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Differing effects of zoledronic acid on bone microarchitecture and bone mineral density in men receiving androgen deprivation therapy: a randomised controlled trial

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Data accessibility statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abstract

Androgen deprivation therapy (ADT) given to men with prostate cancer causes rapid and severe sex steroid deficiency leading to increased bone remodeling and accelerated bone loss. To examine the effects of a single dose of zoledronic acid on bone microarchitecture we conducted a two year randomised placebo controlled trial in 76 men, mean age [IQR] 67.8 years [63.8;73.9] with non-metastatic prostate cancer commencing adjuvant ADT; 39 were randomised to zoledronic acid and 37 to matching placebo. Bone microarchitecture was measured using high resolution-peripheral quantitative computed tomography (HR-pQCT). Using a mixed model, mean adjusted differences (MAD [95% CI]) between the groups are reported as the treatment effect at several time points. Over 24 months, zoledronic acid showed no appreciable treatment effect on the primary outcomes for total volumetric bone mineral density (vBMD); radius (6.7 mg HA/cm^3 [-2.0;15.4], p=0.21) and tibia (1.9 mg HA/cm^3 [-3.3;7.0], p=0.87). Similarly, there were no between group differences in other measures of microarchitecture, with the exception of a modest effect of zoledronic acid over placebo in total cortical vBMD at the radius over 12 months (17.3 mgHA/cm^3 [5.1;29.5]). In contrast, zoledronic acid showed a treatment effect over 24 months on aBMD by DXA at all sites, including lumbar spine (0.10 g/cm^2 [0.07;0.13]), p<0.001), and total hip (0.04 g/cm^2 [0.03;0.05], p<0.001). Bone remodeling markers were initially suppressed in the treatment group then increased but remained lower relative to placebo (MADs at 24 months CTX -176

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ng/l [-275;-76], p<0.001, P1NP -18 mg/L [-32;-5], p<0.001). These findings suggest that a single dose of zoledronic acid over 2 years is ineffective in preventing the unbalanced bone remodeling and severe microstructural deterioration associated with ADT therapy.

Keywords: Androgen deprivation; bone; microarchitecture; bisphosphonates; prostate cancer.

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Introduction

Androgen deprivation therapy (ADT), most commonly using gonadotrophin-releasing hormone (GnRH) analogs, is a standard treatment for prostate cancer, the most common solid organ malignancy in men. By reducing circulating serum testosterone concentrations into the castrate range, ADT improves prostate cancer prognosis in adjuvant and palliative settings [(1)]. However, the severe sex steroid deficiency (of both testosterone and its aromatisation product estradiol) is associated with accelerated bone loss, especially during the first 12 months after ADT initiation [(2)], and increases the risk of fragility fractures [(3)]. Adverse effects of ADT such as increased fracture risk are of particular concern in men with non-metastatic prostate cancer, given that long term cancer-specific survival is about 95% [(1)]. In randomised controlled trials (RCT) in men receiving ADT for prostate cancer, antiresorptive treatment including zoledronic acid [(4)] improves areal bone mineral density (aBMD) assessed by dual energy X-ray absorptiometry (DXA). [(4)] However, while anti-fracture benefit has been reported for the receptor activator of nuclear factor-κB ligand (RANKL) inhibitor denosumab,[(5)] and the selective estrogen receptor modulator (SERM) toremifene [(6)], this has not yet been adequately studied using bisphosphonate therapy.

In an observational study in men with non-metastatic prostate cancer, initiating adjuvant ADT, sex steroid withdrawal led to deterioration of cortical and trabecular microarchitecture with only modest deterioration in aBMD measurements by DXA [(7)]. Despite evidence that HR-pQCT is likely to improve fracture risk prediction [(8-10)], few clinical trials have used HR-pQCT to assess the effects of antiresorptive therapy on bone microarchitecture, and no RCT has

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examined the effects of therapy in men receiving ADT, a unique model of severe sex steroid deficiency and the most common current cause of profound hypogonadism in older men [1].

We therefore conducted a RCT in men with non-metastatic prostate cancer to assess the effects of zoledronic acid, a potent bisphosphonate, on ADT-induced decay of bone microarchitecture as measured using HR-pQCT.

Material and Methods

Study Design

We conducted a double-blind, randomised, parallel group, placebo-controlled trial to compare the effects of a single dose of zoledronic acid treatment with placebo in men with prostate cancer newly commencing ADT. Subjects had bone microarchitecture measured and biochemical assessments at 0, 3 (biochemical only), 6, 12 and 24 months following administration of the research trial medication. The trial was approved by Human Research Ethics Committee at Austin Health (H2010-03833) and was registered at ClinicalTrials.gov as NCT01006395. All participants provided written and informed consent. We followed the CONSORT checklist of information to include when reporting a randomised trial (**Supplementary Table 1**).

Participants and setting

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All participants were men with non-metastatic prostate cancer (T1-3 Nx M0), about to commence treatment with GnRH agonists to suppress androgen production, in whom treatment with ADT was intended for at least 2 years and were able and willing to comply with the study protocol requirements. Localized prostate cancer is not expected to affect structure or function of bone. Participants were independently living in the community, ambulant, fully active, unrestricted in their physical activities with normal performance status (Eastern Co-operative Oncology Group performance status 0), and had no evidence of metastases on bone scan or CT abdomen/pelvis at entry to the study. Men were excluded if they had evidence of androgen deficiency (baseline total testosterone <10 nmol/L), known metabolic bone disease prior to study entry, had active liver, renal or thyroid disease, had previously used antiresorptive or glucocorticoid therapy, had contraindications to zoledronic acid (atrial fibrillation, renal impairment, vitamin D deficiency < 50 nmol/L, active dental disease) or had major depression, recreational drug use, alcohol dependence, known HIV/AIDS or any disease which was likely lead to serious illness or death within the study period. Participants were recruited from an outpatient clinic for men with prostate cancer at a tertiary referral hospital (Austin Health, Melbourne, Australia). Two men (both in the zoledronic acid group) started osteoporosis therapy, a prespecified protocol violation leading to their exclusion from the analyses (**Figure 1**).

Intervention

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Blinded research trial medication (zoledronic acid 5mg or matching placebo) was administered intravenously over 15 minutes as a single dose within 6 weeks of commencement of ADT. All infusions were administered at Austin Health by experienced nursing staff.

Outcomes

The primary endpoints were total volumetric BMD (vBMD) at radius and tibia (HR-pQCT) over 2 years. Secondary endpoints were cortical and trabecular parameters at radius and tibia (HR-pQCT), aBMD parameters by DXA and the bone remodeling markers CTX and P1NP over 2 years.

vBMD and microarchitecture were measured at the distal radius and distal tibia at baseline and at 6, 12 and 24 months using HR-pQCT (XtremeCT; Scanco Medical AG, Bruttisellen, Switzerland). This system enables the simultaneous acquisition of a stack of parallel CT slices with a voxel size of 82 microns. At each skeletal site, 110 CT slices were obtained to deliver a three-dimensional representation of 9 mm in the axial direction. Methods used to process the CT data have been described previously [11]. All analyses were performed using the standard Scanco analysis software. Outcome variables included total, trabecular, and cortical vBMD; cortical area, cortical thickness medullary area and trabecular thickness, number, separation, and bone volume. For follow-up studies, an algorithm automatically uses the cross-sectional area within the periosteal boundary of radius or tibia to match the volumes of interest on baseline and follow-up scans. The precision errors of volumetric densities in our hands were 0.6-1.4% [12].

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aBMD was measured by dual-energy X-ray absorptiometry (Prodigy version 7.51; GE Lunar, Madison, WI, USA) at 0, 6, 12 and 24 months (coefficient of variation (CV) <2% for repeated scans) [7].

All biochemical tests including testosterone and bone remodeling markers were drawn fasting between 8am and 10am. All biochemical tests were analysed after venepuncture using routine methodology available in our centre. Each parameter was analysed on the same platform, with no change in assay methodology in any of the parameters during the course of this study. Fasting serum total testosterone was determined using an immunometric testosterone assay (Access, Beckman Coulter, Inc.) with a minimum detection limit of 0.4 nmol/L and an inter-assay variation of 5.7% at 4.7 nmol/L. The reference range was 10.0–27.6 nmol/L, derived from an independent reference panel of healthy reproductively normal young men [13]. Prostate-specific antigen (PSA) was determined using electrochemiluminescent immunoassay (Cobas e602, Roche Diagnostics) with a minimum detection limit of 0.03 µg/L and an inter-assay variation of 1.83% at 0.63 µg/L. Procollagen type 1 amino-terminal propeptide (P1NP) and beta carboxyl-terminal type I collagen telopeptide (CTX) were measured by electrochemiluminescence on Roche Cobas C8000 (Roche Diagnostics). The lower limit of detection for P1NP is 5 µg/L, with an interassay variation of 5.4% at 73.5 µg/L. The CV for P1NP was 2.8% at 34 ug/L and 2.6% at 205 ug/L. CV for CTX was 1.3% at level of 334 ng/L and 1.3% at 764 ng/L [7].

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Sample size

Power calculations were based on the primary endpoint of bone microarchitecture measured by total vBMD using HR-pQCT. The sample size required for a test with level of significance 0.05 and a power of 0.8 when the mean response of subjects on the treatment is "no change" compared with a decrease equal to the mean of our observational longitudinal study of men with non-metastatic prostate cancer receiving ADT for 12 months [7]. We chose "no change" as this would be considered a clinically important result. Sample size estimates, per group, were 6 for total vBMD at the radius (mean difference -19.43, standard deviation 16.25), and 13 for total vBMD at the tibia (mean difference -11.65, standard deviation 6.13). For cortical HR-pQCT parameters, sample sizes (per group) ranged from 7 to 16 and for trabecular parameters, from 45-329.

Randomisation and blinding

Subjects were randomized with equal probability to the two treatments using randomly permuted blocks of size 2, 4 or 6 (also randomly chosen) stratified by age (< 72 or > 72 years-old). Identical ampoules were dispatched by the Austin Health pharmacy, using subject number to ensure blinding.

Statistical methods

Data were partly non-normally distributed and were presented as median and interquartile range (IQR). Baseline characteristics between zoledronic acid and placebo groups were compared to assess the balance between groups and identify any potential confounders for

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outcome analyses using Wilcoxon signed rank test or chi-square test. Statistical analyses of treatment effects on primary and secondary endpoints followed the intention to treat principle, whereby all randomised subjects who have at least one zoledronic acid (or placebo) dose are included. The treatment effect of bisphosphonate therapy on bone architecture, aBMD, and bone remodeling markers was tested via repeated measures mixed effects models including main effects for the baseline level, bisphosphonate group, time points and the interaction of time point by group. The latter represents the treatment effect, quantified as the mean adjusted between-group difference (MAD). 95% confidence intervals for the MADs were profiled. Statistical significance testing relied on a single p value over all time points (p overall). Where provided for ease of clinical interpretation percentage differences are indicative only. As a sensitivity analysis, we also conducted a per protocol analysis, which included only men who received the study medication and had outcome data available at all time points. Within-variation in a single group was only used for assessing time-sensitive biological effects, not for any treatment effect. A two-sided p-value of <0.05 was considered indicative of statistical significance; as structural bone parameters are intercorrelated, no adjustments for multiple testing were made. Statistical analyses were performed using R statistical package (version 3.6.2 for Mac) together with lme4 1.1-21, effects 4.1-4 and emmeans [14-17].

Results

Participant flow and baseline data

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Of 183 individuals assessed for eligibility, a total of 76 men were randomised, 39 to zoledronic acid and 37 to matching placebo. Participant flow is summarised in the CONSORT flow diagram (**Figure 1**). At baseline, participants had a median age of 67.8 years, and had clinical characteristics typical of men with localised high-risk prostate cancer [(18)]. The majority (95%) received ADT with concurrent radiotherapy as primary treatment for their prostate cancer (**Table 1**). After commencement of ADT, in both groups, serum testosterone declined from a normal baseline concentration to castrate concentrations and PSA declined with no between group differences (**Supplementary Table 1**). Likewise, there were no between group differences in vitamin D concentrations during the study (**Supplementary Table 1**).

Treatment outcomes

Microarchitectural parameters

The primary outcome total vBMD, as measured by HR-pQCT, revealed overall no appreciable treatment effect in the zoledronic acid group, compared to placebo. MADs, both at the radius and the tibia, did not significantly differ between the zoledronic acid group and the placebo group (overall p values of p=0.21 for radius and p=0.87 for tibia respectively), except for a modest transient increase of total vBMD at the radius in the zoledronic acid group compared to placebo at 6 months (MAD 7.8 mgHA/cm^3 [0.2;15.4] (**Figure 2, Supplementary Table 2**).

Similarly, there were no between group differences in secondary microarchitectural outcomes, with the exception of a modest transient increase in total cortical vBMD at the radius in the

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zoledronic acid group compared to placebo at 6 months (MAD 14.0 [2.5;25.6]), and at 12 months (MAD 17.3 mgHA/cm^3 [5.1;29.5], p=0.027) (**Figure 2, Supplementary Table 2**).

DXA parameters

In contrast to total vBMD measured using HR-pQCT, men receiving zoledronic acid, had, compared to placebo higher net aBMD by DXA at the lumbar spine, MAD 0.10 g/cm^2 [0.07;0.13], p<0.001, total hip, MAD 0.04 g/cm^2 [0.03;0.05], p<0.001, and total radius MAD 0.03 g/cm^2 [0.01;0.04], p<0.001 (**Figure 3,** Supplementary **Table 1**). The effect represented an approximate net 8.4% higher aBMD at the lumbar spine, 4.4% at the total hip and 3.7% at the total radius over placebo at 24 months in the zoledronic acid group. In contrast, the effect of zoledronic acid on the ultradistal radius, a predominantly trabecular site, was not significant, MAD 0.01 [0.00;003], p=0.19.

Consistent with the course of the markers (see below), the zoledronic acid group showed an increase in aBMD within the first 6 months of therapy, as seen at the spine (0.04, 95%CI [0.02; 0.06], p<0.001 over baseline), which was not maintained thereafter from 6 to 24 months (-0.02, 95%CI [-0.00; -0.04], p=0.008). At the total hip and total radius, aBMD in the zoledronic acid group remained unchanged over the first six months in the zoledronic acid group (total hip 0.00, [95%CI -0.01; 0.01], p=0.45), total radius 0.01, [95%CI -0.01; 0.02], p=0.33). However, controls experienced a progressive decline in aBMD at the spine over the course of the trial, (-0.08, 95%CI [-0.06; -0.10], p<0.001) (**Figure 3, Supplementary Table 1**).

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Bone remodeling markers

Bone remodeling markers C-telopeptide and P1NP diverged early between the zoledronic acid and placebo group, at 3 months -400 ng/L, [-483; -316], p<0.001, and -26 mg/L, [-38; -15], p<0.001, respectively. From 3 to 24 months, CTX increased by 204 ng/L, [117; 291], p<0.001, in the zoledronic acid group over placebo, while there was no significant between group change in P1NP (5.2 mg/L [-6.3; 16.7], p=0.49). Over 24 months, the markers remained significantly lower in the zoledronic acid group, compared to the placebo group (CTX -176 ng/l [-275; -76], p<0.001, P1NP -18 mg/L [-32; -5], p<0.001, **Figure 4, Supplementary Table 1**).

In the zoledronic acid group, markers were initially suppressed (3 months CTX -219 ng/L, [-259; -179], p<0.001 from baseline, P1NP -26 mg/L [-29; -22], p<0.001), before progressively increasing, with CTX exceeding baseline levels at 24 months (99 ng/L [34; 165], p=0.003) and P1NP returning to baseline (4.1 mg/L [-5; 13], p=0.36). In the placebo group, markers increased over 24 months, CTX 280 ng/L, [211; 350], p<0.001, P1NP 23, 95%CI [13; 32], p<0.001.

Sensitivity analysis

In a sensitivity per protocol analysis, HR-pQCT, DXA and bone remodeling marker outcomes were similar (data not shown).

Harms

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Adverse events are summarised in **Table 2**. There was a higher incidence of study drug-related adverse events in the zoledronic acid group compared with the placebo group, however there was no significant difference in serious adverse events or withdrawals due to adverse event.

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Discussion

In this two year RCT of men with non-metastatic prostate cancer newly commencing ADT, we report that a single dose of zoledronic acid treatment failed to protect against deterioration in bone microarchitecture despite producing a significant treatment effect on aBMD at all sites, with the exception of the ultradistal radius, compared to placebo. While remodeling remained significantly reduced over placebo, zoledronic acid produced only a transient suppression of bone remodeling markers.

The lack of a benefit in preventing microarchitectural deterioration, despite transiently preventing a decline in distal radial cortical vBMD, may be the result of bisphosphonates like zoledronic acid only slowing, not abolishing, unbalanced bone remodeling. Continued unsuppressed unbalanced remodeling persists and reduces both the mineralized bone matrix volume and deteriorates the microarchitecture of the declining bone volume despite treatment. Bone loss is likely to continue because bisphosphonates bind avidly to superficial matrix, zoledronic acid more so than the others [(19)], and fail to penetrate and distribute in high concentration in deeper cortical bone [(20)]; osteoclasts engulfing matrix relatively free of bisphosphonate or having low concentration of the drug continue to resorb bone [(21)].

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By contrast, aBMD measured using DXA, increased during the first 6 months of therapy at the spine and remained stable at the total hip. However, zoledronic acid did not prevent the decline in aBMD measured at the ultradistal radius, a predominantly trabecular site, compared to placebo. These changes are the net result of a prompt reduction in the number of new resorption cavities excavated while concurrently, the many more cavities excavated shortly before treatment refill, albeit incompletely. The matrix just deposited undergoes rapid primary, then slower secondary mineralization while the matrix deposited months earlier is less often remodeled and undergoes more complete secondary mineralization [22].

The slower secondary mineralization may account for the differences seen in aBMD of the spine and hip (measured by DXA) and total vBMD of the distal radius and tibia (measured by pQCT) because the spine and hip are measurements of a larger bone matrix volume than total vBMD of the distal radial metaphyses. The spine includes the posterior processes which account for more of the total bone mass than the vertebral body in women [23,24], the femur is largely cortical. The distal metaphyses have only a thin rim of cortical bone. Most of the early rise in aBMD is the result of rapid primary mineralization of osteoid deposited by many remodeling units generated in the weeks just before treatment only now (in early treatment) entering their formation phase. The slower process of secondary mineralization [21,22] occurs of bone matrix deposited well before treatment and during two years of treatment because this matrix is now less often remodelled.

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Remodeling markers are acutely suppressed by 80-90% within one month of administration of zoledronic acid then less so thereafter [25]. In our study, the first measurement was at 3 months following which the markers increased suggesting unbalanced remodeling settles at a higher steady state remodeling rate eroding the skeleton. As remodeling markers remained lower in zoledronic acid-treated men than controls, this may account for the slower decline in aBMD in the treated group than in the controls receiving ADT alone.

In previous studies zoledronic acid reduced bone remodeling and was effective in slowing the aBMD decline in men receiving ADT. A meta-analysis [26] identified 8 mostly small (median n=22, range 14-122) RCTs using zoledronic acid for the prevention of bone loss in men receiving ADT. RCT duration ranged from 12 to 36 months. Zoledronic acid at dosing intervals from 3-weekly to 12-monthly increased aBMD with a significant treatment effect of 8.1% at the lumbar spine, and of 4.5% at the total femur compared to placebo. Our aBMD findings are consistent with these published observations. However, the only study that assessed the effects of zoledronic acid treatment on bone microarchitecture using HR-pQCT was an open label study in 34 men undergoing kidney transplantation. No significant effects of zoledronic acid on cortical bone parameters were reported [27].

This study has several limitations. We only administered a single dose of zoledronic acid in this two year RCT. Therefore, the effects of zoledronic acid on men with pre-existing osteoporosis, or with repeated dosing, on bone microarchitecture may be different. While many studies suggest that the effects of testosterone on bone architecture are predominantly mediated

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by its metabolite estradiol [28] , we did not measure estradiol, nor was our study designed to address this hypothesis. A reduction in bone volume is not detected using DXA perhaps because mineralization of bone matrix less often remodeled obscures the declining bone matrix volume. Secondary mineralization may not obscure microstructural deterioration measured using HR-pQCT, perhaps because the volume of bone measured at a small region of interest is much less than measured at the spine and hip by DXA. In addition, mineralization may be less complete as matrix of thin trabeculae is more rapidly turned over. Consistent with this we did not find a treatment effect of zoledronic acid on aBMD of the ultradistal radius, a predominantly trabecular site. The discordant findings may also be the result of measurements being at different anatomical sites, which may respond differently to treatment with zoledronic acid. The non-significant findings on trabecular architecture in this RCT are concordant with our previous study reporting greater declines in cortical than trabecular bone during ADT[7]. However, a larger RCT will be required to assess the effects of zoledronic acid on trabecular and cortical bone, and will require methodology that accurately distinguishes trabecular from cortical bone. In this RCT, imaging was threshold-based, using standard Scanco analysis software. This method may incorrectly separate cortical from trabecular bone [29].

While HR-pQCT is not widely available, this technology is likely to improve fracture risk prediction in older adults [8-10]. We have previously shown, using HR-pQCT, that sex steroid withdrawal by means of ADT leads to marked microarchitectural decay [7]. This observation that sex steroids play an important role in the maintenance of bone microarchitecture not adequately detected by DXA has subsequently been confirmed in postmenopausal women

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receiving aromatase inhibitor therapy for breast cancer prevention, and again in this study, the severity of microarchitectural decay was markedly underestimated by DXA [30].

The implications for fracture outcomes are not addressed in our study. In a meta-analysis examining fracture outcomes in bisphosphonate RCTs in men with prostate cancer receiving ADT, relative fracture risk reduction with zoledronic acid was only 23%, indicating that a substantial proportion of men still fracture despite this treatment [31]. Moreover, this meta-analysis included men with metastatic disease, and the authors concluded that the observed fracture risk reduction was largely driven by a reduction in pathological disease-related fractures [31]. The true impact of zoledronic acid on fragility fracture outcomes in men receiving ADT remains unknown.

In contrast to bisphosphonates, denosumab distributes throughout the skeleton and more completely supresses bone remodeling than bisphosphonates [32]. Whether this translates to prevention of bone loss in men is unknown, but this has been demonstrated in women. Anti-fracture benefit in men with non-metastatic prostate cancer receiving ADT has been reported for denosumab [5], but a fracture benefit for bisphosphonates has not been established conclusively, due to the lack of adequately designed and powered RCTs examining fracture fractures as a primary endpoint.

In summary, acute sex hormone depletion using ADT or aromatase inhibitor therapy results in a rapid increase in unbalanced bone remodeling, greater than observed during advancing age

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in either sex and after menopause in women. We propose that this is a possible explanation for the inability of zoledronic acid to prevent microarchitectural decay of bone observed in this study but further research, particularly comparing the effects with those obtained using denosumab, a drug that suppresses remodeling throughout the skeleton are needed to further address this finding.

Zoledronic acid was well tolerated, with no difference in serious adverse events between group; as expected there was a higher incidence in acute phase reactions in the zoledronic acid group, and one case of zoledronic acid-associated uveitis. However, we found no evidence that a single dose of zoledronic acid, given at initiation of ADT prevents the sex steroid deprivation-associated decay of bone microarchitecture, despite the seeming preservation of aBMD. These findings suggest that a single dose of zoledronic acid over 2 years is ineffective in prevention the unbalanced bone remodeling and severe microstructural deterioration associated with ADT therapy. Whether more frequent dosing of zoledronic acid is more effective, will need to be addressed in future studies.

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Figure Legends

Figure 1. Consort flow diagram

Shown is the flow of participants assigned to zoledronic acid or placebo through each phase of the study, and the reasons for exclusion of participants following randomization.

Figure 2. Volumetric bone mineral density in zoledronic acid- and placebo-treated men

Shown are adjusted mean (95% CI) total (A – B), cortical (C – D) and trabecular (E – F) vBMD, measured by HR-pQCT at the radius and at the tibia in zoledronic acid- (ZOL, solid lines) and placebo- (P, dashed lines) treated men at baseline (month 0), and at 6, 12 and 24 months.

Figure 3. Areal bone mineral density in zoledronic acid- and placebo-treated men

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Shown are adjusted mean (95% CI) aBMD at the lumbar spine (A), total hip (B), total (C) and ultradistal radius (D) measured by DXA zoledronic acid- (ZOL, solid lines) and placebo- (P, dashed lines) treated men at baseline (month 0), and at 6, 12 and 24 months.

Figure 4. Bone remodelling markers in zoledronic acid- and placebo-treated men

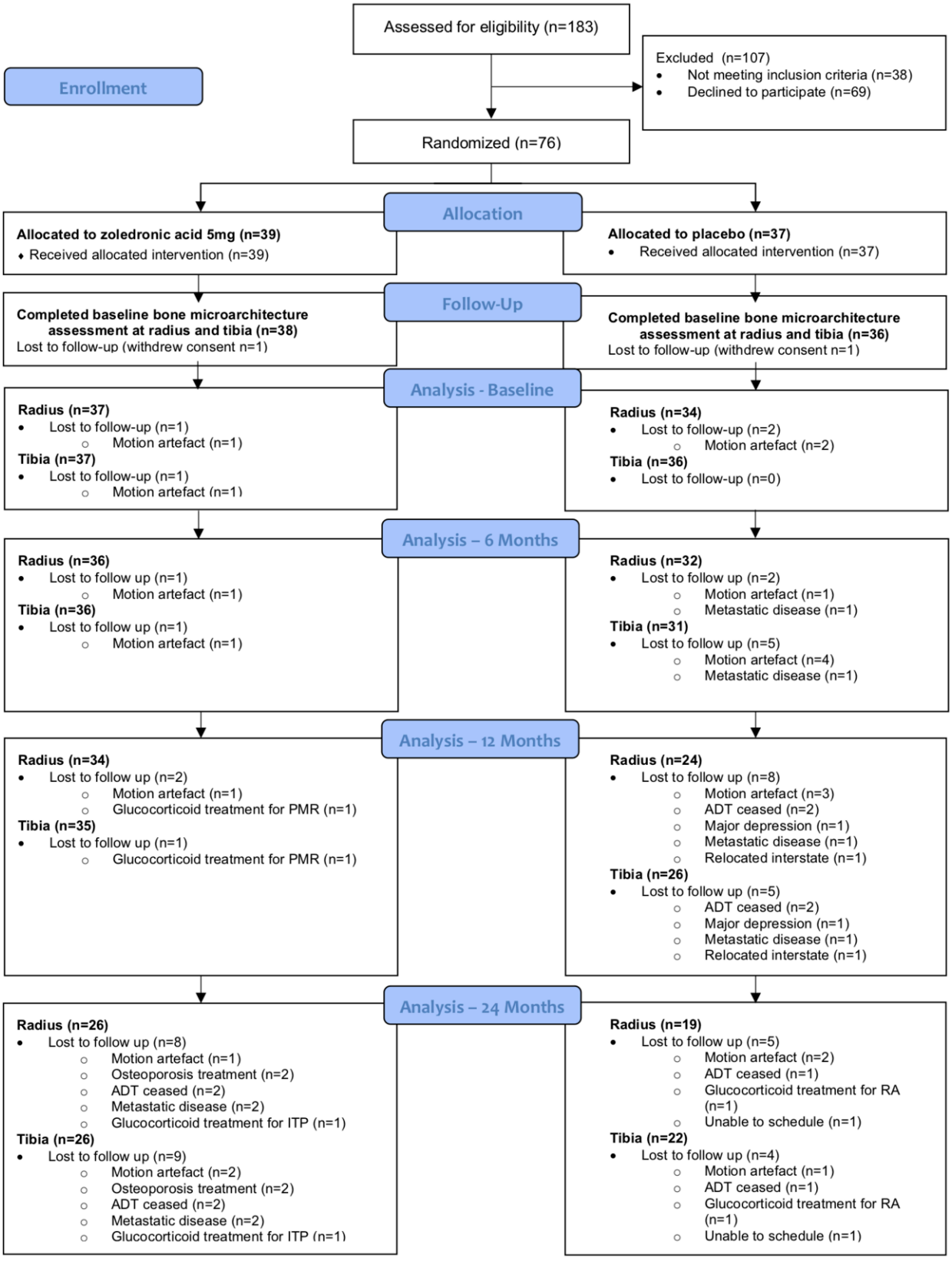
Shown are adjusted mean (95% CI) circulating P1NP (A) and CTX (B) concentrations in in zoledronic acid- (ZOL, solid lines) and placebo- (P, dashed lines) treated men at baseline (month 0), and at 3, 6, 12 and 24 months.

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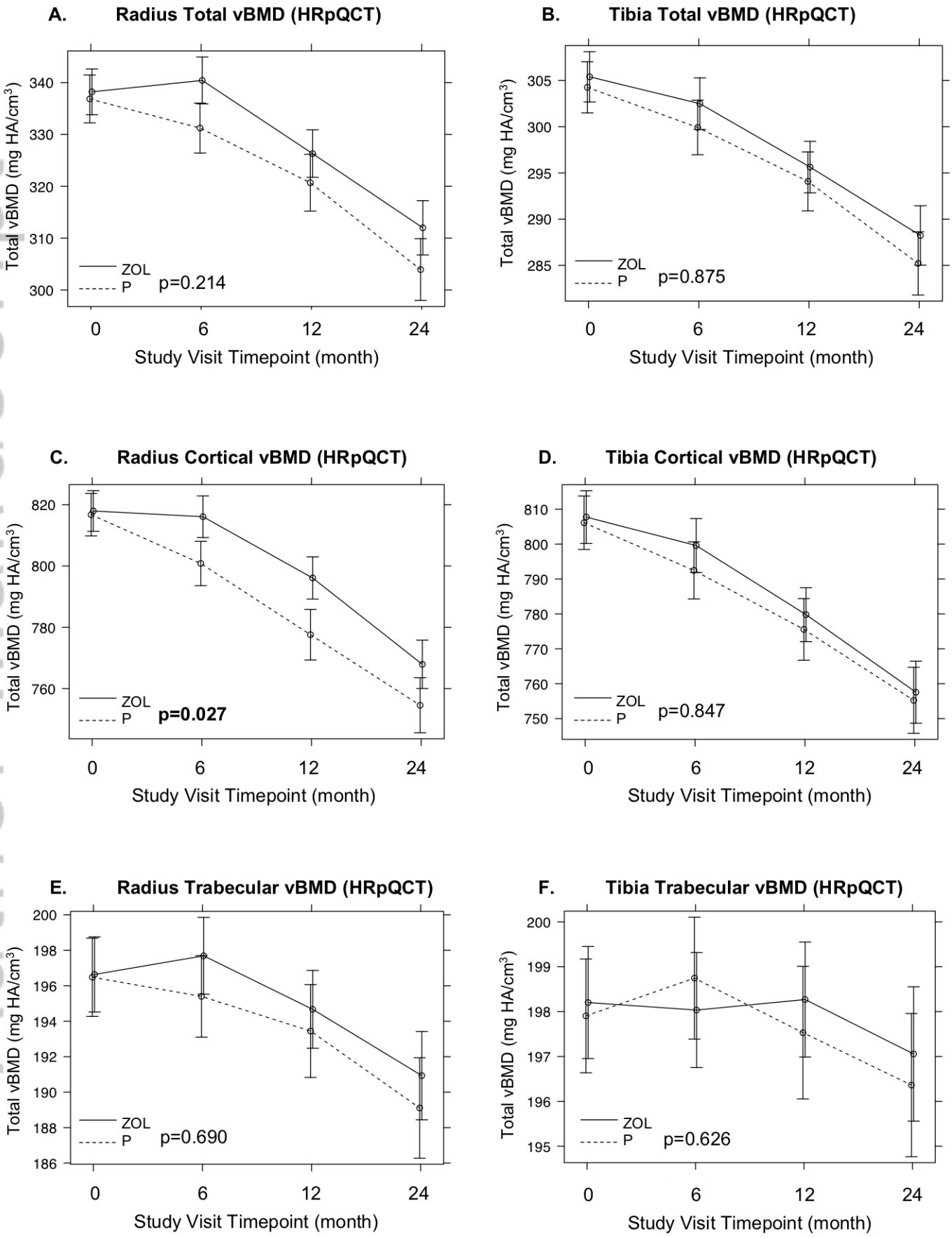
Figure 1. CONSORT Flow Diagram



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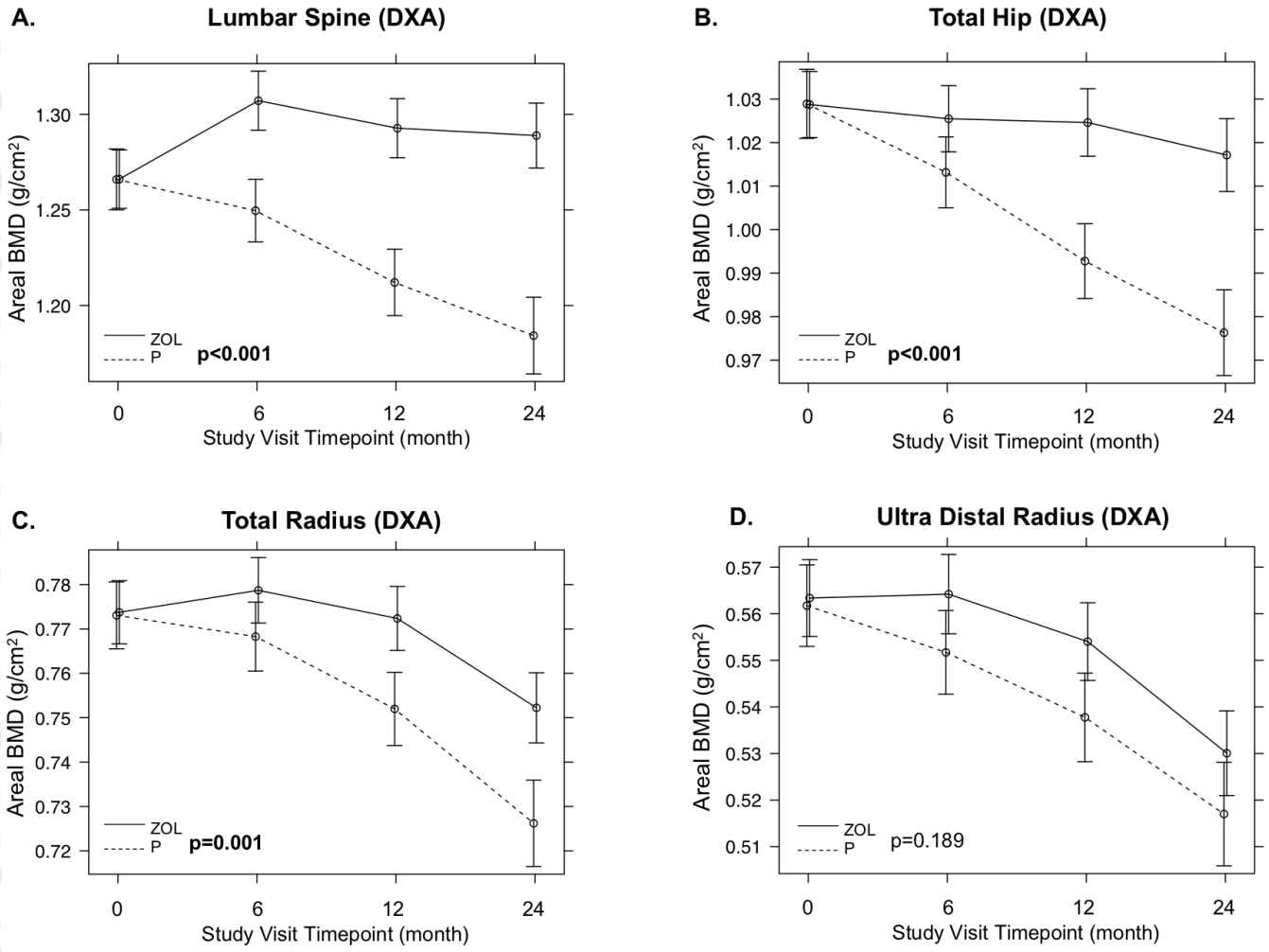
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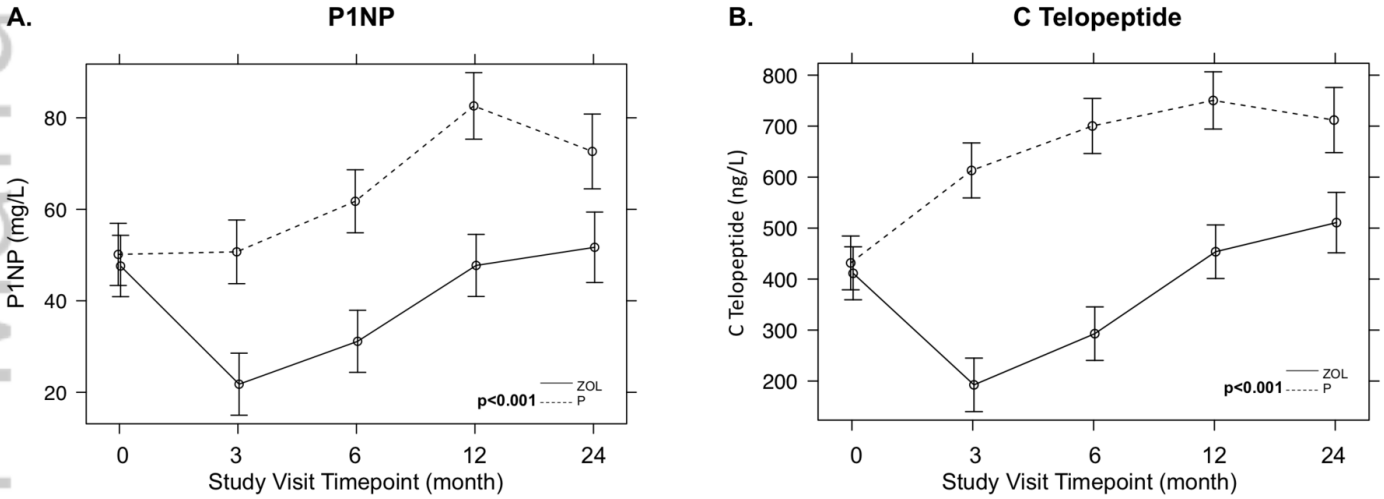
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Table 1 – Baseline participant characteristics

Characteristics	Zoledronic Acid Group	Placebo Group	P Value
Age (years)	68.8 [63.1;73.2]	67.5 [65.2;74.3]	0.62
Body mass index (kg/m^2)	28.8 [25.4;31.1]	27.9 [25.3;32.0]	0.92
Prostate cancer Gleason score	8.00 [7.00;9.00]	8.00 [7.00;9.00]	0.89
Serum total testosterone (nmol/L)	11.7 [7.90;17.5]	12.7 [6.85;18.3]	0.74
Prostate specific antigen (ug/L)	6.47 [0.17;18.8]	4.35 [0.25;15.8]	0.71
Concurrent radiotherapy treatment n(%)	33 (94.3%)	33 (94.3%)	1.00
Smoking status			0.69
Current	2 (5.4%)	4 (11.4%)	
Ex-smoker	16 (43.2%)	13 (37.1%)	
Never smoked	18 (48.6%)	18 (51.4%)	
Ethnic background			0.95
Caucasian	35 (100%)	38 (100%)	
Charlson medical co-morbidity index	2.00 [2.00;3.00]	2.00 [2.00;3.00]	0.62
Medical co-morbidities			
Ischaemic heart disease	10 (26.3%)	8 (22.9%)	0.94
Diabetes mellitus	7 (18.4%)	7 (20.0%)	0.98
Hypercholesterolaemia	17 (44.7%)	20 (57.1%)	0.41
Hypertension	19 (50.0%)	24 (68.6%)	o.17

Values are presented as median [interquartile range] or proportions N(%)

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Table 2 - Incidence of Adverse Events on Treatment

Adverse Event	Placebo Group (n=36) n (%)	Zoledronic Acid Group (n=38) n (%)	P value
OVERALL			
Any adverse event	22 (61%)	27 (71%)	0.46
Serious adverse event	11 (31%)	11 (29%)	1
Withdrawal due to adverse event	5 (14%)	6 (16%)	1
ADVERSE EVENT CATEGORIES			
Study drug-related^			0.002
Flu-like symptoms	8 (22%)	17 (45%)	
Anterior uveitis	0	1 (3%)	
Dermatitis	1 (3%)	0	
Tiredness	8 (22%)	11 (29%)	
Hepatitis	1 (3%)	0	
Leg swelling	1 (3%)	4 (11%)	
Cardiovascular	4 (11%)	3 (8%)	0.71
Prostate cancer progression	2 (6%)	1 (3%)	0.61
Autoimmune disease	1 (3%)	2 (5%)	1
Osteoporosis#	0	2 (5%)	0.49
Other malignancy	2 (6%)	0	0.23

*Study subjects who had at least one adverse event. ^Occurring within 7 days of infusion. #Requiring initiation of osteoporotic drug treatment. Serious adverse events were defined as death, hospitalization, disability, a life-threatening event, or a not immediately life-threatening but clearly of major clinical significance. Serious events included hepatitis, major depression, pancreatic cancer, non-small cell lung cancer, prostate cancer metastases to bone, diabetes mellitus, ischaemic heart disease, cardiac failure, arrhythmia (all occurring > 12 months after study drug administration), stroke, rheumatoid arthritis, anterior uveitis, immune thrombocytopenic purpura, polymyalgia rheumatica, deep vein thrombosis and fracture. Other adverse events included jaw pain, dizziness, abdominal pain, nocturia, arthralgias, and mood disturbance. The statistical difference between groups was determined using Fisher exact test. During the study, 2 fractures occurred, including a fragility neck of femur fracture (in the zoledronic acid group), and a traumatic tibia fracture who fell off a utility vehicle (in the zoledronic group – this man continued in the study). Two men in the zoledronic acid group commenced osteoporosis medication; one who had the fragility neck of femur fracture 18 months after zoledronic acid, and a second one who had a decrease in T score to <-2.5 18 months after zoledronic acid. No deaths occurred in either group during the period of follow-up.

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