# Clinical efficacy of oral alendronate in ankylosing spondylitis: a randomised placebo-controlled trial

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## Abstract

### Objective

*A prospective, double blind, randomised, placebo controlled trial over 2 years was performed to test the efficacy of alendronate, an oral aminobisphosphonate, in improving symptoms and arrest disease progression in patients with mild to severe ankylosing spondylitis (AS).*

### Methods

*180 patients with AS were randomised to receive weekly alendronate 70 mg or placebo (1:1 randomisation). BAS-G was the primary outcome measure with Bath indices as secondary outcomes. Vertebral x-rays were performed at 0 and 24 months. Biomarkers (including CRP, IL-1beta, IL6, VEGF, MMP-1, and MMP-3) were collected during the first 12 months.*

### Results

*There was no significant difference between the placebo and treatment groups in any of the recorded outcomes over the 2 years including clinical indices, biomarkers, and radiology. The change in BAS-G, the primary outcome measure, was -0.21 for the treatment group and -0.42 for the placebo group p=0.57. Change in all other clinical outcome measures were also non-significant; BASDAI p=0.86, BASFI p=0.37, BASMI p=0.021. Sub-group analysis of those subjects with a baseline BASDAI >4 were also non-significant.*

### Conclusion

*This prospective study demonstrates that alendronate 70 mg weekly for 2 years was no more efficacious than placebo in improving clinical or laboratory measures of disease activity or measures of physical impact in subjects with mild to severe active AS. Trial registration: ID SRCTN12308164, registered on 15.12.2015*

### Key words

Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Bath AS Metrology Index (BASMI), Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

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*Abbreviations of indices used:*

| | |
|---|---|
| ASAS: | The Assessment of SpondyloArthritis international Society |
| BASFI: | Bath AS Functional Index |
| BASMI: | Bath AS Metrology Index (CRP, bone turnover measurements, cytokine |
| BASRI: | Bath AS Radiology Index |
| BASG: | Bath Ankylosing Spondylitis Global Score |
| BASDAI: | Bath AS Disease Activity Index |
| mSASSS: | Modified Stoke Ankylosing Spondylitis Spinal Score |

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## Introduction

Ankylosing spondylitis (AS) is one of the most common spondyloarthropathy (SpA) with a prevalence of between 0.1–1.4% (1). It is characterised by inflammatory back pain with progressive fusion of the spine causing significant morbidity and disability.

Attempts to prevent progression and symptomatic improvement remain limited. Physiotherapy and non-steroidal anti-inflammatories (NSAIDs) may be effective: indeed two NSAIDs have been shown to have a small beneficial effect on radiographic progression in AS (2-3) but their effect is not universal and there are concerns about the side-effect profile of NSAIDs in general. Disease modifying anti-rheumatic drugs such as sulphasalazine may help peripheral arthritis but have a limited or negligible effect in patients with axial disease (4-6).

Anti-TNF alpha therapy has been shown to be extremely effective in both peripheral and axial inflammation (7-9). However these drugs do not halt radiographic disease progression (10-11), are expensive, not effective in all patients, their use in some patients is contraindicated, and though registry data is reassuring long-term safety remains a concern. Furthermore in some healthcare systems patients may be ineligible for anti-TNF therapy due to limited disease activity and therefore there clearly remains a need for alternative therapeutic options.

Pamidronate, a parenteral amino-bisphosphonate, was first used in AS in the late 1990s. A Canadian open-labelled study of IV pamidronate in patients with refractory AS compared 30 mg monthly for 3 months followed by 60 mg for an additional 3 months with 60 mg monthly for 3 months. The results showed the BASDAI, BASMI and ESR improved significantly in the group treated for 6 months (12). A randomised controlled double blind study of 84 patients with AS comparing pamidronate 60 mg monthly with a 10 mg monthly dose over 6 months (13) reported a greater than 25% improvement in BASDAI, BASFI and BAS-G, in more than 60% of patients in the 60 mg group compared to less than 35% of those receiving 10 mg. There was no change in ESR or CRP. Less significant improvements have been seen with other pamidronate regimens (14) and modest improvements have been reported recently in two small open labelled studies of the alternative IV bisphophonates, zoledronate and neridronate (15, 16). These studies suggest bisphosphonates may be a useful adjunct in the treatment of axial symptoms in AS.

Further reports have described anti-inflammatory and immunomodulating effects of bisphosphonates which may be of value when treating AS. As well as their anti-osteoclastic effects and the potential that this has to affect disease activity, bisphosphonates have also been shown to reduce interleukin-1 (IL-1), TNF alpha, and IL-6 (17-23) and to inhibit the catalytic activities of several matrix metalloproteinases including MMP3 (24), an indicator of disease activity in patients with AS. In addition, alendronate has been shown to inhibit activity of antigen-presenting cells (17). Administration of monthly intravenous pamidronate is time consuming and relatively expensive in comparison to an oral aminobisphosphonate, such as alendronate. We proposed to investigate the potential disease-modifying properties of alendronate in a population of AS patients with a spectrum of mild to severe disease activity, reflecting routine clinical practice.

## Materials and methods

The study was a double blind randomised controlled trial. Using computerised random number generation patients were allocated in equal numbers to receive either alendronate 70 mg weekly or matching placebo weekly over a 2-year period. Both alendronate and placebo were supplied by MSD. The primary outcome measure was the Bath Ankylosing Spondylitis Global score (BAS-G) (25), assessing overall change in patient's symptoms and general health over the preceding one month.

Secondary outcome measures included disease activity (Bath AS Disease Activity Index (BASDAI)) (26), physical function (Bath AS Functional Index (BASFI)) (27), mobility (Bath AS Metrology Index (BASMI)) (28) and

**Table I.** Exclusion criteria.

| |
|---|
| *Oesophageal/peptic ulceration.*<br>Diagnosed on endoscopy or barium meal within previous 24 months.<br>Oesophageal reflux or peptic ulceration symptoms (heartburn; indigestion; water-brash; dysphagia) more than once a week. |
| *Abnormalities of bone turnover and calcium metabolism.*<br>Paget's disease; hypo/hypercalcaemia; osteomalacia; inflammatory bowel disease (Crohn's disease, ulcerative colitis) |
| *Excluded concomitant medication.*<br>Oral or IV bisphosphonates in the previous 12 months; Oral or IV steroid use within previous 3 months, IA steroids within previous 2 months; Anti-TNF alpha therapy; calcitonin; raloxifene; testosterone; hormone replacement therapy change in previous 6 months.. |
| *Minimal trauma fractures.*<br>≥ 2 low trauma fractures |
| *Allergy/hypersensitivity to bisphosphonates.* |
| *Lumbar spinal surgery.* |
| *Significant renal disease.*<br>Serum creatinine >150µmol/l |
| *Haemoglobin < lower limit of normal for laboratory.* |
| *Planned surgery within the study period* |
| *Pharmaceutical trials.*<br>Any patient taking part in a pharmaceutical trial at the time of the screening assessment or who has taken part in a trial in the previous 12 months |
| *Pregnancy/Contraception.*<br>Any female who is pregnant or planning pregnancy in the next 24 months or is unwilling to use adequate contraception. |
| *Malignancy.*<br>Except those in remission for >5 years |
| *Life expectancy <2years.* |

laboratory measurements (CRP, bone turnover measurements, cytokine profile). Radiographic features were assessed by modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (29) and Bath AS Radiology Index (BASRI) (30). ASAS20 and ASAS40 (31) were also calculated.

The study was powered to detect a minimal clinically important difference of 1.5 in the primary outcome measure (BAS-G) (32). With 95% power to reach 5% level of significance this required a total sample size of 140 (70 in each group). Assuming a 20% dropout rate, 90 patients were required in each group to obtain a sample size of 70.

Eligible patients had to meet the modified New York criteria for the diagnosis of AS (33) which we refined to allow for MRI diagnosis of sacroiliitis, and a requirement for a minimum pre-defined movement restriction (34). They also fulfilled ASAS criteria for axial SpA (35). All patients were aged over 21 years and, if taking NSAID, had been on a stable dose for at least 4 weeks. There was no minimal level of disease activity required for entry to the study.

Exclusion criteria are mentioned in Table I and included any intervention or underlying disease with the potential to effect disease activity or bone density, including treatment with anti-TNF. Patients with bilateral hip replacements or previous back surgery that would prevent accurate bone density measurement by dual x-ray absorptiometry (DXA) were excluded. (Bone density data was collected for a separate study)

Ethical approval was received from Trent MREC (REC reference: 04/4/023) and site specific approval was obtained from the 6 UK participating centres.

Patients were invited to participate from rheumatology outpatients, local National Ankylosing Spondylitis Society (NASS) groups and by letter to patients who had given permission to be contacted through the NASS database held at the RNHRD. Each patient received an information sheet explaining the study and a consent form. Written consent was obtained from all patients according to the Declaration of Helsinki (36).

At baseline, patients completed a sociodemographic questionnaire, date of diagnosis and duration of symptoms. At each time point (baseline, 3, 6, 12, 18, and 24 months) patients completed a questionnaire that included changes in medication and disease-specific measures: BAS-G, BASDAI and BASFI, all scored between 0 and 10 with higher values indicating greater global impact, disease activity and worse physical function respectively. C-reactive protein (CRP) was measured at each time point except 18 months. Physical measures of spinal mobility (BASMI) including tragus to wall distance, cervical rotation, lateral lumbar flexion, intermalleolar distance and modified Schober's index were measured at baseline and 24 months. ASAS20 and ASAS40 were also recorded at baseline and 24 months.

At baseline and 6 months, serum levels of a panel of cytokines and matrix metalloproteinases (including IL-1beta, IL-6, TNF alpha, VEGF, MMP-1 and MMP-3) were measured using multiplex bead-based assays (Life Technologies, Paisley, Renfrewshire, United Kingdom [for cytokines] and R&D Systems Europe, Abingdon, Oxfordshire, UK [for MMPs]) on a Luminex suspension array system (Bio-PlexTM 200). X-rays were recorded at baseline and 24 months. Tablet counts and safety data were recorded at each visit.

The primary analysis, on an "intention to treat" principle, was performed on all randomised patients with data at visit 6 (n=159). A secondary "per protocol" analysis was performed on those who completed treatment (n=147). All data management and analyses were done using SPSS v. 16 (IBM).

Descriptive summary statistics of each group are presented as mean and standard deviation with frequencies and percentages for categorical variables.

Differences between groups for BAS-G, BASDAI, BASFI, BASMI, CRP and ESR at 0 and 24 months were assessed using ANOVA, controlling for age, sex and disease duration. Statistical significance was determined at the 5%-level using 2-sided tests throughout.

## Results

A total of 383 patients were screened. Of these, 83 patients were excluded as they failed to meet the inclusion/exclusion criteria and 120 declined to take part. 180 patients were recruited. 88 patients were randomised to receive alendronate and 92 patients were randomised to receive placebo. Baseline characteristics are summarised by treatment group in Table II. At baseline both groups reflected the anticipated demographics. They were well matched with no significant differences in baseline demographics and measures. They had moderate disease activity (BASDAI mean 4.2 and 4.1).

Follow-up, reported in accordance with CONSORT recommendations, is shown in Figure 1. Only 1 patient,

**Table II.** Disease measures at baseline.

| | Alendronate (88) | SD | Placebo (92) | SD |
|---|---|---|---|---|
| Males | 74 (84%) | | 74 (80%) | |
| Age (yrs.) | 47.1 | 11.6 | 47.4 | 12.3 |
| Disease duration (yrs.) | 19.7 | 10.7 | 20.8 | 12.7 |
| BAS-G | 4.3 | 2.3 | 4.2 | 2.3 |
| BASDAI | 4.2 | 2.4 | 4.1 | 2.1 |
| BASFI | 3.8 | 2.5 | 3.6 | 2.2 |
| BASMI | 2.7 | 1.0 | 2.9 | 1.1 |
| CRP (mg/l) | 14.2 | 17.2 | 11.2 | 11.8 |
| BASRI[a] (0-16) | 9.37 | 2.34 | 9.91 | 2.76 |
| mSASSS[b] (0-72) | 20.88 | 18.25 | 25.07 | 21.05 |

[a]BASRI available on 84 patients treated with alendronate and 82 patients on placebo.
[b]mSASSS available on 76 patients treated with alendronate and 73 patients on placebo.

on placebo, was lost to follow-up. 29 patients discontinued treatment (14 receiving alendronate and 15 receiving placebo). Primary outcome (BAS-G) was available on 87% (159/180) of patients at 24 months. Of those patients completing the study all adhered to the protocol, taking at least 70% of their prescribed medication according to recorded tablet counts. 158 (87%) patients were on concomitant NSAIDs at baseline (84 receiving alendronate and 74 placebo). Commonly used NSAIDs were diclofenac (51 patients) and indo-

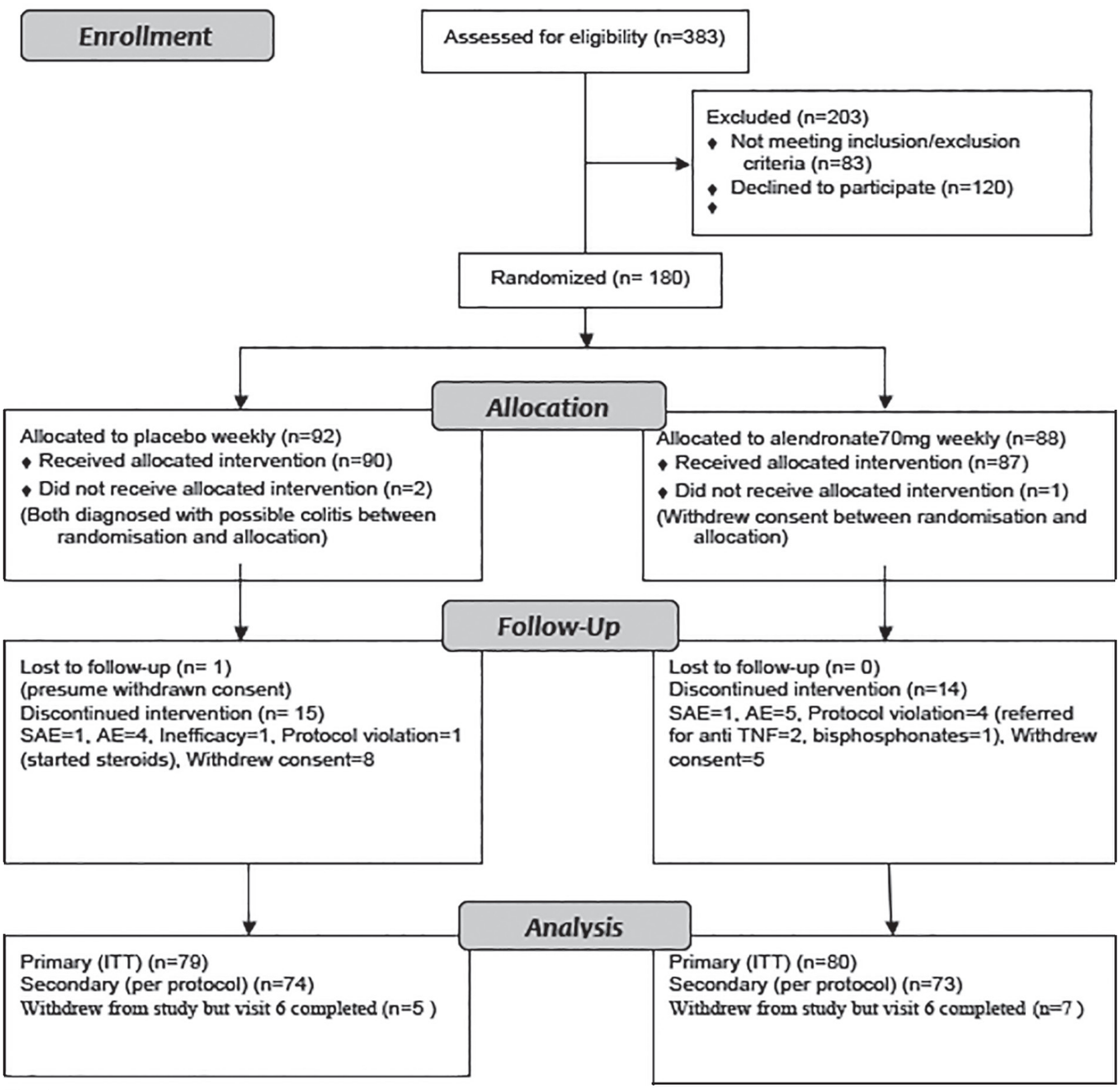


**Fig. 1.** BIAS STUDY CONSORT Flow diagram.

methacin (25 patients). Data on the use of NSAIDs was not collected.

The changes in primary and secondary outcome measures are shown in Table III. Although BAS-G fell during the second year period of the study, this fall was similar in both the treatment and placebo groups. BAS-G fell by 0.21 in the active group and by 0.42 in the placebo group (no significant difference between groups ($p$=0.568). Subgroup analysis of patients with disease activity of BASDAI >4 also showed no significant benefit from alendronate treatment (data not shown). There were no significant differences between groups for changes in any of the other clinical measures including, disease activity (BASDAI, ASAS20, ASAS40), physical function (BASFI). Physical mobility (BASMI), while showing a statistical difference, did not show a clinically meaningful difference. Similarly there were no significant differences for changes in the laboratory markers including: CRP (between 0 and 24 months), IL-1beta, IL-6, TNF-alpha, VEGF, MMP-1 and MMP-3 (between 0 and 6 months). In addition, there were no significant changes in the radiographic measures of BASRI or mSASSS (Table IV). There were no significant differences between the two groups at any other time point. A secondary analysis of those who completed the study as per the protocol showed no significant differences from the primary ITT analysis.

In 11 patients adverse effects were the principal reason for withdrawal from the trial: 6 alendronate (4 upper GI symptoms, 1 dyspnoea (pulmonary fibrosis), and 1 subarachnoid haemorrhage), 5 placebo (3 upper GI symptoms, 1 worsening AS, and 1 duodenal ulcer). 425 adverse events were reported by 120 patients (60 in each treatment group), these were similar to those seen in other studies and are well described in the literature. There were 10 episodes of iritis (8 episodes from 6 patients in the treatment group, 2 from 2 patients from the placebo arm). There were no reports of osteonecrosis of the jaw or subtrochanteric fractures.

Fifteen serious adverse events were reported, 6 on alendronate (1 subarachnoid haemorrhage, 1 pulmonary fibrosis (death), 1 chest pain, 1 diverticulitis, 1 acute hip pain, 1 suicide) and 9 on placebo (1 fracture following fall, 1 pulmonary embolism, 1 lower respiratory tract infection, 1 gastric ulcer, 1 duodenal ulcer (death), 1 diverticulitis, 1 pseudogout, 1 atrial fibrillation, 1 B cell lymphoma). There were 3 unrelated deaths, 2 in the alendronate group both of whom had previously discontinued alendronate and withdrawn from the study.

**Table III.** Change in disease measures (mean change with 95% confidence intervals over 24 months unless stated).

| Variable | Treatment group | Placebo group | $p$-value |
|---|---|---|---|
| BAS-G | -0.21 (-0.72 – 0.31) | -0.42 (-0.96 – 0.12) | 0.568 |
| BASDAI | -0.36 (-0.79 – 0.05) | -0.32 (-0.71 – 0.06) | 0.863 |
| BASFI | -0.13 (-0.46 – 0.21) | 0.12 (-0.28 – 0.51) | 0.367 |
| BASMI | 0.2 (-0.10 – 0.46) | -0.2 (-0.36 – -0.04) | 0.021 |
| ASAS20[a] | 24/79 (30.4) | 17/80 (21.3) | 0.208 |
| ASAS40[a] | 7/79 (8.8) | 10/80 (12.5) | 0.609 |
| CRP (mg/L) | -7.72 (-14.42 – -1.02) | -2.58 (-6.07 – 0.90) | 0.178 |
| IL-1beta[b] | 0.0 (0.0 – 0 .0) | 0.0 (0.0 -2.02) | 0.18 |
| IL-6[b] | 0.475 (0.0 – 0.84) | 0.0 (-0.25 – 1.12) | 0.32 |
| TNF alpha[b] | 0.05 (-0.18 – 0.12) | 0.18 (0.0 – 0.31) | 0.09 |
| VEGF[b] | 0.0 (0.0 – 0.0) | 0.0 (0.0 – 0.01) | 0.63 |
| MMP-1[b] | -64.84 (-199.6 – 127.6) | -59.21 (-309.6 – 117.5) | 0.61 |
| MMP-3[b] | 1098 (117.4 – 2063.1) | 1896 (-228.9 – 2655.3) | 0.93 |

[a]Percentage achieving ASAS20 or 40 over 24 months.
[b]Change over initial 6 months (median (95% confidence intervals) pg/ml.

**Table IV.** Change in radiology measures of mSASSS and BASRI over 24 months (n=60 in each group).

| | Group | Baseline (SD) | 24 months (SD) |
|---|---|---|---|
| mSASSS* | Treatment | 18.83 (17.11) | 19.88 (17.47) |
| | Placebo | 24.97 (21.53) | 26.26 (22.15) |

*Baseline between group difference $p$=0.086.
24 month difference adjusted for baseline $p$=0.752.

| | Group | Baseline (SD) | 24 months (SD) |
|---|---|---|---|
| BASRI+ | Treatment | 9.19 (2.18) | 9.39 (2.12) |
| | Placebo | 9.65 (2.70) | 10.48 (6.58) |

+Baseline between group difference $p$=0.309.
24 month difference adjusted for baseline $p$=0.433.

## Discussion

This is the largest double blind placebo controlled study of bisphosphonates in AS and, at 2 years, is significantly longer than previous studies. The primary aim of this study was to determine the impact of oral alendronate on global or disease specific symptoms and outcome measures in patients with AS. Alendronate given for twenty four months was no more likely than placebo to improve a global response index in AS (BAS-G) irrespective of baseline disease activity. In addition, alendronate had no benefits over placebo on clinical or laboratory measures of disease activity, or measures of physical impact. We conclude there is no evidence that alendronate, given at a dose of 70 mg weekly, improves clinical AS symptoms, disease activity or function. Designed to replicate "real life" treatment, no minimal disease activity level was required to take part in the study but mean BASDAI levels at baseline reflect those found in epidemiological studies of AS (37-39), indicating that patients recruited were typical of those attending rheumatology outpatients. Though the study was not powered for subgroup analysis of disease activity, we found no difference between those receiving placebo or alendronate, over

the two years, in whom the baseline BASDAI was greater than 4.

The positive findings from previous studies using intravenous pamidronate may be related to smaller study size, shorter duration, the inability to achieve true blinding due to pamidronate side effects and a, more heterogeneous spondyloarthropathy population (12-16). While it is possible that the response to treatment in patients with AS differs between different bisphosphonates, there is a concern that the apparent, specific, beneficial effect of pamidronate may be explained by a placebo effect of an intervention (intravenous infusions). In this study, even in the placebo group, ASAS20 and ASAS40 response was reached in 21% and 12%. However, we cannot exclude the fact that pharmacokinetics of parental bisphosphonate may differ and yield an effect on immune cells which may be therapeutic.

A detailed description of the effect of alendronate on BMD and vertebral deformity will be reported separately (Creamer et al manuscript submitted). However the lack of improvement in BAS-G, radiology and spinal pain would suggest that even if there is an improvement in bone density, and consequent reduction in microfractures, this does not affect symptoms in the short-to-medium term. There may still be a role for bisphosphonates in AS by improving bone strength and reducing fracture risk.

## Conclusion

In summary, double blind, placebo-controlled study does not support the use of alendronate for control of symptoms or disease activity in AS.

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