Secondary endpoints to evaluate clinical efficacy were based on established patient-reported outcome measures including a visual analogue scale (VAS) for current pain (last 24 hours), the pain disability index (PDI), and a bone-specific quality of life questionnaire (Qualeffo-41). Assessment of safety and tolerability comprised descriptive analysis of adverse events and changes in laboratory markers.

Patient selection and course of treatment

The study enrolled adult male and female patients ≥ 18 years with an MRI-confirmed diagnosis of a bone marrow lesion. Selection criteria were specified to exclude patients with contraindications to ZOL as well as patients with a persistent cause for the development of a bone marrow lesion. A detailed listing of inclusion/exclusion criteria is provided in Supplement 1 in Appendix S1. Enrollment took place from July 2011 to August 2015. After written informed consent and assessment for eligibility by the treating physician at the orthopedic hospital, a physical examination and laboratory testing were performed. All participants were started on vitamin D supplementation 1000 IU/d and advised to reduce weight-bearing to below their individual threshold of pain. All participants were advised to have a preventive dental check-up, and a standardized MRI of the bone marrow lesion was scheduled. At baseline (day 0), randomized treatment group allocation and supply with the blinded, indistinguishable investigational medicinal product/IMP (ZOL 5 mg/100 mL or 0.9% NaCl/100 mL) was accomplished by the central pharmacy based on a predefined randomization list provided by the statisticians (CROSNT) to warrant blinding of the treating physician, the radiologist, and the patient. The IMP was administered intravenously over 30 minutes at the study center. All subjects were provided with calcium supplementation of 1000 mg/d for the first 20 days after IMP application. Follow-up visits were scheduled at 3 and 6 weeks after baseline with the 6-week/end of study (EoS) visit including an MRI and subsequent unblinding. As agreed with the ethics committee, further treatment strategies were discussed at that point, including off-label treatment with ZOL in subjects who had been randomized to the placebo group so as not to disadvantage individual participants by withholding potential treatment options. All participants were offered two optional follow-up visits (weeks 9 and 12) to warrant appropriate care and monitor long-term outcome.

Outcome measures

MRI scans were performed without contrast agent at day 0 and day 42 using a 3-Tesla system (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The scanning protocol contained short TI inversion recovery (STIR), fat-saturated T2-weighted turbo spin-echo (TSE), and T1-weighted turbo spin-echo (TSE) sequences (slice thickness 3 mm). Quantitation of bone marrow edema volume was accomplished by two independent radiologists.

Clinical course of the disease was assessed collecting the VAS pain scale, the PDI questionnaire,⁽¹⁸⁾ and the Qualeffo-41 questionnaire,⁽¹⁹⁾ at all visits. Information regarding days of illness,

additional medicinal visits, safety, and adverse events including fractures and osteonecrosis of the jaw were also asked at each visit (visit schedule provided in Supplement 2 in Appendix S1).

Statistics

Sample size is based on the null hypothesis (H0) that reduction of edema volume upon treatment with ZOL is not different compared with placebo. Assuming an average reduction of bone marrow edema volume of about 28% for ZOL and 15% for PBO and a standard deviation of the difference of 15% and applying a randomization ratio ZOL/PBO of 2:1, a total of 48 evaluable patients were required to reject H0 with an error probability of 0.05 and a power of 80%. Using a block-randomization approach, within distinct groups of 12 subjects, 8 were assigned to ZOL and 4 to PBO. Considering variability of baseline edema volume, between-group differences for the primary endpoint were analyzed using an ANCOVA with “change in volumetric size of the lesion” as dependent variable and “baseline size” as covariate in addition to the initial statistical analysis plan. Accordingly, ANCOVA was also used for comparing pain and health-related quality of life (QoL) between both treatment arms. Student's *t* test was used to analyze within-cohort differences at defined time points. In case of a significant effect, effect size was calculated accordingly. Quantitative variables are summarized giving absolute numbers and proportions, arithmetic mean, SD, minimum, and maximum. Categorical variables are summarized by using frequency distribution and percentages. No imputation of missing data was necessary nor performed for the primary analysis. Only the non-missing values were evaluated for computing summary statistics for secondary analyses.

Ethics/approval/registration

The trial was reviewed and approved by the competent ethics committee at Wuerzburg University (EC vote number: 222/10_ff). The study was registered with ClinicalTrials.gov, Identifier NCT01348269, and the European Medicines Agency, EudraCT-No. 2010-019415-38.

Results

A total of 63 patients were screened and enrolled of which 48 patients were allocated to treatment. Of these, 34 subjects (12 female) were randomized to ZOL, while 14 subjects (4 female) received PBO. Details are given in the CONSORT Scheme provided in Fig. 1.

All 48 patients completed the EOS visit 6 weeks after IMP administration. Compliance of concomitant calcium intake was complete (defined as intake of $\geq 90\%$ of capsules) for both groups, compliance of concomitant vitamin D3 supplementation was high with approximately 80% not missing any dose, and about 20% in both groups (ZOL 17.6%, PBO 21.4%) missing solitary doses. Considering a 2:1 randomization ratio, treatment assignment was balanced in terms of sex, age, weight, height, and affected joint area (Table 1).

Efficacy results

Mean BML volume decreased from 69.74 (SD 75.36) cm^3 to 25.17 (SD 55.95) cm^3 with ZOL and from 44.01 (SD 74.61) cm^3 to 19.56 (SD 43.57) cm^3 with PBO from baseline to 6 weeks, respectively. Median values decreased from 35.4 cm^3 to 1.37 cm^3 for ZOL and

from 6.60 cm^3 to 4.63 cm^3 for PBO. The difference in edema reduction between both treatment arms was statistically significant ($p = 0.011$; effect size $r = 0.368$).

Individual case analysis (Supplement 3 in Appendix S1) revealed that the outcome for one patient in the PBO group might have biased the result in favor of ZOL because this patient experienced a substantial deterioration with a $>500\%$ increase in volumetric size of the lesion and can be considered a significant outlier. Hence, an additional, more defensive analysis was performed on a modified intention-to-treat cohort (mITT), excluding this patient's data. The difference in the mean reduction between ZOL and PBO was still statistically significant ($p = 0.009$, $r = 0.380$) in line with rejection of the Null-Hypothesis (Table 2; Fig. 2). A decrease of bone marrow edema volume was observed in 26/34 of patients receiving ZOL (76.5%) and in 7/14 of the patients receiving PBO (50%) with 13/34 ZOL (38.2%) and 3/14 with PBO (21.4%) experiencing 100% decrease, ie, complete resolution of the lesion.

Pain as assessed by VAS was balanced between both groups at screening and baseline, respectively. However, over time between screening and baseline, ie, before treatment group allocation, there was a significant improvement regarding pain level for the entire cohort ($p = 0.014$, effect size $d_z = 0.423$) (Fig. 3).

In the ZOL group, there was a further significant decrease in pain at week 3 ($p = 0.011$, $d_z = 0.523$) and week 6 ($p = 0.002$, $d_z = 0.639$) compared with baseline. This improvement in the ZOL group persisted over the follow-up through week 12. Subjects receiving PBO had an initial, non-significant numerical decrease in pain at 3 weeks versus baseline ($p = 0.147$) with worsening of pain at week 6 ($p = 0.894$). After 6 weeks of treatment, there was a significant difference between ZOL and PBO in the VAS pain values ($p = 0.042$, $r = 0.328$). The numerical difference in pain on the VAS between ZOL versus PBO persisted from week 6 through week 12 follow-up (Fig. 4).

Regarding pain-associated disabilities according to the PDI, there were non-significant numerical improvements in the categories family/home responsibilities ($p = 0.151$), recreation ($p = 0.384$), and occupation ($p = 0.598$), whereas limitations regarding social activities ($p = 0.797$), sexuality ($p = 0.103$), and life support activities ($p = 0.600$) were stable over time. Upon treatment application, each post baseline mean value of the distinct domain was numerically lower for patients receiving ZOL in all groups, indicating fewer limitations compared with PBO, even though longitudinal improvements were also found in the PBO group (Supplement 4 in Appendix S1).

There were no clinically meaningful changes in any of the five QoL categories covered by the Qualeffo-41 from baseline through week 12 irrespective of treatment group allocation (Supplement 4 in Appendix S1). The average number of days of illness was numerically lower in ZOL versus PBO.

Biochemically, there was a significant decrease of serum-calcium with ZOL versus PBO ($p = 0.011$, $r = 0.368$) along with a non-significant trend to slightly reduced ALP ($p = 0.178$) at the 6-week visit, while there were no significant differences between both groups regarding creatinine ($p = 0.231$), C-reactive protein ($p = 0.058$), and phosphate ($p = 0.701$) (Supplement 5 in Appendix S1).

Safety/adverse events

In total, 191 adverse events (AE) (ZOL 135; PBO 54) were documented in 45 patients (ZOL 34; PBO 11), including 6 serious AE (ZOL 5; PBO 1) with none of the latter being related to the study drug. Based on patients' reports, 96 AEs were assigned adverse

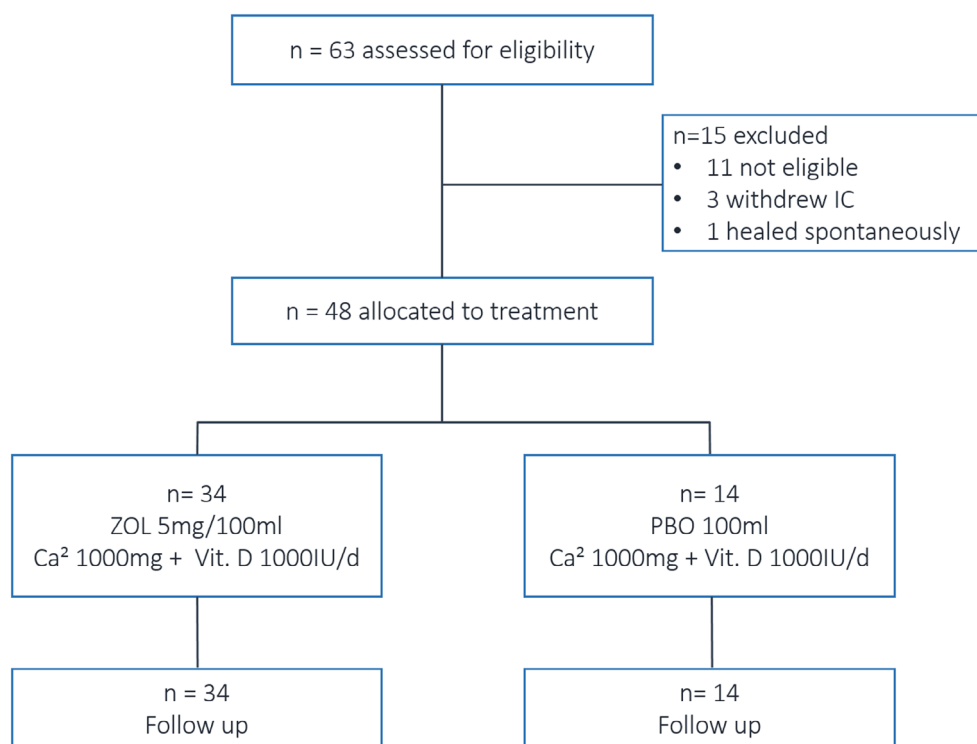


Fig. 1. Patient flow according to CONSORT scheme.

Table 1. Baseline Characteristics

	ZOL 5 mg (n = 34)	PBO (n = 14)	All patients (n = 48)
Sex			
Female	12 (35.3%)	4 (28.6%)	16 (33.3%)
Male	22 (64.7%)	10 (71.4%)	32 (66.7%)
Height (cm)			
Mean (SD)	174.1 (8.9)	174.3 (9.7)	174.2 (9.0)
Median (IQR)	175.5 (13.3)	174.0 (11.8)	174.5 (13.3)
Range (min to max)	150 to 190	160 to 194	150 to 194
Weight (kg)			
Mean (SD)	87.54 (19.58)	81.49 (18.69)	85.78 (19.32)
Median (IQR)	85.00 (26.5)	84.00 (17.3)	85.00 (26.5)
Range (min to max)	50.0 to 132.0	53.0 to 125.0	50.0 to 132.0
Age (years) at enrollment			
Mean (SD)	50.19 (13.12)	53.60 (7.10)	51.18 (11.72)
Median (IQR)	51.19 (14.1)	55.70 (6.8)	52.27 (11.0)
Range (min to max)	18.80 to 71.80	36.43 to 65.49	18.80 to 71.80
Skeletal region affected			
Hip	7	3	10
Knee	12	5	17
Foot/ankle	13	5	18
Other	2	1	3

ZOL = zoledronate; PBO = placebo; SD = standard deviation; IQR = interquartile range.

drug reactions (ADR) with a supposed association with IMP administration (ZOL 83 in 31 patients; PBO 13 in 6 patients). All reactions were within the range of expected side effects of ZOL, commonly summarized as flu-like symptoms. Most

frequently reported ADR were headache (ZOL 13 patients, 14 events; PBO 5 patients, 6 events), pain in extremities (ZOL 11 patients, 11 events; PBO 3 patients, 4 events), and fatigue (ZOL 10 patients, 11 events; PBO 3 patients, 3 events). There were

Table 2. Comparison of Edema Reduction in Both Treatment Arms for ITT and mITT

	ITT		mITT	
	ZOL	PBO	ZOL	PBO
Mean edema size (cm ³) wscreening (SD)	69.74 (75.4)	44.01 (74.6)	69.74 (75.4)	46.99 (76.8)
Median edema size (cm ³) screening (IQR)	35.4(113.9)	6.60 (53.1)	35.40 (113.9)	7.80 (58.4)
Mean edema size (cm ³) week 6 (SD)	25.17 (56.0)	19.56 (43.6)	25.17 (56.0)	18.56 (45.2)
Median edema size (cm ³) week 6 (IQR)	1.37 (7.2)	4.63 (14.6)	1.37 (7.2)	4.50 (11.1)
Mean reduction (%) (SD)	64.53 (42.0)	-14.43 (150.5)	64.53 (41.9)	23.97 (46.5)
Median reduction (%) (IQR)	90.29 (87.5)	3.47 (64.2)	90.29 (87.5)	6.94 (70.5)
ANCOVA (<i>p</i> value)	0.011		0.009	

ITT = intention to treat; mITT = modified intention to treat; ZOL = zoledronate; PBO = placebo; SD = standard deviation; IQR = interquartile range.

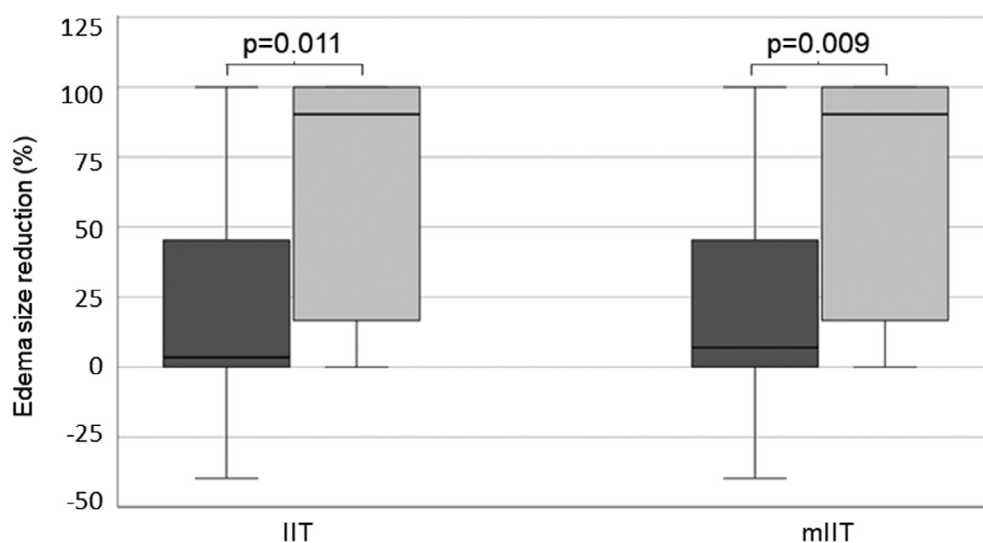


Fig. 2. Difference in mean edema size reduction after 6 weeks between zoledronate (ZOL) and placebo (PBO) for intention to treat (ITT) and the modified intention to treat (mITT) cohorts. Light shading = ZOL group; dark shading = PBO group.

no cases of osteonecrosis of the jaw, transition of a lesion into an osteonecrosis, or fracture.

Discussion

BMLs result from and are promoted by numerous conditions or combinations of these and are associated with excessive bone turnover and compromised mechanical stability.^(1,3) Irrespective of underlying factors, painful BML can cause long-term disability, particularly when a vicious cycle of trabecular deterioration, increased turnover with enhanced resorption, and precipitous, mechanically insufficient bone regeneration and further deterioration develops.⁽²⁰⁾ Beyond the therapeutic requirement to eliminate predisposing factors, there is an unmet need to better understand how excessive local turnover can be mitigated to enable coordinated, mechanically competent osseous regeneration.

This prospective, triple-blind RCT was intended to evaluate efficacy, safety, and tolerability of a single-dose ZOL 5 mg iv with regards to mitigating excessive local turnover reflected in BML expansion on water-sensitive MRI sequences compared with placebo over 6 weeks. The results confirm with medium to large effect size a superior reduction of BML volume along with a

reduction of pain after treatment with ZOL 5 mg iv compared with placebo, scientifically substantiating suggestive findings of previous retrospective and open-label trials using bisphosphonates to treat bone marrow lesions.⁽²¹⁻²⁸⁾

Pathophysiologically, high-affinity ZOL can be considered to accumulate on the actively remodeling trabecular surface of the lesion where it is incorporated by active osteoclasts, thus precluding further bone resorption^(14,15) and potentially impeding pathologic vascularization,^(29,30) eventually moderating excessive bone turnover while still enabling or hypothetically even promoting regeneration of deteriorated bone.⁽³¹⁾ Although in vitro data regarding the effects of ZOL on bone formation are controversial, current evidence supports a positive effect on osteoblast differentiation and mineralization,^(12,32) and clinical data confirm stimulation of mineral apposition^(16,33) without negative impact on fracture healing.⁽³⁴⁾

The significant reduction of pain (VAS) and similar positive trends in various PDI categories observed in the overall cohort from screening to baseline before treatment group allocation supports the relevance of appropriate counseling with regard to suspended weight bearing and baseline vitamin D supplementation. Persistence of this positive development in the PDI categories throughout the study even in the PBO cohort further

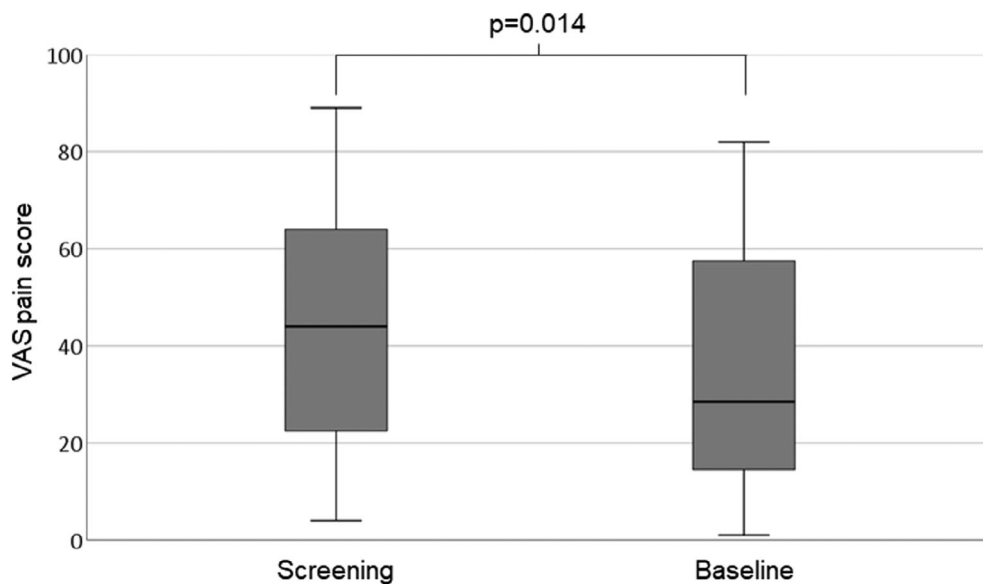


Fig. 3. Visual analogue scale (VAS) pain score change for overall patient cohort before screening and baseline before treatment group allocation.

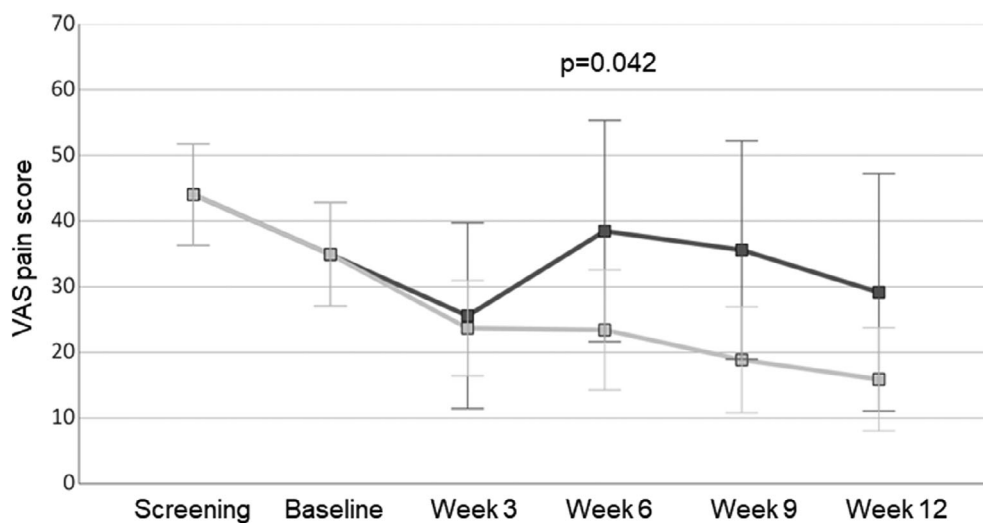


Fig. 4. Longitudinal representation of pain on visual analogue scale (VAS) pain score in both groups. Statistically significant between-group difference at end of study/6 weeks. Light shading = ZOL group; dark shading = PBO group.

confirms the healing potential and self-limiting nature of these lesions with restricted weight bearing. Accordingly, the likeliest explanation for substantially increased edema volume along with exacerbation of pain in the one negative outlier in the PBO group was insufficient adherence to the recommended weight-bearing restrictions. Correspondingly, the continuous improvement with further significant reduction of pain level (VAS) from baseline to 6 weeks and beyond without reversal (Fig. 4) may also be a consequence of ZOL, attenuating bone loss associated with suspended weight bearing.

Changes in biochemistry and adverse events observed in this study were in line with known effects of ZOL. The high proportion of supposed drug-related reactions in 91.2% of participants

receiving ZOL has to be reflected in the context of 42.9% of participants reporting such issues in the PBO group. One relevant explanation is a high level of sensitization for this aspect after comprehensive information and subsequent overcautious reporting of any perceived adverse symptomatology. Importantly, there was no incidence of aseptic osteonecrosis developing from any lesion, consistent with the understanding of aseptic osteonecrosis and bone marrow edema being two different entities. Furthermore, no osteonecrosis of the jaw and no fractures occurred.

Potential limitations of the study include the limited number and heterogeneity of patients, along with the fact that participants were not matched for baseline marrow edema volume.

Otherwise, the triple-blind, randomized, placebo-controlled design of this trial with an independently assessed, objective endpoint is unique in the field, making the results highly valuable. Further research is warranted to validate these findings.

In conclusion, the results of this trial confirm that adding single-dose ZOL 5 mg to suspended weight bearing and vitamin D can enhance healing capacity of painful BML by significantly reducing BML volume as a marker of excessive, unstructured remodeling.

Disclosures

LS has received honoraria for lectures and consultation from Amgen, Alexion, KyowaKirin, Lilly, MSD, Novartis, and Servier and has received unrestricted research grants to his institution (University of Wuerzburg) from Novartis, KyowaKirin, and Alexion and is involved in clinical trials related to osteoporosis drugs initiated by Amgen, Novartis, and Servier. FG has received speaker honoraria from Alexion, Lilly, and Abbvie. JB, AH, and RM have no conflicts of interest. FJ has received honoraria for lectures and advice from Lilly, Amgen, Novartis, MSD, Nycomed, Servier, Roche, Enobia, and Alexion, has received unrestricted research grants from Novartis, and is involved in clinical studies related to osteoporosis drugs initiated by Lilly, Amgen, Servier, and Novartis.

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Authors' roles: LS designed and conducted the trial, contributed to acquisition and analysis of data, and wrote the manuscript. FG contributed to acquisition, analysis, and interpretation of data and revised the manuscript. JB contributed to acquisition and analysis of data and manuscript preparation. AH contributed to acquisition, analysis, and interpretation of data and revised the manuscript. RM contributed to conception and design of the study and analysis and interpretation of data and revised the manuscript. FJ initiated the study and contributed to conception and design of the study, interpretation of data, and revised the manuscript.

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Author Contributions

Lothar Seefried: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing; **Franca Genest:** Formal analysis, Investigation, Visualization, Writing – review & editing; **Jasmin Baumann:** Investigation, Project administration, Writing – review & editing; **Anke Heidemeier:** Data curation, Investigation, Writing – review & editing; **Rainer Meffert:** Resources,

Writing – review & editing; **Franz Jakob:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/jbmr.4493>.

DATA AVAILABILITY STATEMENT

Data Availability Statement: All data and study material is stored at the Departments of orthopedics at the University of Wuerzburg for 10 years. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The Study report as well as all the findings not explicitly mentioned in this study are found within the supplementary material.

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