Jason Cheung ORCID iD: 0000-0002-7052-0875
Dino Samartzis ORCID iD: 0000-0002-7473-1311

Oral Zoledronic acid bisphosphonate for the treatment of chronic low back pain with associated Modic changes: a pilot randomized controlled trial

Authors:
[1]Graham Ka Hon Shea (hkgshea@gmail.com)
[1]Changmeng Zhang (changmeng587.com@126.com)
[1]Wai Shan Suen (wai.suen1@myport.ac.uk)
[1]Prudence Wing Hang Cheung (gnuehcp6@hotmail.com)
[1]Jason Pui Yin Cheung (jcheung98@hotmail.com)
[2] Juhani Maatta (juhani.h.maatta@gmail.com)
[2,3,4] Jaro Karppinen (Jaro.Karppinen@ttl.fi)
[5,6] Dino Samartzis (Dino_Samartzis@rush.edu)

Affiliations:
[1] Department of Orthopaedics and Traumatology, The University of Hong Kong, Pokfulam, SAR, China
[2]Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[3]Center for Life Course Health Research, University of Oulu, Finland
[4]Finnish Institute of Occupational Health, Oulu, Finland
[5]Department of Orthopedic Surgery, Rush University Medical Center, Chicago, Illinois, USA
[6] International Spine Research Innovation Initiative, Rush University Medical Center, Chicago, Illinois, USA

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Correspondence:

Graham Ka Hon Shea
Department of Orthopaedics and Traumatology
General Office, Professorial Block
Queen Mary Hospital
Pokfulam,
Hong Kong
Tel: +852-2255-4654

Dino Samartzis
Department of Orthopedic Surgery
Rush University Medical Center
Orthopaedic Building, Suite 204-G
1611 W. Harrison Street
Chicago, IL 60612
USA
Tel: +1-312-522-6105

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Fax:+852-2817-4392
Email: gkshea@hku.hk

Fax: +1-312-942-2101
Email: Dino_Samartzis@rush.edu

ABSTRACT

To assess the safety and efficacy of oral 50mg Zoledronic acid (ZA) bisphosphate once-a-week for 6-weeks to placebo among patients with chronic low back pain (cLBP) and Modic changes (MC) on MRI. A parallel, double-blinded randomized controlled study was performed at a single center, consisted of 25 subjects with cLBP and MC that received ZA (n=13) or placebo (n=12). Evaluation was at baseline, 2-weeks, 4-weeks, 3-months and 6-months for assessment of LBP/leg pain intensity, disability (Oswestry-Disability-Index:ODI), health-related quality-of-life (RAND-36), and mental component summary scores (MCS). Type 2 MC at baseline (56%) were prevalent. In the ZA group, LBP intensity was lower at 4-weeks in comparison to placebo (5.1±1.9 vs. 6.9±1.8, p=0.038) (minimal clinically important difference (MCID)=1.5). LBP intensity reduced at 4-weeks and 3-months in the ZA-treated group in comparison to baseline. Although there was no difference in ODI, subscale RAND-36 metrics for physical function (p=0.038), energy/fatigue (p=0.040) and pain (p=0.003) were improved at 3-months compared to placebo, with moderate significant difference for pain at 6-months (p=0.051). Correlated MCS scores to baseline also improved at 3-months (p=0.035) and 6-months (p=0.028) by 6.9 and 6.8, respectively, (MCID=3.8). A reduction in MC endplate affected area at 6-month follow-up was noted in the ZA group (-0.67±0.69 cm^2), while in the placebo group no change in size was observed (0.0±0.15; p=0.041). Three subjects withdrew from the study and no long-lasting adverse events. Oral ZA was a safe and effective treatment that reduced MC volume, improved LBP symptoms and quality-of-life measures in cLBP subjects with MCs.

Keywords: Modic; disc degeneration; low back pain; randomized; bisphosphonate; Zoledronic acid

INTRODUCTION

Low back pain (LBP) is the world's most disabling condition, affecting all populations.[1] It is believed that chronic LBP may affect 1 to 1.4 billion individuals worldwide.[1] Such pain can result in decreased daily activity and function, time off from work, psychological stress, lost wages and increased health-care costs.[2] Overall, LBP is a tremendous socioeconomic global burden. In the United States, over 100 billion USD is spent annually on direct and indirect costs for treatment, with similar adjusted rates in other countries (e.g. Hong Kong, Finland, etc).[3] Evidence-based treatments of LBP, including medications, have only resulted in small effect sizes.[4] In fact, the modest results of previous interventions are thought to be due to heterogeneity of the LBP phenotype.[4,5] For example, approximately 90% of LBP patients present with no clear pathoanatomical diagnosis, or there is a lack of understanding anatomical imaging phenotypes to facilitate the process, which can present a challenge to the treating health-care professional to devise optimal management and prognosticate outcomes.[6] For patients that fail conservative treatment, surgical intervention is an option (e.g. fusion, disc replacement, etc.). However, risks associated with surgery include peri-operative complications and the potential of unsatisfactory outcomes, necessitating prolonged clinical management.[7] As a result, the health-care costs for such treatment are substantial. Additional cost-effective and easily administered measures must be sought to treat specific subsets of chronic LBP.

One such specific subset entails the imaging phenotype of Modic changes (MC) on magnetic resonance imaging (MRI). These phenotypes are subchondral vertebral bone marrow non-neoplastic lesions that were initially described the last 1980s and are largely characterized as Type 1 (M1: inflammation/edema), Type II (M2: fatty infiltration), and Type 3 (M3:sclerosis) **(Figure 1)**. [8,9] The prevalence of MC among patients suffering from LBP has been reported to exceed 50%.[10,11] Critically, a clinicopathological correlate has been demonstrated between MC and the severity of LBP.[12-15] In particular, M1 changes are most strongly correlated with incidence of LBP [16]. It is postulated that MC result from disc and endplate damage, followed by persistence of an inflammatory stimulus within the adjacent vertebral body. These result in their pathognomonic imaging appearance and generate pain.[9]

A reduction in bone marrow edema indicative of M1 changes upon MRI images has been reported in patients on long-term bisphosphonates.[17] This provided the rationale for

"intravenous" Zoledronic acid (ZA) as a novel therapeutic agent for LBP. Zoledronic acid is a potent bisphosphonate that has demonstrated via an intravenous route safety and efficacy in the treatment of LBP in the presence of MC, reducing symptoms at one-month post-treatment in comparison to placebo.[18] In addition, participants receiving ZA reported significantly less non-steroidal anti-inflammatory drug (NSAID) use at one year than those in the placebo group. In a follow-up study, the investigators also noted a trend whereby individuals with chronic LBP who were treated with ZA had conversion of their M1 to a more benign M2 with a regression or less volume/extent of MC affecting the vertebral body/subchondral bone region.[19] In further support, a recent study among patients with chronic LBP found that 180 mg intravenous Pamidronate bisphosphonate effectively reduced LBP symptoms.[20] Subcutaneous injection of denosumab has more recently been reported to exhibit a similar alleviating effect.[21] Based on the pharmacodynamic effects and findings from other studies focusing on arthritis, the mechanism of ZA action reflects potent inhibition of osteoclast activity (i.e. recruitment, differentiation, function), non-promotion of apoptosis, reduction of bone edema progression and impact upon pain generating regions. In addition, intravenous delivery and subcutaneous injection require nursing expertise and are of lesser convenience, and potentially less acceptable to the patient. With potent oral bisphosphonate preparations readily available, we asked whether these could provide similar relief to LBP individuals.

In lieu of the above, we performed a parallel, double-blinded randomized controlled trial to assess the safety and efficacy of "oral" ZA, in comparison to placebo, in the short- and mid-term relief of LBP. Secondarily, we also assessed the impact of ZA upon the structural phenotype of MC on MRI. In order to determine sample size calculation and proper power for a larger-scale study, herewith we report our preliminary findings based on our pilot trial.

METHODS

Subject Recruitment

Subjects were recruited from the spinal disorders outpatient clinic on the basis of having suffered from LBP for at least 3 months with a score over past week of at least 5 on a 0 – 10 numerical rating scale (NRS), or ODI of at least 30%. Patients of both sexes were recruited but were limited to between the ages of 18 – 70. MC needed to be demonstrable (**Figure 1**) upon MRIs performed within 1-month of recruitment. Patients were excluded

when suffering predominantly from symptoms or signs compatible with nerve root entrapment or spinal stenosis, upon presence of local or generalized infection, claustrophobia or metallic implants restricting the use of MRI, a BMI of > 40 kg / m^2, vertebral fractures, high grade spondylolisthesis, back surgery within 6-months, invasive spinal procedures within 3-months, hyperthyroidism, hypocalcemia, clinically significant psychiatric disorders, contraindications to bisphosphonates (allergy, abnormalities of esophagus, recent tooth extraction, poor dental hygiene), prior use of bisphoshonates, calcitonin or systemic steroids, alcohol addiction, and pending evaluation for disability compensation. All patients were of Chinese ethnicity. This study was approved by Institutional Review Board (IRB) of The University of Hong Kong / Hong Kong West Cluster, and written informed consent was obtained from all participating subjects. The trial has been registered via ClinicalTrials.gov (Identifier: NCT01330238).

Baseline Examination

Eligible subjects underwent a comprehensive baseline assessment. Demographic details regarding occupation, smoking status, educational level, and marital status were recorded. A thorough history was obtained regarding current and prior back symptoms as well as received treatment (medications, physical therapy, surgery, injections). A routine clinical examination included bodyweight and height, straight leg raise test to rule out nerve root tension, as well as a review of systems with notice given to dental hygiene to exclude periodontal disease. Patients were administered the Beck Depression Inventory to exclude mood disorders. Baseline blood tests (complete blood count, liver and renal function test, calcium phosphate, C-reactive protein and pregnancy test for women) were performed to rule out ineligible subjects. Subjects who did not have an MRI performed within 1 month were scheduled for a plain scan including T1-weighted (T1W) and T2-weighted (T2W) sequences.

Randomization

Block randomization was performed using a computer-generated number list with varying block size (4, 6 or 8). Subjects received a case number according to the order of recruitment that could be traced to their group assignment. This was concealed from the subject, doctor, research staff, radiographer, and all allied health professionals with potential interaction with the subject. Oral ZA and placebo tablets were supplied in identical packaging via the manufacturer after obtaining a drug import license. The tablets

containing ZA and the placebo did not differ by look, taste or smell. The treatment allocation was concealed to subjects and researchers in sealed envelopes until completion of final follow-up for statistical analyses.

Treatment Intervention

After confirmation of eligibility, subjects were randomized as described above to receive either 50 mg oral ZA or placebo once a week for 6 weeks. The first dose was administered under observation at a second morning outpatient session arranged after baseline assessment, when blood results as well as recent MRI scans were available. Subjects were instructed to swallow the tablet in conjunction with a full glass of water after an overnight fast, to remain in an upright position for 30 minutes after dosing, and to wait at least 60 minutes prior to consuming the first food or beverage of the day. Subjects received daily calcium phosphate supplement to prevent hypocalcemia, as well as paracetamol 500mg Q6H and diclofenac sodium 100mg daily for as-required ingestion for relief of flu-like symptoms after bisphosphonate intake. Subjects were contacted by the research nurse on a weekly basis to ensure compliance of proper timing and method of drug ingestion.

Oral Zoledronic Acid Preparation

Oral ZA tablets (50 mg, disodium zoledronate tetrahydrate; AXS-02) were provided by Axsome Therapeutic. AXS-02 reduced serum C-terminal telopeptide levels (CTx, a biomarker for bone resorption) by 80-90% in the 50, 100, and 150 mg oral dose groups at 7 days post-dose, compared to an 84% reduction in the IV dose group in a Phase I clinical trial involving 36 subjects (unpublished results). Orally administered AXS-02 was also well tolerated (unpublished results). Adverse events in the 50 mg dose group were mild to moderate, resolved within several days post-dosing, and consisted of fever, musculoskeletal pain, and transient reduction in lymphocyte counts.

Primary and Secondary Outcomes

After baseline assessment, patients were reviewed at 2 weeks, 4 weeks, 3 months, and at 6 months after receiving the first tablet. The primary outcome was the intensity of LBP (0-10 NRS) at up to 3 months, which we hypothesized would be decreased in the treatment group in comparison to placebo. Secondary outcomes included leg pain intensity (0-10 NRS), disability (Oswestry Disability Index, ODI), health-related quality of life assessed (RAND-36), and changes in MC type, area, and volume. Physical component

summary (PCS) and mental component summary (MCS) scores were able to be extracted from the RAND-36. Patient-reported outcomes were assessed by means of questionnaires given in the patient's preferred language (Traditional Chinese or English) during clinic attendance. Radiological assessment of the Modic phenotype, level, and extent of involvement was assessed at baseline and compared to repeated imaging at 3- and 6- month follow-ups using the assessment protocol as described below.

MRI Assessment

The MRI examinations were largely performed using a 1.5T scanner (Siemens, Munich, Germany or Philips, Best, The Netherlands). Conventional sequences (T1-weighted (T1W) and T2-weighted (T2W) sagittal scans, axial T1W scans) were obtained at baseline and upon reassessment. The endplates and vertebra could be evaluated from the upper endplate of T12 down to the upper endplate of S1. Detection and phenotyping of MC at screening were assessed via consensus by two orthopaedic surgeons for the purposes of patient recruitment. Since several individuals had multiple MC, the primary MC was defined in accordance with the most likely LBP generator. [22] As previously described, the severity of the lesion was assumed as follows: M1 > predominating M1 > predominating M2 > M2. In cases where patients had multiple MC of the same type at different levels, the largest MC with regards to volume of involvement was selected as the primary MC. The area of MC (cm^2) was measured at baseline, 3 months and 6 months as previously described[21] based on the sagittal cut demonstrating maximal vertebral involvement contiguous with the endplate (**Supplementary Figure 1**). Measurements were repeated three times with the average reading recorded. The volume of MC was calculated over the worst-affected vertebral level by summating area of MC across a series of sagittal images, multiplied by the slice thickness of 4mm. Pfirrmann grading of degeneration over the intervertebral disc adjacent to the primary MC lesion for each subject was assessed by a single orthopaedic surgeon.

Safety Parameters

Safety was assessed by recording and monitoring of adverse events (AE) and concomitant medication use by treatment assignment. Rates of AE's were summarized overall and by organ system class, severity, and suspected relationship to study drug by treatment assignment.

Discontinuation Criteria

Subjects were discontinued from the study upon pregnancy, developing signs and symptoms of organ dysfunction, and manifesting intolerable adverse events. Appropriate follow-up assessment and treatment was provided via the spinal disorders clinic for those participants who were discontinued from the study. These subjects were excluded from analysis.

Statistical Analysis

A total of 25 subjects were recruited, with data from 21 patients analysed due to three early withdrawals from the treatment group and one subject lost to follow-up. Baseline demographic data, primary, and secondary outcomes were analysed by means of t-testing, paired t-testing, and ANOVA. For paired testing, we compared baseline values prior to oral ZA / placebo intake to those obtained at 2 weeks / 4 weeks / 3 months / 6 months after. Statistical significance was established at $p<0.05$.

RESULTS

Baseline Subject Demographics

Of the 21 subjects completing treatment, 9 received oral ZA, and 12 the placebo. Baseline demographic details are summarized in **Table 1**. Subjects receiving ZA had a mean age of 59 ± 6.7 years (51 – 69 years) and in comparison, the mean age in the placebo group was 54 ± 9.2 years (40 – 70 years), which was not statistically significant ($p = 0.193$). In the treatment group there were 2 males and 7 females as compared to 5 males and 6 females in the placebo group ($p = 0.642$). Similarly, there were no statistically significant differences between the groups with regards to height ($p = 0.753$), weight ($p = 0.243$), marital status ($p = 0.869$), educational level ($p = 1.0$), employment ($p = 0.673$) or smoking status ($p = 0.735$).

Low Back Pain Intensity

Upon comparison between groups, NRS scores of LBP intensity were similar at baseline (6.8 ± 1.5 in the ZA group vs. 6.7 ± 2.3 in the placebo group; $p = 0.900$). However, at 4 weeks, there was a significantly reduced NRS score in the group receiving ZA as compared to placebo (5.1± 1.9 vs. 6.9 ± 1.8; $p = 0.038$). There were no significant differences at 2 weeks ($p = 0.699$), 3 months ($p = 0.373$), or 6 months ($p = 0.821$) post-intervention. Paired comparison with baseline NRS score revealed that there was a significant decline at 2 weeks in the placebo group (6.7 ± 2.3 vs. 5.9 ± 2.1; $p = 0.021$) although subsequently scores remained similar to baseline. In the treatment group, a

reduction in NRS score in comparison to baseline was maximal at 4 weeks (5.1 ± 1.9; p = 0.017) and persisted at 3 months (5.2 ± 1.9; p = 0.023). NRS score at 6-months after recruitment and administration of ZA remained reduced compared to baseline but failed to reach statistical significance (5.8 ± 1.3 vs. 6.8 ± 1.5; p = 0.053). A bar chart comparing low back pain NRS scores at different time points is shown in **Figure 2A**.

Leg Pain

NRS scores for leg pain were assessed in subjects at baseline, 2 weeks, 4 weeks, 3 months and 6 months (**Table 2**). Upon comparison between groups, there was no statistical difference at any time point. Paired t-tests performed for within-group comparison however demonstrated amongst subjects receiving ZA that there was a significant reduction in leg pain NRS at 4 weeks (3.9 ± 0.8 vs. 5.9 ± 0.8; p = 0.031). There was no within-group difference in the placebo group. A bar chart comparing leg pain NRS pain scores at different time points is shown in **Figure 2B**.

Disability

ODI scores were not found to be significantly different between the ZA and placebo groups at baseline (32.9 ± 2.8 vs. 40.5 ± 3.4; p = 0.116). Comparison between intervention groups failed to demonstrate significant difference at any of the measured time points (**Table 3**). Similarly, within-group comparison failed to demonstrate statistical significance.

RAND-36 scores

RAND-36 scores were compared between ZA administration and placebo groups (**Table 4**). Whilst there was a tendency towards lower subscales amongst the placebo group at baseline, only general health scores were found to be significantly reduced (25.0 ± 7.1 vs. 47.5 ± 4.8, p = 0.021). At 3-months post-intervention, there were significantly higher scores in the treatment group for physical functioning (68.0 ± 6.7 vs. 49.0 ± 5.3; p = 0.038), energy / fatigue (47.5 ± 7.0 vs. 39.0 ± 6.3; p = 0.04) and pain (55.8 ± 27.3 ± vs. 6.8; p = 0.003). Upon paired intragroup comparison, there was improved pain subscale at 3-months as compared to baseline after ZA intake (55.8 ± 4.7 vs. 38.3 ± 4.3; p = 0.034).

Physical component summary (PCS) scores demonstrated no difference between treatment and placebo at baseline, 3-months, or 6-months post-intervention, nor upon intragroup analysis. Mental component summary (MCS) scores demonstrated higher scores amongst the treatment group at baseline, 3-months, and 6-months post-intervention. More importantly, intragroup analysis in comparison to baseline demonstrated an improvement

for the treatment group alone in uncorrelated scores at 3 months (49.6 ± 8.8 vs. 43.7 ± 3.0; p = 0.021) and 6 months (49.1 ± 2.6 vs. 43.7 ± 3.0; p = 0.030), as well as correlated scores at 3 months (48.1 ± 3.4 vs. 41.2 ± 3.4; p = 0.035) and 6 months (48.0 ± 3.1 vs. 41.2 ± 3.4; p = 0.028).

Modic Changes on MRI

To verify the reliability of the MRI quantification, we calculated test-retest reliability coefficient. The results showed excellent reliability (Pearson correlation coefficient r= 0.993, p<0.001). For both treatment and control groups, Type II MC (6/9, 8/11) were most common. The lower lumbar endplates over L4/5 and L5/S1 levels were most often the primary site affected by MC (8/9 in treatment, 8/11 in controls). One subject with mixed M1/2 changes converted to M2 predominance after treatment with a corresponding reduction in back and leg NRS. Comparison between treatment and control groups did not demonstrate a significant difference in the area of MC (cm^2) at baseline, nor at 3- and 6-months (**Table 5**). With regards to change in area affected by MC at 6-months in comparison to baseline, subjects given ZA demonstrated a reduction (-0.67±0.69 cm^2) as opposed to no change in the placebo group (0.00±0.15 cm^2), which was statistically significant (p = 0.041). Intra-group analysis also revealed that there was a significant decrease in total area with MC at baseline vs. 6 months (p = 0.042). With regards to volume of MC, subjects given ZA demonstrated a reduction at 6 months vs 3 months (-0.30±0.28 cm^2) in comparison to an increase in the placebo group (+0.07 ± 0.23, p = 0.035). Intragroup analysis also demonstrated a significant reduction in volume of MC at 6 months vs. 3 months following treatment (p = 0.029) while there was no significant difference between time points after placebo.

Adverse Events

Three subjects from the treatment group withdrew due to AEs. One subject withdrew after the 1st dosing due to flu-like symptoms with fevers and chills. Another subject withdrew after the 2nd dose due to fever and myalgia. The remaining subject withdrew after the 2nd dose after experiencing epigastrium discomfort. There was complete relief of symptoms upon drug discontinuation, and subjects did not experience long-lasting sequelae.

DISCUSSION

In as many as 85% of patients with LBP, the definitive cause of their symptoms is non-specific. Whilst there is evidence for the non-discriminatory use of analgesics such as NSAIDs and opioids for relief of back pain[23], the association of MC with vertebral marrow pathology promises targeted therapy for a select group of patients. Having previously demonstrated that intravenous ZA attenuates back pain among patients with MC, we proceeded to investigate whether oral preparations had a similar effect. We found that oral ZA was well tolerated, and, in comparison to placebo, reduced back pain, leg pain, and RAND-36 subscale scores. Crucially, these changes were associated with a reduction in MC area following active treatment.

Primary and Secondary Outcome Findings

According to our primary outcome of low back pain NRS scores, we found that the effect of oral ZA in comparison to placebo had maximal benefit at 4-weeks post-treatment, reducing NRS scores by 1.8 (5.1 ± 1.9 vs 6.9 ± 1.9, $p = 0.038$). A sizeable reduction in NRS of 1.6 persisted at 3-months upon comparison to baseline, and it is likely that with larger sample sizes, the efficacy of oral ZA would have been statistically significant at 6-months ($p = 0.053$). In patients with moderate to severe chronic LBP, the minimal clinically important difference (MCID) has been reported to be 1.5,[24] and the value to reflect patient satisfaction following back surgery is 1.2.[25] Reduced pain score between baseline and 2-weeks amongst controls was likely attributed to placebo effect. Intriguingly, we also identified a reduction in leg pain after treatment at 4-weeks. Potential biological mechanisms include the known effects of bisphosphonates on relieving knee osteoarthritis associated with bone marrow lesions[26], and on attenuating allodynia resulting from cutaneous inflammation[27].

With regards to RAND-36 physical component summary (PCS) scores and mental component summary (MCS) scores, cut-offs of > 3.3 and > 3.8 respectively have been described as the MCID.[28] The threshold for MCS was surpassed following treatment in both uncorrelated and correlated scores at 3 months (+5.9 / +6.9) as well as 6 months (+5.4 / +6.8). Despite significant benefit to pain and energy / fatigue subscales, consideration of factor scoring coefficients utilised to calculate PCS resulted in an overall failure to reach MCID.[29]

Bisphosphonate use for LBP

Zoledronic acid is the most potent third-generation nitrogenous bisphosphonate preparation currently available. A once-off dose of IV ZA resulted in significantly reduced LBP at 1 month but not at 1 year,[18] whilst another study incorporating subcutaneous denosumab as an additional treatment arm demonstrated that reduction in back pain persisted in both groups at 6 months.[21] The efficacy of these bone agents to attenuate MC-associated LBP have been attributed to regulation of osteoclast activity[30] and inflammation.[31] In comparison to IV administration, our oral preparation has an obvious advantage being non-invasive and economical. A disadvantage of repeated oral dosing was in our drop-out rate of 25% (3/12 subjects) owing to subject intolerance of side effects after the first few doses. It is therefore essential to explore whether there are alternative oral bisphosphonate preparations that have comparable efficacy, yet improved tolerability. Adverse effects from IV ZA, predominantly entailing acute phase reactions, approached 100%.[21] Nevertheless, long-lasting effects were not dependent on repeated administration.

M1 are most strongly correlated with LBP, and IV Zoledronic acid accelerates conversion to M2 changes[19] whilst reducing back pain.[18] Our study has progressed upon these findings by demonstrating efficacy of bisphosphonates in a study population with predominantly M2 changes. Furthermore, our ethnically Chinese population differed from prior studies focused on cohorts of Caucasian descent. Contributing to our M2-predominant cohort, recruitment was carried amongst regular attendees at our spine clinic. The majority of these subjects had suffered from back pain for years. Over time, the natural evolution of M1 changes is conversion to the M2 phenotype.[30] LBP progresses to chronicity in 2 – 7% of patients, and amongst them there is a high risk of recurrence.[32] The efficacy of oral ZA amongst our cohort therefore, is particularly promising in view of their chronic, recalcitrant symptomatology.

Dose and Mechanism of ZA

An oral ZA preparation, AXS-02 (disodium zoledronate tetrahydrate), has been developed for the treatment of chronic pain, including LBP associated with MCs. Potential benefits of an oral formulation (6 tablets over 6 weeks) over the existing intravenous formulation include: improved safety, patient and prescriber convenience, and lower ancillary costs. A Phase I clinical trial involving 36 subjects to assess for oral bioavailability of ZA and its pharmacodynamics biomarker effects rapidly reduced serum

C-terminal telopeptide levels by 84%, 90%, and 83% in the 50 mg, 100 mg, and 150 mg oral dose groups seven days post-dose, respectively, compared to an 84% reduction in the intravenous dose (IV) dose group. Based on this pharmacodynamic effect and findings from other studies focusing on arthritis, the mechanism of ZA action reflects potent inhibition of osteoclast activity (i.e. recruitment, differentiation, function), non-promotion of apoptosis, and reduction of bone edema progression. These proposed mechanisms strongly suggest the potential for oral ZA to provide a clinically meaningful effect in LBP associated with MCs, knee osteoarthritis that is associated with bone marrow lesions, and complex-regional-pain-syndrome (CRPS). Osteoclasts can create an acidic microenvironment in remodelled bone, can generate inflammation and induce pain; therefore, osteoclast targeted therapy in the setting of chronic LBP and Modic changes is a viable option. Orally administered ZA has been shown to be well tolerated. Adverse events in the 50 mg dose group were mild to moderate, resolved within several days post-dosing, and consisted of fever, musculoskeletal pain, and transient reduction in lymphocyte counts as is seen with the intravenous formulation and other oral and intravenously administered bisphosphonates. There have been no serious adverse events (SAEs) with any dose and no subject has discontinued the medication due to an adverse event. In short, the proposed dose for the investigators' current proposed study – 50 mg oral ZA once weekly for six weeks – provides a cumulative dose that is equivalent to approximately 6 mg IV. This approximates the 5 mg IV dose used in our previous RCT in LBP associated with MCs.[18]

Strengths and Limitations

As with any clinical trial, limitations may exist. For one, our study consisted of a small sample size. This was an unforeseen setback being that the manufacturing of AXS-02 was discontinued by the supplying pharmaceutical company; however, this action was not due to safety concerns. Regardless, our study maintained Level 1 evidence, being a parallel, double blinded randomized controlled trial with greater than 95% follow-up at six months' post-treatment. However, and as expected, post-hoc one-tailed power analysis demonstrated that our study was consequently underpowered (0.719). Nonetheless, our pilot study was able to determine an effect size with regards to the primary outcome. Therefore, a sample size of 22 participants per arm will be required for future prospective randomized studies to achieve a 90% power for two-tailed comparison of LBP NRS at 3 months, with a reduced sample size a more conservative power is desirable. In addition, our

participants were all of Chinese descent, and were predominantly affected by M2 changes. Larger studies are needed in other ethnic populations to validate our findings and assess generalizability, at least with respect to the pain outcome. However, participants having received the ZA treatment were noted to have structural imaging changes of the MC phenotype, which may not be driven by ethnicity and further replicate the findings of a Caucasian population who received IV dose of ZA.

CONCLUSIONS

Our randomized controlled trial demonstrated the safety and efficacy of oral ZA in the relief of chronic LBP with associated lumbar MC on MRI. Our study further noted that ZA may reduce the size of MC within 6 months of administration. Our pilot study substantiates the need and utility for larger-scale studies. Nonetheless, our study lends further credence to targeted and personalized spine phenotype therapeutics. Such tailored therapy has the potential to ultimately be cost-effective for back pain patients and does not compromise the immune system while avoiding prolonged physical therapy or costly surgery that may be riddled with complications.

Author contributions

JK and DS conceived the project. DS, GKHS and JK provided supervision. GKHS and DS provided administrative support. GKHS and DS wrote the paper. JK, JM, PWHC and JPYC provided edits. All authors reviewed the paper and interpreted the findings. GKHS, CZ, WSS, PWHC and JPYC collected the data. GKHS, CZ and WSS analysed the data.

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Conflict of interest

None of the authors have any competing or financial interests in relation to this work. None of the authors have any current financial relations with the pharmaceutical company, Axsome Therapeutics, that provided the medication.

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FIGURE LEGENDS

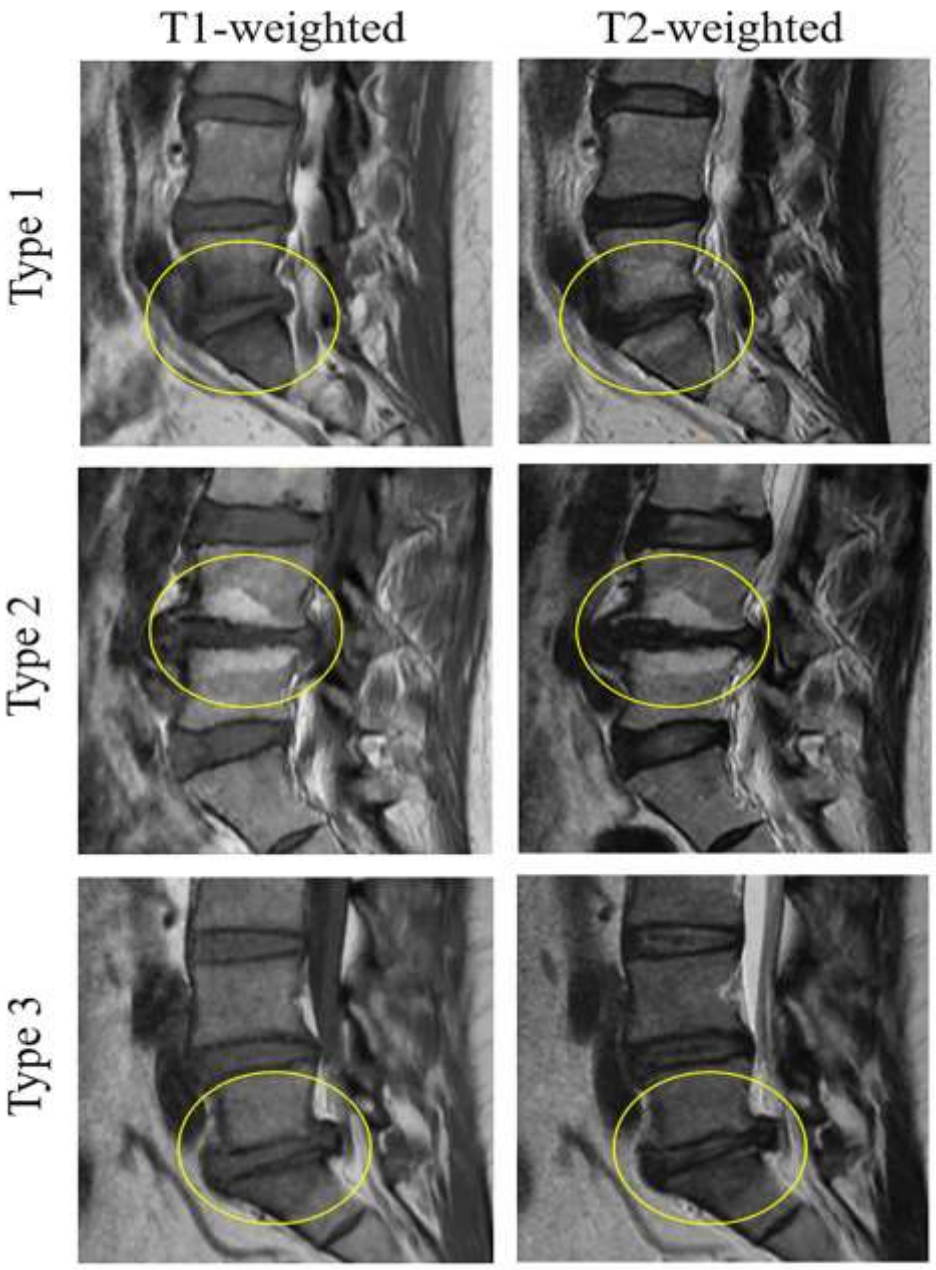

Figure 1: Examples of Modic changes (MC). Circled regions denote Type 1, Type 2, and Type 3 MC in accordance to their signal intensities upon sagittal MRI images.

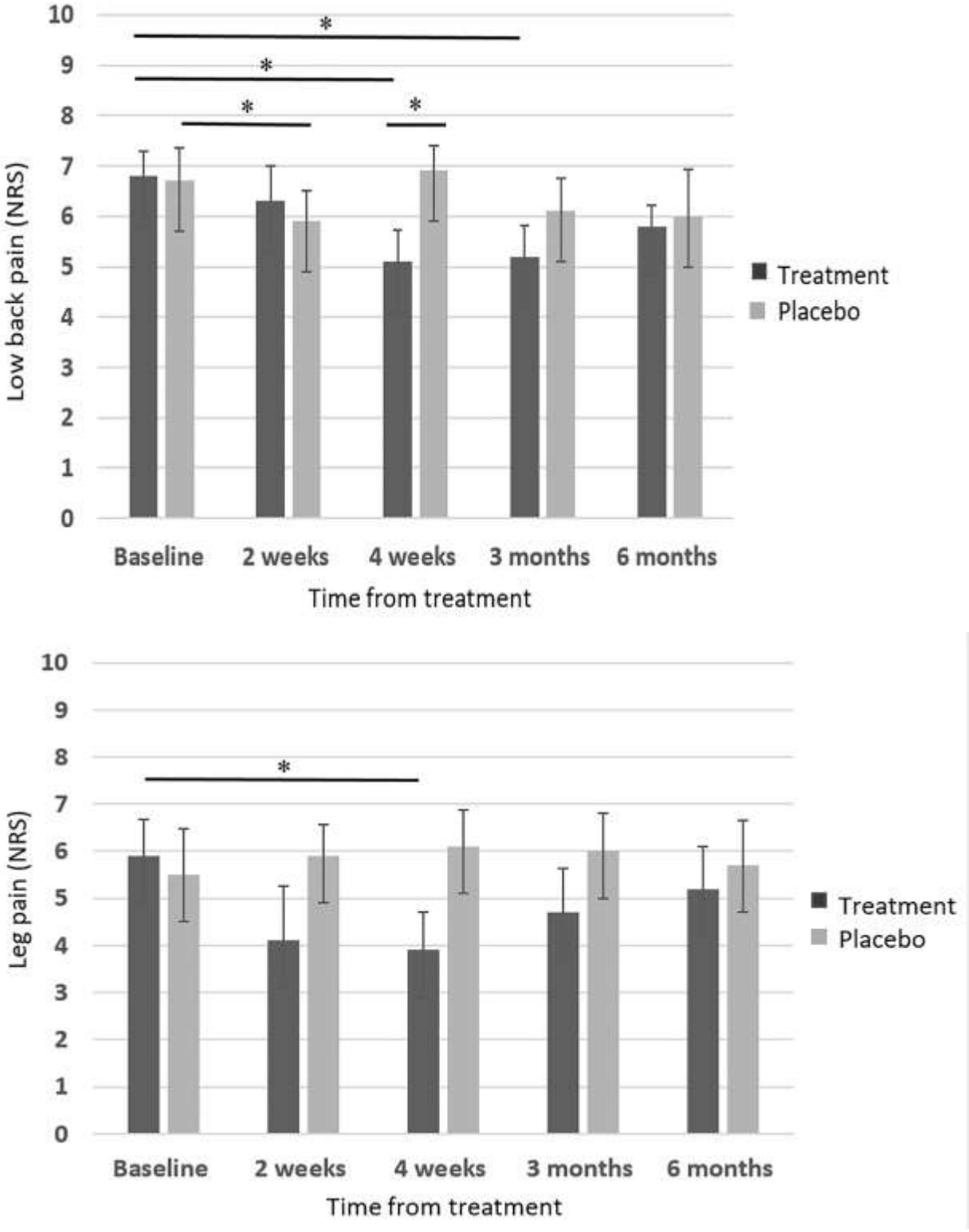

Figure 2: Changes in **(A)** lower back and **(B)** leg pain over time in comparison of treatment (oral Zoledronic acid) and placebo groups. * $p < 0.05$ upon comparison between groups.

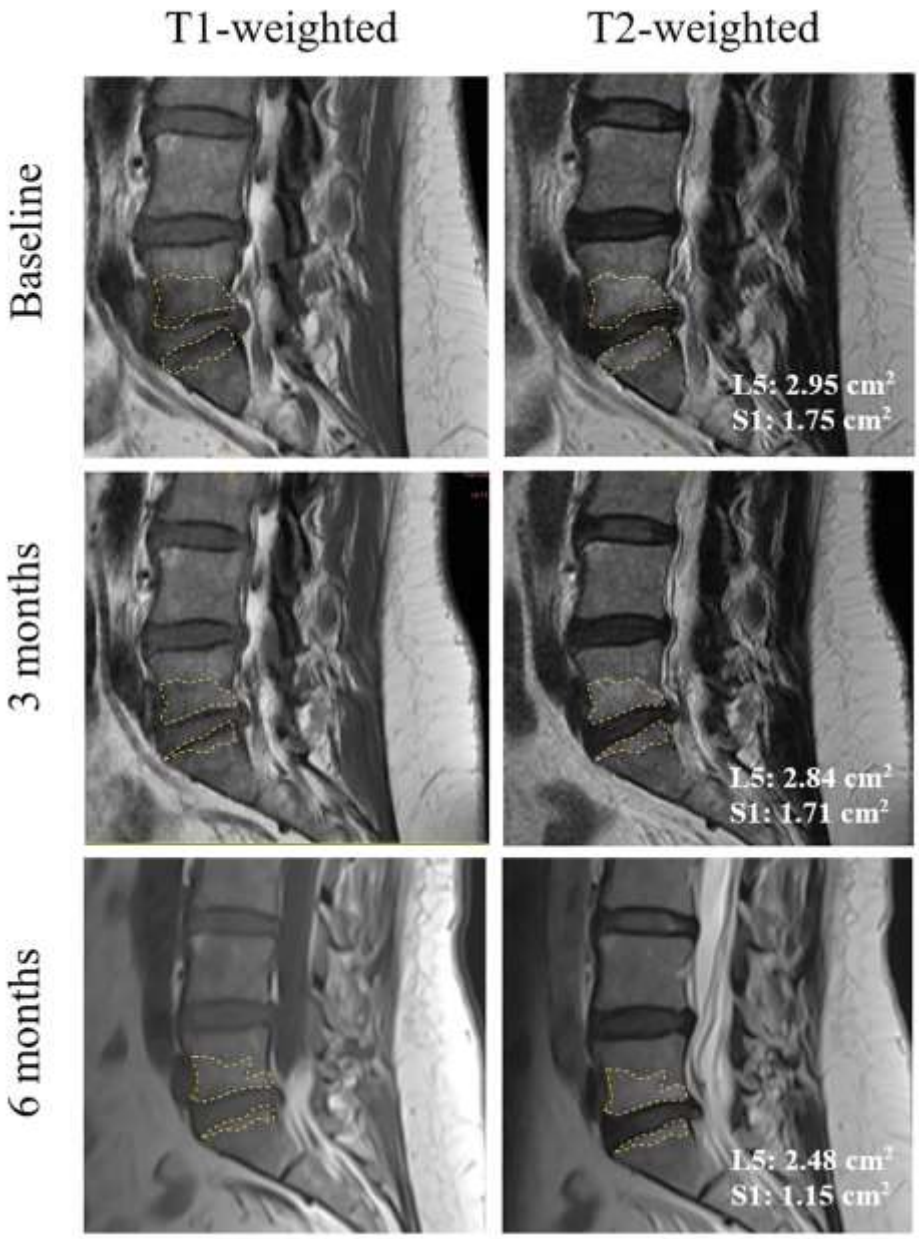

Figure 3: Reduction in area (outlined) affected by Type 1 Modic changes at 3-months and 6-months over L5/S1 as compared to baseline.

Table 1. Baseline characteristics of subjects by intervention-type.

	Zoledronic acid (n = 9)	**Placebo (n =12)**	**P-value**
Age (years)	59 ± 6.7 (51 - 69)	54 ± 9.2 (40 - 70)	0.193
Sex	2M, 7F	5M, 6F	0.642
Marital status	7 Married, 2 Single	9 Married, 3 Single	0.882
Education level	1 Primary School, 6 Secondary school, 2 Higher education	2 Primary School, 8 Secondary School, 2 Higher education	1.0
Height (cm)	161 ± 6.9 (155 - 176)	162.4 ± 11.4 (148 - 178)	0.753
Weight (kg)	64.0 ± 9.2 (51.5 - 74.6)	72.1 ± 19.1 (50.2 - 109.1)	0.243
Employment status	5 employed, 4 unemployed	8 employed, 4 unemployed	0.673
Smoking status	8 Non-smoker, 1 Smoker	9 Non-smoker, 1 Smoker, 2 Ex-smoker	0.735

Table 2. Numerical rating scale changes in lower back pain and leg pain between treatment and placebo groups. Note, p-values in bold type are considered to be statistically significant ($p<0.05$).
SEM = standard error of the mean

Lower Back Pain			
Time from treatment	**Treatment (mean ± SEM)**	**Placebo (mean ± SEM)**	**P-value**
Baseline	6.8 ± 0.5	6.7 ± 0.7	0.900
2 weeks	6.3 ± 0.7	5.9 ± 0.6	0.699
4 weeks	5.1 ± 0.6	6.9 ± 0.5	**0.038**
3 months	5.2 ± 0.6	6.1 ± 0.7	0.373
6 months	5.8 ± 0.4	6.0 ± 0.9	0.821

Pre- to post-treatment interval comparisons	**Treatment (P-value)**	**Placebo (P-value)**
Baseline vs. 2 weeks	0.195	**0.021**
Baseline vs. 4 weeks	**0.017**	0.491
Baseline vs. 3 months	**0.023**	0.551
Baseline vs. 6 months	0.053	0.461

Leg Pain

Time from treatment	**Treatment (mean ± SEM)**	**Placebo (mean ± SEM)**	**P-value**
Baseline	5.9 ± 0.8	5.5 ± 1.0	0.807
2 weeks	4.1 ± 1.2	5.9 ± 0.7	0.154
4 weeks	3.9 ± 0.8	6.1 ± 0.8	0.070
3 months	4.7 ± 0.9	6.0 ± 0.8	0.314
6 months	5.2 ± 0.9	5.7 ± 1.0	0.748

Pre- to post-treatment interval comparisons	**Treatment (P-value)**	**Placebo (P-value)**
Baseline vs. 2 weeks	0.352	0.645
Baseline vs. 4 weeks	**0.031**	0.380
Baseline vs. 3 months	0.178	0.182
Baseline vs. 6 months	0.369	1.0

Table 3. Changes in Oswestry Disability Index (ODI) between treatment and placebo groups.
SEM = standard error of the mean

Comparison between groups

Time from treatment	**Treatment (mean ± SEM)**	**Placebo (mean ± SEM)**	**P-value**
Baseline	32.9 ± 2.8	40.5 ± 3.4	0.116
2 weeks	32.7 ± 3.6	44.0 ± 4.6	0.080
4 weeks	33.6 ± 3.6	42.2 ± 3.8	0.130
3 months	31.1 ± 5.5	43.1 ± 6.6	0.195

6 months	40.4 ± 6.3	49.6 ± 7.2	0.371

Pre- to post-treatment interval comparisons

Time from treatment	**Treatment (P-value)**	**Placebo (P-value)**
Baseline vs. 2 weeks	0.894	0.377
Baseline vs. 4 weeks	0.859	0.667
Baseline vs. 3 months	0.681	0.775
Baseline vs. 6 months	0.161	0.118

Table 4. Changes in RAND-36 scores, uncorrelated and correlated physical component summary (PCS) score, uncorrelated and correlated mental component summary (MCS) score between treatment and placebo groups. Note, p-values in bold type are considered to be statistically significant ($p<0.05$). Increased RAND-36 subscale scores indicate improvement. SEM = standard error of the mean.

Comparison between groups

RAND-36 Subscales	**Baseline (Mean±SEM)**			**post-3 months (Mean±SEM)**			**post-6 months (Mean±SEM)**		
	Treatment	**Placebo**	**P-value**	**Treatment**	**Placebo**	**P-value**	**Treatment**	**Placebo**	**P-value**
Physical functioning	60.0 ± 4.7	49.3 ± 6.6	.218	68.0 ± 6.7	49.0 ± 5.3	**.038**	68.0 ± 6.0	51.5 ± 5.4	.053
Role limitation due to physical health	25.0 ± 11.8	12.5 ± 7.2	.359	35.0 ± 13.5	27.5 ± 9.5	.655	50.0 ± 14.9	37.5 ± 11.3	.504
Role limitation due to emotional problems	43.3 ± 12.2	27.3 ± 12.6	.373	63.3 ± 13.6	46.7 ± 11.3	.358	70.0 ± 13.6	41.7 ± 12.4	.139
Energy/fatigue	44.0 ± 5.2	35.4 ± 6.4	.452	47.5 ± 7.0	39.0 ± 6.3	**.040**	49.0 ± 7.1	40.4 ± 6.2	.406

Emotional well-being	63.2 ± 6.4	51.2 ± 5.6	.323	72.4 ± 5.1	57.2 ± 6.6	.381	73.6 ± 5.1	57.3 ± 7.4	.371
Social functioning	62.5 ± 5.6	53.1 ± 10.1	.173	81.3 ± 8.0	55.0 ± 8.8	.085	68.8 ± 8.2	58.3 ± 8.9	.098
Pain	38.3 ± 4.3	31.9 ± 4.6	.335	55.8 ± 4.7	27.3 ± 6.8	**.003**	50.0 ± 3.4	32.7 ± 7.4	.051
General health	47.5 ± 4.8	25.0 ± 7.1	**.021**	44.5 ± 8.5	31.5 ± 6.3	.237	45.5 ± 6.0	36.3 ± 6.8	.329
Physical component summary (PCS) score, uncorrelated	35.0 ± 2.0	33.9 ± 3.1	0.780	37.2 ± 3.4	35.1 ± 3.1	0.646	37.7 ± 2.7	38.5 ± 3.0	0.85
Physical component summary (PCS) score, correlated	37.0 ± 1.9	36.3 ± 2.6	0.828	38.2 ± 3.3	37.0 ± 2.7	0.779	38.8 ± 2.7	40.3 ± 2.5	0.684
Mental component summary (MCS) score, uncorrelated	43.7 ± 3.0	33.7 ± 2.4	**0.016**	49.6 ± 8.8	32.1 ±10.1	**<0.01**	49.1 ± 2.6	36.3 ± 2.8	**<0.01**
Mental component summary (MCS) score, correlated	41.2 ± 3.4	31.7 ± 2.5	**0.032**	48.1 ± 3.4	29.9 ± 3.2	**<0.01**	48.0 ± 3.1	34.3 ± 3.1	**<0.01**

Pre- to post-treatment interval comparisons

RAND-36 Subscales	Baseline vs. 3 months (P value)		Baseline vs. 6 months (P value)	
	Treatment	Placebo	Treatment	Placebo

Physical functioning	0.600	1	0.556	1
Role limitations due to physical health	0.844	0.848	0.406	0.196
Role limitations due to emotional problems	0.529	0.846	0.333	1
Energy/fatigue	0.916	1	0.839	1
Emotional well-being	0.518	1	0.435	1
Social functioning	0.163	1	0.805	1
Pain	**0.034**	1	0.110	1
General health	0.95	1	0.963	0.72
Physical component summary (PCS) score, uncorrelated	0.384	0.783	0.401	0.090
Physical component summary (PCS) score, correlated	0.631	0.842	0.586	0.085
Mental component summary (MCS) score, uncorrelated	**0.021**	0.700	**0.030**	0.321
Mental component summary (MCS) score, correlated	**0.035**	0.685	**0.028**	0.331

Table 5. Comparison of Modic changes between treatment and placebo groups. Note, p-values in bold type are considered to be statistically significant ($p<0.05$).

Location of Modic changes			
	Treatment (n)	**Placebo (n)**	**P-value**
Type of primary MC (n) (Type I / Type II / Mixed type)	1 / 6 / 2	1 / 8 / 2	0.958
Level of primary MC (n) (L2/3 / L3/4 / L4/5 / L5/S1)	1 / 0 / 4 / 4	1 / 2 / 3 / 5	0.557
Pfirrmann Grading of discs at worst MC-lesion, n (II / III / IV / V)	0 / 1 / 4 / 4	1 / 2 / 5 / 3	0.705
Type of primary MC (n-number) (Type I / Type II / Mixed type)	1 / 6 / 2	1 / 8/ 2	0.958
Level of primary MC (n-number) (L2/3 / L3/4 / L4/5 / L5/S1)	1 / 0 / 4 / 4	1 / 2 / 3 / 5	0.557
Area with Modic changes			
	Treatment (cm^2)	**Placebo (cm^2)**	**P-value**
Area at baseline	7.97 ± 6.59	5.88 ± 4.54	0.557
Area at 3-months	7.54 ± 6.57	5.83 ± 4.51	0.627
Area at 6-months	7.29 ± 7.03	5.89 ± 4.62	0.705
Change in area of MC (baseline to 3 months)	-0.42± 0.51	-0.06 ± 0.23	0.167
Change in area of MC (baseline to 6 months)	-0.67 ± 0.69	0.00 ± 0.15	**0.041**
Change in area of MC (3 months to 6 months)	-0.25± 0.70	0.06 ± 0.21	0.368
Volume of Modic changes			
	Treatment	**Placebo**	**P-value**

	(cm^3)	**(cm^3)**	
Volume of MC baseline	7.29 ± 6.94	6.60 ± 6.10	0.862
Volume of MC in 3-months	7.16 ± 7.55	6.80 ± 6.15	0.932
Volume of MC in 6-months	6.85 ± 7.75	6.86 ± 6.31	0.998
Change of MC Volume (baseline to 3 months)	-0.14 ± 1.01	0.19 ± 0.21	0.527
Change of MC Volume (baseline to 6 months)	-0.44 ± 1.29	0.26 ± 0.32	0.264
Change of MC Volume (3 month to 6 months)	-0.30 ± 0.28	0.07 ± 0.23	**0.035**
Pre- to post-treatment interval comparisons (within-group)			
Area with Modic change	**Treatment (P-value)**	**Placebo (P-value)**	
Baseline vs. 3 months	0.149	0.610	
Baseline vs. 6 months	**0.042**	0.954	
3 months vs. 6 months	0.384	0.563	
Volume with Modic change	**Treatment (P-value)**	**Placebo (P-value)**	
Baseline vs. 3 months	0.750	0.112	
Baseline vs. 6 months	0.398	0.147	
3 months vs. 6 months	**0.029**	0.545	