Clinical Trial

Effect of zoledronic acid and denosumab in patients with low back pain and Modic change: a proof of principle trial†

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ABSTRACT

The aim of this study was to evaluate the effect of zoledronic acid (ZA) and denosumab on low back pain (LBP) and Modic change (MC) over 6 months. Adults aged ≥40 years with significant LBP for at least 6 months duration and MC (type 1, 2 or mixed) were randomised to receive ZA (5mg/100ml), denosumab (60mg), or placebo. LBP was measured monthly by Visual Analogue Scale (VAS) and the LBP Rating Scale (RS). MC was measured from MRIs of T12-S1 vertebrae at screening and 6 months. 103 participants with moderate/severe LBP (mean VAS=57mm, mean RS=18) and median total MC area 538 mm^2, were enrolled. Compared to placebo, LBP reduced significantly at 6 months in the ZA group for RS (-3.3, 95% CI -5.9 to -0.7) but not VAS (-8.2, 95% CI -18.8 to +2.4) with similar findings for denosumab (RS -3.0, 95% CI -5.7 to -0.3, VAS -10.7, 95% CI -21.7 to +0.2). There was little change in areal MC size overall and no difference between groups with the exception of denosumab in those with type 1 Modic change (-22.1mm^2, 95% CI -41.5 to -2.7). In post-hoc analyses, both medications significantly reduced VAS LBP in participants with milder disc degeneration and non-neuropathic pain, and denosumab reduced VAS LBP in those with type 1 MC over 6 months, compared to placebo. Adverse events were more frequent in the ZA group. These results suggests a potential therapeutic role for ZA and denosumab in MC-associated LBP.

Key words: Bisphosphonate; denosumab; low back pain; Modic changes; magnetic resonance imaging

INTRODUCTION

Chronic low back pain (LBP) is a common and disabling problem, for which there are few treatment options.[1] While no specific pathologies are present in the majority of people with LBP (>85%),[2] a subset of patients have one type of pathology, Modic changes (MC), which is strongly associated with non-specific LBP.[3] MC is an independent risk factor for LBP,[4 5] suggesting it is an independent source of pain and a treatment target for LBP.

Modic et al.[6 7] described three types of vertebral endplate bone abnormalities (MC) which are visualised on MRI. Type 1 MC is proposed as the initial stage, indicating inflammation and oedema; type 2 and 3 MC are considered stable stages and represent fatty degeneration and bone sclerosis, respectively. Previous population-based research reported that type 1 MC is more likely to be associated with LBP and poor prognosis than other MC types.[8-10] Types of MC can transform from one type to another, and the distinction between different types of MC are complex,[11-13] but transformation of type 1 MC to type 2 correlates with improvement in symptoms.[14]

A few clinical trials have been performed in MC-associated LBP. An uncontrolled trial of rest versus exercise showed similar and small effects on LBP over one year.[15] Intra-discal glucocorticoid injection reduced LBP intensity at 1 month but pain rebounded quickly.[16] Oral antibiotics significantly improved LBP symptoms and decreased MC size.[17] However, a recent study failed to replicate these results,[18] and side effects may limit usage. Intravenous bisphosphonates, such as zoledronic acid (ZA) and pamidronate, have shown analgesic effects on LBP.[19-21] Moreover, in a small study ZA had a short-term effect on pain in patients with LBP and MC, but no MRI endpoints were reported.[21] ZA is effective for knee osteoarthritis related bone marrow lesions (BMLs),[22] which have similar characteristics and MRI appearance to MC,[23] suggesting similar pathology. An observational study reported that

denosumab, a fully human monoclonal antibody, was effective in the treatment of bone marrow oedema with lower extremity pain,[24] but there are no studies in LBP. Therefore, the aim of this proof of principle study was to assess the effect of ZA (5mg) and denosumab (60mg) on LBP symptoms and MRI-detected MC, in participants with LBP and type 1, 2 or mixed MC.

METHODS

Trial design

This study is a single-centre, double-blind, placebo-controlled, randomised parallel-group trial of a single dose of either intravenous ZA (5mg) or subcutaneous denosumab (60mg) versus placebo with a 1:1:1 allocation ratio.

Setting and participants

Participants were recruited from August 2014 to October 2015 from the back pain clinic of the Royal Hobart Hospital and through local advertising. Participants aged ≥40 years with significant LBP (≥40 on a 100mm visual analogue scale (VAS)) for at least 6 months, and at least one endplate from T12-S1 with MC (type 1, 2 or mixed) were eligible for inclusion.

Exclusion criteria are detailed in Supplementary Table 1. Potential participants then had a screening MRI, and those with no MC or with only type 3 MC were excluded. Regular use of other medication was allowed except for high dose opiates.

Informed consent was obtained from all participants, and ethics approval for the study was granted by the Tasmanian Human Research Ethics Committee. This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000719639).

Randomisation and interventions

Participants were randomised to receive one of three treatments: zoledronic acid 5mg/100ml, denosumab 60mg/1ml, placebo (saline 100ml/1ml) using a double dummy approach. Participants were randomised into one of three study arms based on computer-generating random numbers using adaptive allocation, stratified by type 1 MC (with or without). This was conducted by a staff member with no direct involvement in the study. The allocated treatment was dispensed by one author (LLL) and administered by a nurse who was unblinded, neither of whom assessed any study outcomes. All participants and assessors were blinded to treatment allocation throughout the trial.

Outcomes

Chief outcomes were changes in LBP assessed using VAS (0-100mm), and total MC size (mm^2) on MRI over 6 months.

Other outcomes were changes in LBP (the Low Back Pain Rating Scale (RS)),[25] disability (the Roland-Morris Disability Questionnaire (RMDQ)),[26] utility (calculated using the Assessment of Quality of Life (AQoL) questionnaire)[27], response to therapy (based on the Osteoarthritis Research Society International (OARSI) responder criteria for clinical trials)[28] after 3 and 6 months, and change in the proportion of participants with type 1 MC after 6 months. Safety outcomes included acute phase reactions[29] and any adverse events over 6 months. Blinding was assessed after 6 months to determine whether participants correctly guessed which treatment arm they were allocated to.

Participants who withdrew from the study before 6 months were invited to have a second MRI

scan at the sixth month.

Pain and disability

LBP was assessed using a 100mm VAS from 0 (none) to 100 (unbearable) by asking "Thinking about your low back, where would you rate your pain? Use the last seven days as a time frame".

The pain subscale of the RS (score range 0-30) was also used to assess LBP, combining three sub-questions rated from (0 (no pain) to 10 (worst pain imaginable)) for current pain intensity and the worst (0-10) and average pain (0-10) in the past two weeks.[25] RMDQ (0-24 scores) was used to evaluate disability due to back pain with 24 indicating the worst.[26] LBP (VAS and RS) and disability scores were recorded at baseline and then monthly. Clinically significant improvements were defined as a 15mm reduction in VAS and 5 in RMDQ.[30]

MRI assessment

MRI scans were performed at screening and 6 months with a 1.5T non-contrast scan (GE Optima 450W, Milwaukee, USA). The imaging sequences were sagittal T1-weighted and fat-saturated T2-weighted Fast Spin Echo (FSE), and T2-weighted Fast Recovery Fast Spin Echo (FRFSE) (T1 FSE: repetition time 489ms, echo time 10ms; fat-saturated T2 FSE: repetition time 3490ms, echo time 102ms; T2 FRFSE: repetition time 3206ms, echo time 102ms). Other technical specifications included a slice thickness of 4mm with spacing 0.5mm, matrix 416×224 and a field of view 32cm.

Presence and location of MC at screening was assessed by a radiologist (AH) for the purposes of patient enrolment. Scoring of MC was performed by a trained observer (GC), blinded to treatment allocation using OsiriX software (University of Geneva, Geneva, Switzerland).

Screening and 6 months scans were read paired with the chronological order known to the reader. The endplates were measured from the upper endplate of T12 down to the upper endplate of S1, which is the field of view of the MR images. The maximum area (mm^2) of MC at each endplate was measured (excepting endplates with type 3 MC), and these were summed to create total MC size at screening and 6 months (Figure 1). The type of MC at each vertebral endplate was determined according to previous descriptions.[11] Disc degeneration of each intervertebral disc at screening was measured using the Pfirrmann Grading System (level 1-5),[31] where 5 was considered severe, and the maximum level of disc degeneration for each participant was recorded. There was excellent intra-observer repeatability for disc degeneration, MC size and MC type, with intraclass correlation coefficients from 0.93 to 0.99.

Responder criteria

The OARSI responder criteria combines improvements of pain, function and patient's global assessment to create a treatment effect which is based on osteoarthritis clinical trials.[28] We adapted this approach for use in LBP, combining patient's global assessments, LBP VAS for pain and RMDQ scores for function to generate a treatment responder variable (0: no responder; 1: responder). Patient's global assessments were assessed using a 100mm VAS, with 0 indicating very well and 100 very poorly.

Other measures

Utility scores (0-1) were calculated based on the 4-dimension AQoL questionnaire, with 0 indicating the worst health state and 1 the best.[27] Neuropathic pain was assessed by the painDETECT questionnaire (-1 to 38) at screening. A painDETECT score <12 was defined as unlikely neuropathic pain, and 13-18 as possible neuropathic pain.[32] Depression (as assessed

using the Patient Health Questionnaire (PHQ-9) (0-9))[33] and use of concomitant medications at baseline were recorded to address their potential effects on pain. Blinding was assessed by asking participants "What treatment do you think you received" with offering the following options: "Zoledronic acid" or "Denosumab" or "Placebo" or "Either active treatment" or "Not sure".

Sample size

This study was a proof of principle study, and therefore no formal sample size calculation was performed.[34] In consideration of the similarity between MC and BMLs, we based the sample size on our previous study of ZA in knee osteoarthritis,[22] in which we were able to demonstrate a statistically significant difference in knee pain and BML size with a sample size of n=30 per group. Thus, we planned to recruit at least 90 participants in this study.

Statistical analysis

All analyses followed an intention-to-treat principle. Changes in LBP, size of MC, proportion of participants with type 1 MC, disability and utility scores were analysed using mixed-effect modelling and generalised estimating equations. In mixed-effect modelling, fixed effects were month, treatment group and their interaction; random intercept was participant identification. Missing values (6%-13% missing) on these six repeated measure outcomes were addressed using maximum-likelihood estimation (mixed-effect modelling and generalised estimating equations).[35] The adjustments for clinically important covariates at baseline (age, gender, depression, type 1 MC, size of MC, duration of symptoms and/or concomitant medication) made no meaningful change to the model coefficients, so we did not include any of them in the final models.

Treatment responders were regressed on treatment allocation using log binomial models separately at 3 and 6 months. Multiple imputations by chained equations were used to address missing values on treatment responders (10%-14% missing). Twenty imputations were performed using baseline variables with complete data assuming missing at random (age, gender, BMI, concomitant medication, type 1 MC and treatment allocation).

Post-hoc analyses were performed to identify subgroups in which these treatments may be more effective. For change in VAS LBP and disability we examined potential interactions between treatment effects (treatment over time) and severity of disc degeneration (severe/milder), presence or absence of type 1 MC and size of MC (above/below the median size) at screening. Given the exploratory nature of this study, interactions were only evaluated as whether they were potentially clinically important rather than by statistical significance. If the effect size of an interaction item was clinically significant, stratified analysis was performed. A pre-specified sensitivity analysis was used to determine whether the change in LBP (VAS and RS) was influenced by persons in whom the presence of neuropathic pain was uncertain (painDETECT score 12-19).[32] Additionally, we performed a subgroup analysis for the change of MC size in endplates with only type 1 MC at screening. Time-course analysis was used to explore the trajectory of treatment effects on LBP and disability. Analyses were performed using Stata version 14.2 (Stata Corporation). A two-sided *p*-value of 0.05 was considered statistically significant.

RESULTS

Participants

A total of 171 participants were screened and 103 participants randomised to receive either ZA (n=35), denosumab (n=31), or placebo (n=37). Six participants (6%) withdrew from the study

during the 6 months follow-up. Ninety-five (92%) participants completed questionnaires and 96 (93%) had MRIs at 6 months. Figure 2 shows the trial flowchart.

At baseline, participants were older adults (mean age 59.8±10.1), who were predominantly males (39% females) with moderate to severe LBP (mean VAS of 57mm) and MC visible at 1 or more lumbar vertebrae (median size of 538 mm^2). The three groups were generally well matched on baseline characteristics except for sex and MC size (Table 1).

Chief outcomes

The chief outcomes are presented in Table 2. Compared to baseline, VAS LBP reduced in all three groups over 6 months. There were no statistically significant differences in the reductions of VAS LBP between either the ZA or the denosumab group and placebo, though the 10.7 mm greater reduction in the denosumab group compared to placebo approached statistical significance (p=0.06). The size of all MC changed little in any group and there were no significant between group differences.

Other outcomes

Other outcomes are shown in Table 2. Compared to placebo, both ZA and denosumab significantly improved LBP (as assessed by the RS) after 6 months; ZA also decreased RS and disability scores after 3 months. There was no change in the proportion of participants with type 1 MC or in utility scores in either treatment group, compared to placebo. Proportions of responders at 3 and 6 months were higher in the ZA and denosumab group than that in the placebo group, but these differences were not statistically significant. For assessment of blinding, 30% participants in the ZA group, 10% in the denosumab group and 18% in the

placebo group correctly guessed what they had been allocated to (Supplementary table 2).

Post-hoc analyses

Post-hoc analyses are also presented in Table 2. Effect sizes of interactions with both severity of disc degeneration and presence or absence of type 1 MC for VAS LBP reached clinical significance. In stratified analyses, both ZA and denosumab significantly improved LBP in persons with milder disc degeneration over 6 months, and denosumab improved LBP in those with type 1 MC, compared to placebo. Subgroup analysis showed that the size of type 1 MC was increased in the ZA and the placebo groups, but was slightly decreased in the denosumab group and this difference was statistically significant when compared to placebo. Sensitivity analysis found both treatments significantly improved LBP (VAS and RS) compared to placebo in participants without neuropathic pain.

Time-course analysis showed that LBP and disability scores in the ZA group decreased significantly after one month and remained relatively stable over the remaining 5 months (Figure 3). The effect of denosumab on LBP peaked at 2 months with little change between 2 and 6 months.

Adverse events

Adverse events were common, with all 35 participants (100%) in the ZA group, 27 (87%) in the denosumab group and 25 (68%) in the placebo group reporting at least one adverse event over 6 months (Table 3). Most of the adverse events were acute phase reactions in the ZA group: primarily flu-like symptoms, headache-dizzy, musculoskeletal pain and stiffness, and psychological effects (eg. malaise, insomnia and depression). Three participants experienced

one serious adverse event (non-elective hospital admission): from the placebo group one participant had a food allergy and another severe vomiting and dehydration while traveling; one participant from the ZA group fell after taking diazepam. Two participants from the placebo group withdrew due to adverse events.

DISCUSSION

In this proof of principle study, one-off treatment with either infusion of ZA (5mg/100ml) or subcutaneous injection of denosumab (60mg/1ml) were effective for the treatment of MC-associated LBP assessed by LBP RS but not VAS, but did not significantly change overall areal MC size over 6 months. Furthermore, post-hoc analyses suggested both therapies had significant benefit for LBP in patients with specific MRI characteristics (milder disc degeneration or type 1 MC) and non-neuropathic pain. These pilot findings imply these therapies will work better in persons with earlier disease with non-neuropathic pain.

There were differences in the effects of ZA and denosumab compared to placebo on pain depending on the method of pain assessment used. There were no statistically significant between-group differences in LBP assessed by VAS, though there was a trend to a statistically significant reduction for the denosumab group compared to the placebo group ($p=0.06$), although the magnitude (10.7mm) was not clinically important. In contrast, improvements in LBP as assessed by the RS were statistical significant in both active treatment groups over 6 months, compared to placebo. This discrepancy may be due to the different time anchors (VAS pain – last 7 days vs. RS – last two weeks plus the present), or slight differences in wording. Also, while RS specifies 3 questions for the worst, average and current pain, VAS in this study recorded the average LBP only. These differences may make RS more sensitive than VAS for

LBP assessment.

The effects on pain from ZA occurred early in the treatment period (1 month) for both LBP and disability. This was similar to a previous trial where ZA significantly reduced LBP (using a 10cm VAS) after 1 month but not after 12 months.[21] ZA predominantly showed a long but not short term effect on LBP in this trial, but the pain curves did separate at 1 month. This result was unexpected but is consistent with the very rapid effect of ZA on bone turnover markers in osteoporosis [36] and Paget's disease.[37] Maximal effects on LBP were observed after 2 months in the denosumab-treated patients. The effect of denosumab on bone resorption wears off quickly from around the five month mark. We expected this would correlate with change in pain but did not observe any worsening of pain before the end of the trial. A longer duration of follow up would be required to explore this further.

The analgesic effects of ZA and denosumab on MC-associated LBP may be due to their role in osteoclast inhibition[38 39] or inflammation.[40] Elevated levels of osteoclast activators have been detected in intervertebral discs with adjacent MC compared to those without,[41] meaning osteoclasts may be involved in the pathogenesis of MC. In animal experiments, osteoclastic bone resorption has been associated with inflammatory skeletal pain,[42] which can be improved by the administration of bone-active agents.[43 44] Biomechanical theory suggests that traumatic inflammation in the endplates may be a source of MC-associated LBP.[6 45] Upregulation of pro-inflammatory cytokines has been found in endplates with MC,[46-48] and localised anti-inflammatory therapy has shown a short-term effect on MC-associated LBP.[16] Hence, the anti-inflammatory effect of ZA may also contribute to relieving LBP associated with MC.

In post-hoc analysis, both therapies were more effective on LBP in persons with milder disc degeneration than with severe disc degeneration, suggesting they may work better earlier in the disease course. Previous research has been inconclusive about whether the size or type of MC

is associated with LBP symptoms.[8 9 49] We observed that denosumab reduced VAS LBP more in persons with type 1 MC. Both medications statistically significantly relieved LBP in persons without neuropathic pain, which would be expected given their mechanism of action.

There was little change in MC size (<10mm^2 or 1% of baseline size) in any treatment group over the course of the trial. This is in contrast to our previous study, where ZA reduced knee osteoarthritis related BML area by 164mm^2 (35% of baseline size) compared to placebo over 6 months.[22] MC pathology may be different to BML pathology and may take longer to respond to treatment with bone-active agents. Our study may not have been long enough to observe an effect. Similarly, in a small randomised controlled trial, Koivisto et al found that ZA did not significantly reduce the size of MC over one year, but ZA accelerated the conversion of type 1-dominant to type 2-dominant MC.[50] The progression of LBP symptoms and MC may be at least partially independent of each other and this is a potential reason why the treatments in our trial improved LBP symptoms but did not significantly change MC size or type. However, we found that denosumab prevented an increase in type 1 MC size, but the change was small in magnitude.

As expected, adverse events were more frequent in the ZA group than that in the placebo group. The major adverse events in the ZA group were similar to those previously described,[29] and no new safety signals were identified.

Strengths of this study include the high follow-up (94%) over 6 months, areal measurements for MC and detailed records of clinical symptoms at each month of follow-up. The study also has limitations. Firstly, this was a proof of principle study, in which the sample size was modest, so this study should be regarded as hypothesis generating for subsequent trials. Secondly, the follow-up may not have been long enough to detect a structural change, and a recent study suggested that one year follow-up may be required.[50] Therefore, we cannot be sure of whether

the treatment effect on LBP was related to the changes in MC size or type, or to other MC characteristics that were not measured. Thirdly, the frequency of acute phase reactions in ZA-treated group was higher than in other two groups, this might weaken the strength of blinding. However, patient-reported assessment of treatment blinding demonstrated that only 30% of patients in the ZA group correctly guessed that they were given ZA; this is no better than chance and suggests that blinding has been successful. Finally, results from post hoc analyses were exploratory and should be confirmed further.

In conclusion, both ZA and denosumab may reduce LBP but do not change overall MC area over 6 months, but denosumab may reduce type 1 MC size. This study suggests a potential therapeutic role for ZA and denosumab in MC-associated LBP.

Contributors

GC and LLL contributed equally to this study. GJ and LLL designed the study. LLL obtained funding. AH, DS and GJ screened participants. GC, DA and AH read and interpreted MRIs. GC cleaned and analysed data. PO and FP provided statistical advice. GC, LLL, DA, TMW and GJ participated in data interpretation. GC drafted the initial manuscript. All authors critically reviewed and edited the manuscript and approved the final version.

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Competing interests

No authors have competing interests for this trial.

Role of the Sponsor

Tasmanian Community Fund and Arthritis Australia had no role in design or conduct of the study, collection or analysis of the data, or preparation of the manuscript.

Ethics approval

Tasmanian Human Research Ethics Committee (Reference No. H0013961)

Clinical trial registration number

ACTRN12614000719639

No authors have competing interests for this trial.

Supplemental Table: 2

Supplemental Figure: 0

Figure Legends

Figure 1. Measurement of the total area of Modic changes. The maximum size of Modic changes was measured for each participant at each endplate. In this example, the maximum size of Modic changes at each endplate was recorded (lower endplates of L4 (A) and L5 (C), and upper endplates of L5 (B) and S1 (D)), and the total area of Modic changes for this participant was the sum of the maximum area of Modic changes at these four endplates.

Figure 2. Study flow diagram. *Missed appointments are defined as no questionnaire available at the follow-up

Figure 3. The changes of LBP (VAS and RS) and disability (RMDQ) among different treatments (placebo) over 6-month follow-up, p-values indicate the individual between-group changes (active vs placebo) at 6 months.

Table 1. Baseline Characteristics of study participants, by treatment received [†]

	Zoledronic Acid (N = 35)	Denosumab (N = 31)	Placebo (N = 37)
Age, years	57.7 (8.5)	60.0 (11.0)	61.5 (10.5)
Female, n (%)	11 (31)	16 (52)	13 (35)
BMI [‡], kg/m^2	29.2 (5.6)	29.8 (5.3)	29.8 (5.4)
Duration of LBP, years, median (IQR)	25 (4-30)	20 (5-30)	10 (5-20)
Size of MC, mm^2, median (IQR)	697 (273-1155)	532 (255-893)	389 (164-780)
Types of MC [*], n (%)			
Any type 1 MC	9 (26)	11 (35)	9 (24)
Any type 2 MC	24 (69)	23 (74)	26 (70)
Any mixed-type MC	32 (91)	30 (97)	33 (89)
LBP VAS, 0-100	59.5 (15.5)	55.3 (16.8)	56.3 (21.8)
LBP RS, 0-30	18.7 (4.4)	17.3 (4.6)	16.8 (5.7)
RMDQ, 0-24	11.5 (4.5)	10.5 (4.8)	11.1 (5.3)
Utility, 0-1	0.56 (0.23)	0.61 (0.17)	0.60 (0.22)
PHQ-9, 0-27, median (IQR)	6 (3-10)	5 (1-6)	4 (2-8)
Disc degeneration, (%)			
Severe (level 5)	17 (49)	15 (48)	15 (41)
Milder (level 2-4) [$]	18 (51)	16 (52)	22 (59)
PainDetect, n (%)			
Uncertain neuropathic pain	1 (3)	4 (13)	1 (3)
Non-neuropathic pain	34 (97)	27 (87)	36 (97)
Medication use [£], n (%)			
Cox-2 inhibitor	4 (11)	1 (3)	2 (5)
Fish oil	8 (23)	7 (23)	7 (20)
Glucosamine	4 (11)	4 (13)	3 (8)
NSAIDs	13 (37)	10 (32)	16 (43)
Paracetamol	19 (54)	21 (68)	21 (57)
Number of analgesics	1 (1-2)	1 (1-2)	1 (1-2)

Abbreviations: BMI, body mass index; IQR: interquartile range; LBP, low back pain; MRI, magnetic resonance imaging; NSAIDs, non-steroid anti-inflammatory drugs; PHQ-9, patient health questionnaire; RMDQ, Roland-Morris disability questionnaire; RS, rating scale; VAS, visual analogue scale.

[†] Values of this table were presented as mean (SD) unless otherwise specified (n (%) or median (IQR));

[‡] BMI were calculated as weight in kilograms divided by height in meters squared;

[*] One participant might have different types of MC at different endplates;

[$] All participants have at least level 2 disc degeneration (using the Pfirrmann Grading System);

[£] Participants may use more than one type of these medications.

Table 2. Change in study outcomes between active treatments (ZA or denosumab) and placebo over 3 and 6 months [†]

	Mean change from baseline (95%CI)			Zoledronic Acid vs. Placebo		Denosumab vs. Placebo	
	Zoledronic Acid (N = 35)	Denosumab (N =31)	Placebo (N=37)	Absolute Difference Mean (95% CI)	Relative Risk (95% CI)	Absolute Difference Mean (95% CI)	Relative Risk (95% CI)
Chief outcomes (6 months)							
LBP VAS, 0-100	-21.5 (-29.1 to -13.9)	-24.0 (-32.1 to -16.0)	-13.3 (-20.8 to -5.8)	-8.2 (-18.8 to 2.4)	-	-10.7 (-21.7 to 0.2)	-
Size of MC, mm^2	-1.1 (-16.8 to 14.7)	-4.1 (-20.7 to 12.4)	-3.9 (-19.6 to 11.9)	2.8 (-19.5 to 25.1)	-	-0.3 (-23.1 to 22.6)	-
Other outcomes							
3 Months							
LBP RS, 0-30	-5.4 (-7.3 to -3.5)	-4.3 (-6.3 to -2.2)	-1.9 (-3.9 to 0)	**-3.5 (-6.2 to -0.8)**	-	-2.3 (-5.1 to 0.5)	-
RMDQ, 0-24	-3.5 (-4.9 to -2.2)	-1.2 (-2.6 to 0.2)	-1.4 (-2.8 to -0.1)	**-2.1 (-4.0 to -0.2)**	-	0.3 (-1.7 to 2.2)	-
Utility, 0-1	0.03 (-0.02 to 0.08)	0.01 (-0.04 to 0.07)	0.02 (-0.03 to 0.07)	0.01 (-0.06 to 0.08)	-	-0.01 (-0.08 to 0.06)	-
Responders [‡], n/N (%)	19/32 (59.4)	13/28 (46.4)	12/29 (41.4)	18.0 (-7.7 to 43.6)	1.4 (0.8 to 2.4)	5.0 (-21.7 to 31.8)	1.1 (0.6 to 2.0)
6 Months							
LBP RS, 0-30	-6.3 (-8.2 to -4.4)	-6.0 (-8.0 to -4.0)	-3.0 (-4.9 to -1.1)	**-3.3 (-5.9 to -0.7)**	-	**-3.0 (-5.7 to -0.3)**	-
RMDQ, 0-24	-3.2 (-4.5 to -1.9)	-1.6 (-3.0 to -0.2)	-1.8 (-3.1 to -0.5)	-1.4 (-3.2 to 0.5)	-	0.2 (-1.7 to 2.1)	-
Utility, 0-1	0.09 (0.04 to 0.13)	0.02 (-0.03 to 0.08)	0.05 (0 to 0.10)	0.03 (-0.04 to 0.10)	-	-0.03 (-0.10 to 0.04)	-
Type 1 MC [*], (%)	0.4 (-10.3 to 11.1)	-16.2 (-27.7 to -4.7)	-10.3 (-20.0 to -1.0)	10.7 (-3.7 to 25.0)	1.8 (0.9 to 3.6)	-5.9 (-20.9 to 9.2)	0.9 (0.4 to 2.0)
Responders [‡], n/N (%)	22/33 (66.7)	16/29 (55.2)	15/31 (48.4)	18.3 (-6.4 to 42.9)	1.3 (0.8 to 2.0)	6.8 (-19.4 to 33.0)	1.1 (0.7 to 1.7)
Post-hoc outcomes (LBP VAS over 6 months)							
Severe disc degeneration	-17.0 (-28.0 to -6.0)	-21.7 (-33.1 to -10.3)	-18.8 (-30.8 to -6.8)	1.8 (-14.5 to 18.0)	-	-2.9 (-19.4 to 13.7)	-
Milder disc degeneration [1]	-25.1 (-35.2 to -14.9)	-26.3 (-37.3 to -15.3)	-10.3 (-19.7 to -1.0)	**-14.7 (-28.5 to -0.9)**	-	**-16.0 (-30.4 to -1.5)**	-
With type 1 MC [2]	-22.6 (-36.9 to -8.2)	-35.6 (-48.6 to -22.6)	-13.0 (-29.6 to 3.6)	-9.6 (-31.5 to 12.4)	-	**-22.7 (-43.8 to -1.6)**	-
Without type 1 MC	-21.1 (-29.8 to -12.4)	-17.2 (-27.2 to -7.3)	-13.3 (-21.5 to -5.1)	-7.8 (-19.8 to 4.2)	-	-3.9 (-16.9 to 9.0)	-
Participants with non-neuropathic pain [3]							
LBP VAS, 0-100	-23.0 (-30.6 to -15.3)	-25.8 (-34.4 to -17.2)	-12.2 (-19.8 to -4.7)	**-10.8 (-21.5 to 0.0)**	-	**-13.6 (-25.0 to -2.1)**	-
LBP RS, 0-30	-6.5 (-8.4 to -4.6)	-6.3 (-8.5 to -4.2)	-2.7 (-4.6 to -0.9)	**-3.8 (-6.5 to -1.1)**	-	**-3.6 (-6.4 to -0.8)**	-
Subgroup analysis							
Size of Type 1 MC, mm^2	17.9 (4.5 to 31.3)	-4.6 (-16.7 to 7.5)	17.5 (2.3 to 32.7)	0.4 (-19.8 to 20.7)	-	**-22.1 (-41.5 to -2.7)**	-

Abbreviations: CI: confidence interval; LBP, low back pain; RMDQ, Roland-Morris disability questionnaire; RS, rating scale; VAS, visual analogue scale.

[†] Changes from baseline to 3 and 6 months among the three groups were compared using mixed-effects linear regression, unless otherwise specified;

[‡] Responder were evaluated using the OARSI responder criteria. The number and proportion of responders in each group were displayed at 3 and 6 months; absolute difference and relative risk (RR) were calculated by treatment group minus placebo group using log binomial regression after multiple imputation for missing values;

[*] Absolute difference and relative risk (RR) in the proportion of participants with type 1 MC were calculated by treatment group minus placebo group using generalised estimating equations;

[1] Sample size in milder disc degeneration subgroups: n=18 in the ZA group, n=16 in the denosumab group and n=22 in the placebo group;

[2] Sample size in type 1 MC subgroups: n=9 in the ZA group, n=11 in the denosumab group and n=9 in the placebo group;

[3] Sample size in non-neuropathic pain (painDETECT score of <12) subgroups: n=34 in the ZA group, n=27 in the denosumab group and n=36 in the placebo group;

Bolder numbers indicate statistical significance ($p<0.05$).

Table 3. Adverse events †

	Zoledronic Acid (N = 35)	Denosumab (N = 31)	Placebo (N = 37)
Participants with at least one adverse event	35 (100)	27 (87)	25 (68)
Acute Phase Reactions ‡, n	85	33	26
Constipation	0 (0)	0 (0)	1 (3)
Diarrhoea	3 (9)	0 (0)	1 (3)
Flu-like	22 (63)	5 (16)	7 (19)
Headache-dizzy	20 (57)	10 (32)	8 (22)
Musculoskeletal pain and stiffness	18 (51)	8 (25)	2 (5)
Psychological effects *	21 (60)	10 (32)	7 (19)
Rash	1 (3)	0 (0)	0 (0)
Other adverse events ‡, n	10	13	18
Conjunctivitis	0 (0)	1 (3)	0 (0)
Flu-like	0 (0)	1 (3)	1 (3)
Headache-dizzy	0 (0)	0 (0)	2 (5)
Musculoskeletal pain and stiffness	7 (20)	9 (29)	12 (32)
Psychological effects *	2 (6)	2 (6)	3 (8)
Pneumonia	1 (3)	0 (0)	0 (0)
Elective surgery (other than back problem)	2 (6)	2 (6)	2 (5)
Serious adverse events			
Non-elective hospital admission	1 (3)	0 (0)	2 (5)

† Values of this table are presented as n (%) unless otherwise specified (n);
‡ Some participants may experience more than one adverse event; acute phase indicates within 3 days post therapy;
* Psychological effects in this study mainly included malaise, insomnia and depression.

REFERENCES

1. Morlion B. Chronic low back pain: pharmacological, interventional and surgical strategies. Nat Rev Neurol. 2013;9:462-473.
2. Deyo RA, Weinstein JN. Low back pain. N Engl J Med. 2001;344:363-370.
3. Jensen TS, Karppinen J, Sorensen JS, Niinimaki J, Leboeuf-Yde C. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. Eur Spine J. 2008;17:1407-1422.
4. Jensen RK, Leboeuf-Yde C. Is the presence of modic changes associated with the outcomes of different treatments? A systematic critical review. BMC Musculoskelet Disord. 2011;12:183.
5. Jensen OK, Nielsen CV, Sorensen JS, Stengaard-Pedersen K. Type 1 Modic changes was a significant risk factor for 1-year outcome in sick-listed low back pain patients: A nested cohort study using magnetic resonance imaging of the lumbar spine. Spine J. 2014;14:2568-2581.
6. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology. 1988;166:193-199.
7. Modic MT, Masaryk TJ, Ross JS, Carter JR. Imaging of degenerative disk disease. Radiology. 1988;168:177-186.
8. Kuisma M, Karppinen J, Niinimaki J, *et al.* Modic changes in endplates of lumbar vertebral bodies: Prevalence and association with low back and sciatic pain among middle-aged male workers. Spine. 2007;32:1116-1122.
9. Kaapa E, Luoma K, Pitkaniemi J, Kerttula L, Gronblad M. Correlation of size and type of modic types 1 and 2 lesions with clinical symptoms: a descriptive study in a subgroup of patients with chronic low back pain on the basis of a university hospital patient sample. Spine (Phila Pa 1976). 2012;37:134-139.
10. Jensen RK, Leboeuf-Yde C, Wedderkopp N, Sorensen JS, Jensen TS, Manniche C. Is the development of Modic changes associated with clinical symptoms? A 14-month cohort study with MRI. European Spine Journal. 2012;21:2271-2279.
11. Rahme R, Moussa R. The modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. AJNR Am J Neuroradiol. 2008;29:838-842.
12. Kuisma M, Karppinen J, Niinimaki J, *et al.* A three-year follow-up of lumbar spine endplate (Modic) changes. Spine (Phila Pa 1976). 2006;31:1714-1718.
13. Marshman LAG, Trewhella M, Friesem T, Bhatia CK, Krishna M. Reverse transformation of modic type 2 changes to modic type 1 changes during sustained chronic low-back pain severity: Report of two cases and review of the literature. Journal of Neurosurgery: Spine. 2007;6:152-155.
14. Mitra D, Cassar-Pullicino VN, McCall IW. Longitudinal study of vertebral type-1 end-plate changes on MR of the lumbar spine. Eur Radiol. 2004;14:1574-1581.
15. Jensen RK, Leboeuf-Yde C, Wedderkopp N, Sorensen JS, Manniche C. Rest versus exercise as treatment for patients with low back pain and Modic changes. A randomized controlled clinical trial. BMC Med. 2012;10:22.
16. Nguyen C, Boutron I, Baron G, *et al.* Intradiscal Glucocorticoid Injection for Patients With Chronic Low Back Pain Associated With Active Discopathy: A Randomized Trial. Ann Intern Med. 2017;166:547-556.
17. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J. 2013;22:697-707.

18. Palazzo C, Ferrari M, Lefevre-Colau MM, Nguyen C, Rannou F, Poiraudeau S. Lack of effectiveness of antibiotics in chronic low back pain with Modic 1 changes. Joint Bone Spine. 2016.
19. Cauley JA, Black D, Boonen S, *et al.* Once-yearly zoledronic acid and days of disability, bed rest, and back pain: randomized, controlled HORIZON Pivotal Fracture Trial. J Bone Miner Res. 2011;26:984-992.
20. Pappagallo M, Breuer B, Lin HM, *et al.* A pilot trial of intravenous pamidronate for chronic low back pain. Pain. 2014;155:108-117.
21. Koivisto K, Kyllonen E, Haapea M, *et al.* Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging. BMC Musculoskelet Disord. 2014;15:64.
22. Laslett LL, Dore DA, Quinn SJ, *et al.* Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Ann Rheum Dis. 2012;71:1322-1328.
23. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. Eur Spine J. 2016;25:3723-3734.
24. Rolvien T, Schmidt T, Butscheidt S, Amling M, Barvencik F. Denosumab is effective in the treatment of bone marrow oedema syndrome. Injury. 2017;48:874-879.
25. Manniche C, Asmussen K, Lauritsen B, Vinterberg H, Kreiner S, Jordan A. Low Back Pain Rating scale: validation of a tool for assessment of low back pain. Pain. 1994;57:317-326.
26. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976). 1983;8:141-144.
27. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Qual Life Res. 1999;8:209-224.
28. Pham T, van der Heijde D, Altman RD, *et al.* OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12:389-399.
29. 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;95:4380-4387.
30. Tubach F, Ravaud P, Martin-Mola E, *et al.* Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res (Hoboken). 2012;64:1699-1707.
31. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976). 2001;26:1873-1878.
32. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22:1911-1920.
33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-613.
34. Eldridge SM, Chan CL, Campbell MJ, *et al.* CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355:i5239.
35. Daniels MJ, Wang C. Missing Data Methods in Longitudinal Studies: A Review. Test (Madr). 2009;18:51-58.

36. Devogelaer JP, Sambrook P, Reid DM, *et al.* Effect on bone turnover markers of once-yearly intravenous infusion of zoledronic acid versus daily oral risedronate in patients treated with glucocorticoids. Rheumatology (Oxford). 2013;52:1058-1069.
37. Reid IR, Miller P, Lyles K, *et al.* Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med. 2005;353:898-908.
38. Roelofs AJ, Thompson K, Ebetino FH, Rogers MJ, Coxon FP. Bisphosphonates: molecular mechanisms of action and effects on bone cells, monocytes and macrophages. Curr Pharm Des. 2010;16:2950-2960.
39. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone. 2011;48:677-692.
40. Walter PM. Bisphosphonates-Anti-Inflammatory Properties. Current Medicinal Chemistry - Anti-Inflammatory & Anti-Allergy Agents. 2002;1:15-28.
41. Torkki M, Majuri ML, Wolff H, *et al.* Osteoclast activators are elevated in intervertebral disks with Modic changes among patients operated for herniated nucleus pulposus. European Spine Journal. 2016;25:207-216.
42. 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;39:1107-1115.
43. Dohke T, Iba K, Hanaka M, *et al.* Regional osteoporosis due to osteoclast activation as a trigger for the pain-like behaviors in tail-suspended mice. J Orthop Res. 2017;35:1226-1236.
44. Abe Y, Iba K, Sasaki K, *et al.* Inhibitory effect of bisphosphonate on osteoclast function contributes to improved skeletal pain in ovariectomized mice. J Bone Miner Metab. 2015;33:125-134.
45. Nguyen C, Poiraudeau S, Rannou F. From Modic 1 vertebral-endplate subchondral bone signal changes detected by MRI to the concept of 'active discopathy'. Ann Rheum Dis. 2015;74:1488-1494.
46. Ohtori S, Inoue G, Ito T, *et al.* Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine (Phila Pa 1976). 2006;31:1026-1031.
47. Fields AJ, Liebenberg EC, Lotz JC. Innervation of pathologies in the lumbar vertebral end plate and intervertebral disc. Spine Journal. 2014;14:513-521.
48. Chen S, Huang Y, Zhou ZJ, *et al.* Upregulation of tumor necrosis factor alpha and ADAMTS-5, but not ADAMTS-4, in human intervertebral cartilage endplate with modic changes. Spine. 2014;39:E817-E825.
49. Weishaupt D, Zanetti M, Hodler J, *et al.* Painful Lumbar Disk Derangement: Relevance of Endplate Abnormalities at MR Imaging. Radiology. 2001;218:420-427.
50. Koivisto K, Jarvinen J, Karppinen J, *et al.* The effect of zoledronic acid on type and volume of Modic changes among patients with low back pain. BMC Musculoskelet Disord. 2017;18:274.

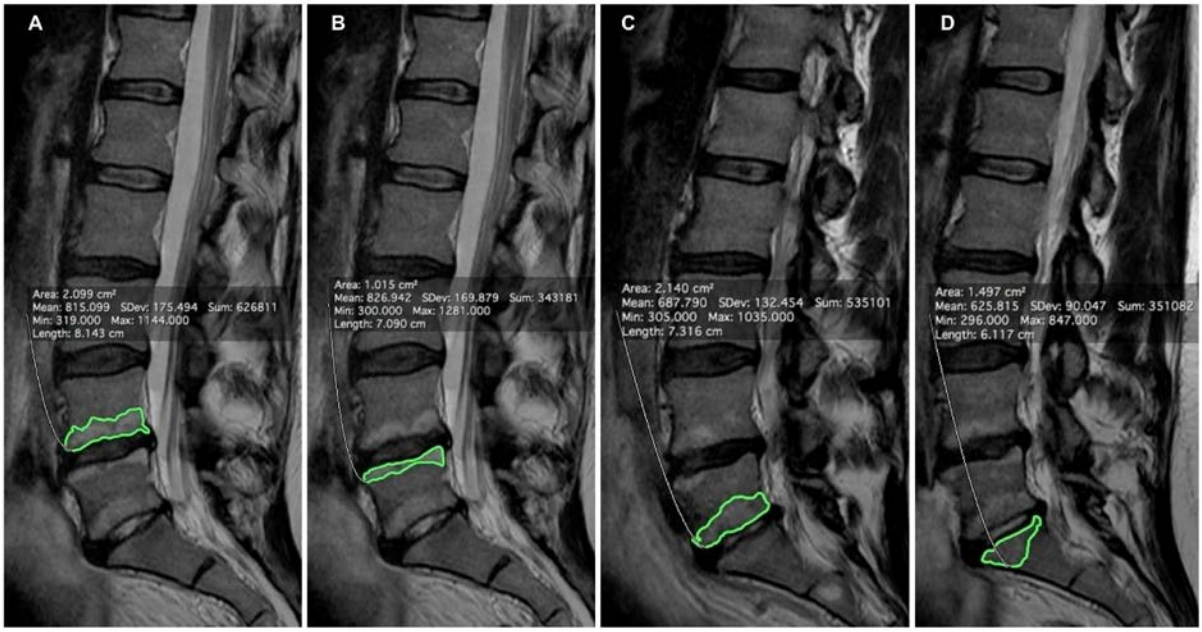

Figure 1

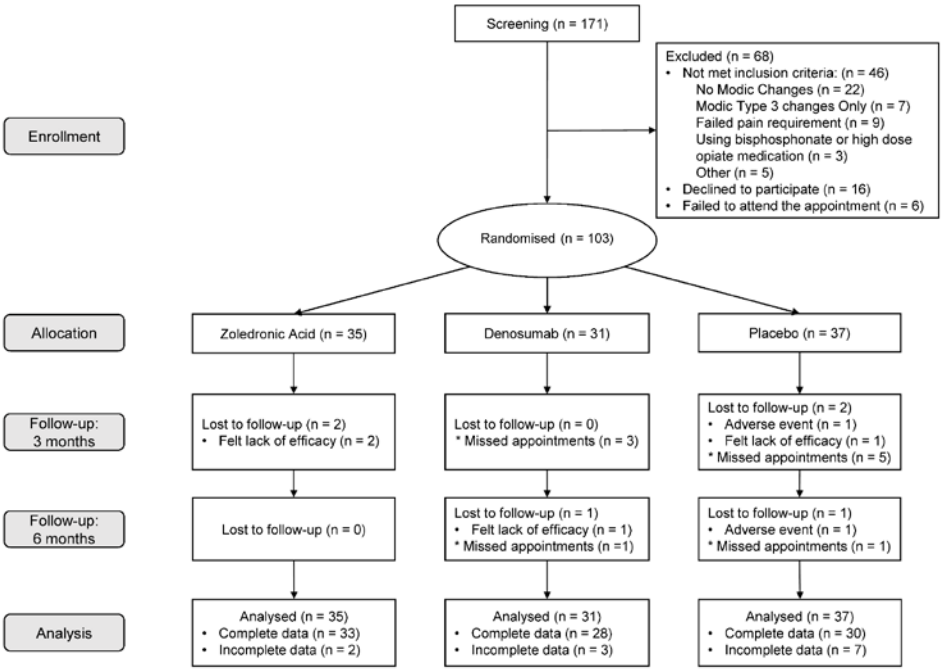

Figure 2

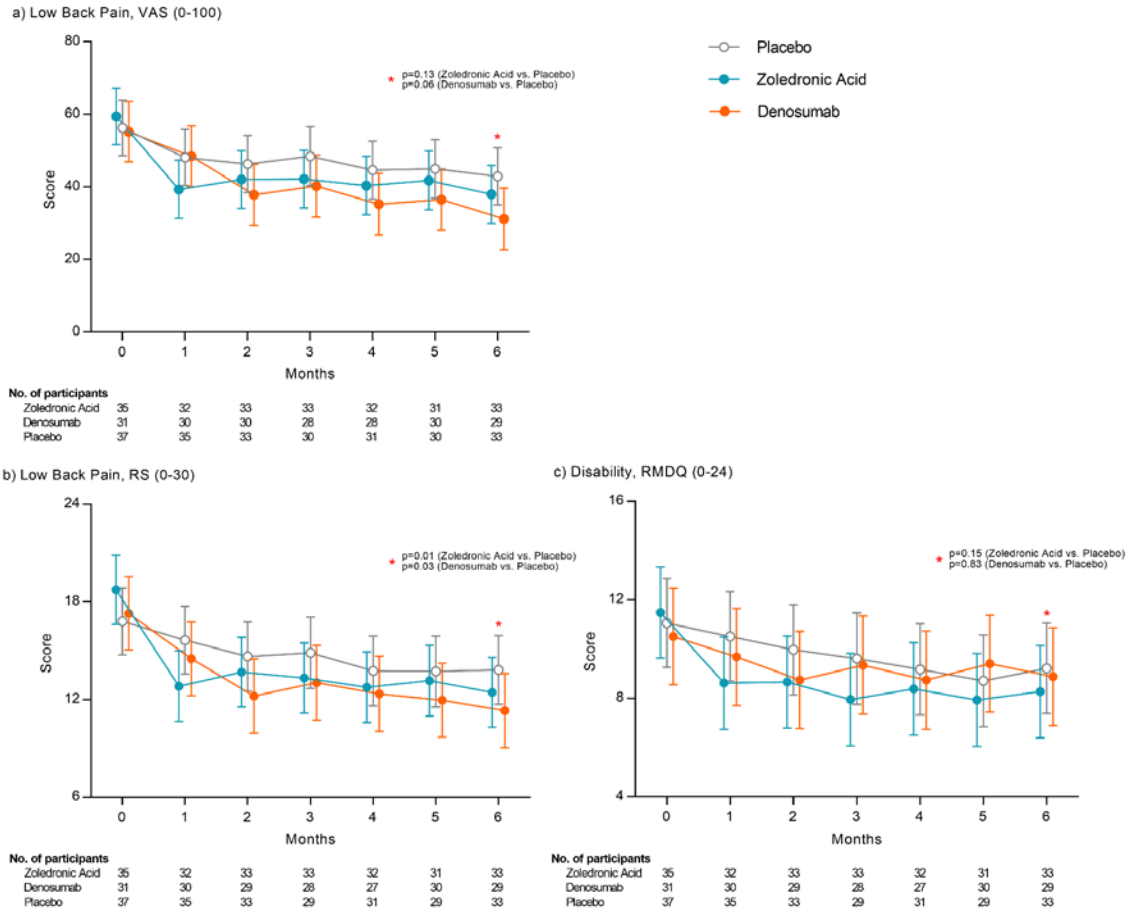

Figure 3