A double blind controlled clinical trial to assess the efficacy of risendronate for the maintenance of alveolar bone in chronic adult periodontitis

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Introduction

Periodontitis is a multifactorial disease involving bacterial biofilms in a susceptible host. The results is an inflammatory response the latter cases the major part of the periodontal tissue breakdown. Alveolar bone resorption is a major component of the periodontal destruction observed in periodontitis. Treatment of periodontal disease has included antibiotics and antimicrobial and other novel treatment modalities such as non-steroidal inflammatory drugs (Jeffcoat 1995) to control and modulate the host response to bacterial aggression.

Drugs such as bisphosphonates (BPs) are proven antiresorptive agents that can potentially inhibit alveolar bone resorption in both animal studies (Weinreb, M, et al 1994, Buduneli, E. et al 2004,Menezes, A. M. et al 2005) and human studies (Rocha et al 2001,2004,Lane 2005,Jeffcoat, 2006). BPs are known as highly effective inhibitors of osteoclastic bone resorption that selectively affect osteoclasts (Hou et al 2003, Mc Cauley,et al 2002). They are world wildly used for the treatment of metabolic bone diseases with excessive bone resorption such as osteoporosis and Paget's disease, and other skeletal conditions. We therefore hypothesized that BPs may be efficacious when used in addition to scaling and root planning for slowing bone loss in periodontitis. This in turn may be may be an auxiliary to the management of periodontitis

Material and Methods

Study Design

This is a randomized placebo-controlled trial conducted in 69 patients with moderate to severe periodontitis. The study design is illustrated in figure 1. Subjects were randomized to the 35 mg per week risendronate (Actonel, Warner Chilcott) group or the placebo group. Drug therapy was administered in conjunction with conventional non-surgical periodontal treament. The primary woutcome was change in alveolar bone height. A secondary objective was to determine the safety of risendronate (Actonel), and noting any adverse event occurrence.

Study Population

. 70 Subjects were recruited from both advertisements and the University of Pennsylvania periodontal clinic. This study was approved by the University of Pennsylvania institution review board was conducted under the Food and Drug Administration guidelines for Good Clinical Practice. All study patients signed informed consent.

35 Subjects for each arm of the study who are at risk of alveolar bone loss within the age range of 18-70.years old. All subjects were in general good health. Female subjects must not be of childbearing

potential or must be using birth control or must have a negative pregnancy test at baseline and be using birth control.

All subjects with moderate to severe periodontitis defined on the basis of mean full-mouth CAL measurements were eligible for the study. Moderate periodontitis was defined as mean CAL loss ≥3 mm distributed in at least two posterior quadrants or in at least six teeth (not counting straight buccal and lingual surfaces and distal surfaces of the second molars). Presence of severe periodontitis defined as having at least two posterior teeth in each quadrant with alveolar bone loss of at least 3 mm and pockets depth of at least 5 mm.

Subject Exclusion Criteria included:

1. The Presence of generalized disease of bone (other than from chronic periodontitis), prior Bisphophonate use, calcitonin or paretartite treatment within one year prior to the start of the study.
2. Estimated daily calcium intake outside of the range of 400 -1500 mg elemental calcium per day or a major change in calcium intake (> 500mg/day)
3. Investigational new drug treatment within 6 weeks of entering the study. Antibiotic, systemic corticosteroids or immunosuppressive treatment within one month entering the study
4. Hypersensitivity or a severe adverse reaction to bisphophonates.

5. Medical conditions such as metabolic bone disease parathyoid, thyroid, Paget's disease, osteognesis imperfecta, osteomalacia, sustained hypertension, oesophagitis, reflux disease, peptic ulcers, ulcerative colitis, or any other condition making it inadvisable for the patient to participate in the study.

   Smoking history was recorded as " non-smoker," and "current smoker."

Conventional Periodontal Treatment

All subjects received conventional non-surgical treatment.

The conventional therapy consisted of full-mouth SRP at the baseline visit, oral hygiene and plaque control instructions, and periodontal maintenance visits at 3-month intervals. Fluoride toothpaste, dental floss and interpoximal brushes as well as good oral hygiene instructions were given

The maintenance visits included reinforcement of oral hygiene instructions, supragingival and subgingival SRP as needed, and removal of supragingival plaque and stain by coronal polishing.

Study Design:

(Refer to Table 1. Diagram 1)

Outcome Measures

Periodontal assessments. Standardized vertical bite-wing E speed (double film packs) radiographs were taken at baseline and at the 9-month follow-up visit. Clinical periodontal measurements were performed on six surfaces of each tooth (mesio-buccal, buccal, distobuccal, mesio-lingual, lingual, disto-lingual) at baseline and 6 and 9 months. Periodontal measurements included: CAL in mm, PD in mm, BOP scored as 0 for no bleeding and 1 for bleeding present, and Silness and Löe plaque index (PI) score ranging from 0 to 3 CAL(Silness and Löe 1964) assessment was performed throughout the study by two examiner

Radiographic methods. Standardized vertical bite-wings were taken the vertical bite-wings were scanned and digitized. The operator was masked to the group assignment (i.e., bisphosphonate or placebo). In each patient, a minimum of 3 and a maximum of eight interproximal sites were selected depending on the inclusion and exclusion criteria. For inclusion, interproximal sites of posterior teeth had to be clearly visible on sequentially taken bite-wing radiographs and interproximal sites had the two adjacent teeth present. Exclusion criteria were inability to clearly define a region of interest, and/or unreadable films due to technical problems. The quantitative method utilizes a variation of subtraction radiography. The subtraction image and the original radiograph are used in combination to permit: Isolation of the area(s) of bone change that have occurred beyond the “noise” of the subtraction image Superimposition of the area of bone change on the original radiograph to facilitate visualization of the region of change. The methodology corrected the brightness and contrast of each image to facilitate comparison over time. Assessment of the change in alveolar bone height was performed by projecting the region of bony change on the root surface.

Statistical Analysis

The Mean loss of bone height and bone density per randomized group was analyzed with Multivariate analysis of variance (MANOVA)

Results

They were 103 patients that signed an informed consent to enroll in this study. 27 were excluded before baseline visit, 3 withdrew before study assignment and 3 were pending (Figure 2). The remaining 70 were randomized, 35 in risendronate group, received Actonel 35mg/week for 6 months, 35 in placebo group. At this time 15 patients (177 site) from the risendronate group completed the 9 months trial and 10 (117 sites) in the placebo group.

Table 2 compares changes in alveolar bone height (Mean Differences Between Baseline and nine months in mm). When all the sites were analyzed, the risendronate group improved by 2.25 mm while placebo improved only by 1.76mm ($p<0.02$). When baseline CAL of more than 3.5mm was included the difference was 2.82mm for risendronate group, 2.18 mm for placebo group ($p< 0.01$). When baseline CAL of more than 4mm was included the difference was 3.85mm for risendronate, and 2.62 mm for placebo. ($p<0.004$). The difference was statistically significant ($p<0.05$) in all situations of CAL.

Table 3 describes the periodontal pocket depth (PPD) changes during the course of the study. No statistically significance was noted between both groups.

Table 4 a) describes the adverse events occurrence, No major or common side effect was noted in either groups during the course of the study. More importantly 0% of ONJ was noted .10 unrelated events were noted in the risendronate group (Prostate enlargment, Vaginal polyps, Broken ankle etc..) 2 unrelated events were noted in the placebo group (Tinning in ear, Flu.)

Discussion

This nine month study demonstrated the efficacy of bisphosphonates in improving outcomes of conventional non-surgical periodontal therapy. Bisphosphonates are analogues of pyrophosphates which localize to bone and inhibit osteoclast function, recruitment and activity. (Rezka 2003). Human studies have demonstrated the efficacy of oral BP's (Alendronate) in reducing bone loss in comparison to conventional scaling root planning therapy. (Rocha et al 2001,2004,Lane 2005,Jeffcoat, 2006). Rocha 2001 In a controlled double-blind, randomized study evaluated prospectively diabetic and established periodontitis patients paired by gender and years since diagnosis for 6 months. They were randomly allocated to alendronate (10mg/daily) or placebo treatment for 6 months. In type-2 diabetic patients, alendronate induced more improvement in alveolar bone crest height than control therapy.(1.3 ± 1.33 mm), a trend also observed by the same authors, Rocha (2004) on post-menopausal women with periodontitis treated with alendronate (10mg/day) for 6 months.

Lane et al (2005) in a randomized, double-masked, placebo-controlled study conducted in patients with chronic periodontitis evaluated the effect of bisphosphonate therapy as an adjunct to non-surgical periodontal treatment on a 12 months period using alendronate at 10 mg/day) or risedronate 5 mg/day plus calcium citrate at 1,000 mg/day and vitamin D3 at 400 IU per day and found an improvement in CAL, PD, and BOP relative to placebo in patients. Jeffcoat (2006) in a double blinded placebo controlled

prospective study, tested the effect of alendronate (70mg/weekly)vs placebo on alveolar bone height on a 2 years period; Found a significant increase in Alveolar bone height in the BP group with normal bone mineral density values. Furthermore, in study 2 of the same report (Jeffcoat 2006), the authors followed 210 implants on a period of 3 years on 50 patients receiving either BP therapy or placebo (equally matched). The present study has demonstrated the efficacy of bisphophonates in improving CAL and further advancement of periodontal disease relative to placebo in patients with chronic periodontitis. The statistically significant improvement was similar to the other human clinical trials.(Rocha et al 2001,2004,Lane 2005,Jeffcoat, 2006)

No evidence of osteonecrosis of the Jaw (ONJ) was noted in any of the cases. Jeffcoat 2006 concluded that oral bisphophonates are beneficial to use to protect individuals from periodontal bone loss and osteoporosis and most importantly the study demonstrates the absence of ONJ in a large multicenter study population. Similarly Fugazzotto et al 2007 Patients with a history of oral bisphosphonate therapy of various durations were treated with implant placement and restoration or tooth extraction, immediate placement, and restoration. These patients were followed for 12 to 24 months after implant placement. .No osteonecrosis was noted immediately postoperatively or during the follow-up period in 61 patients. On the same note, Koka et a 2010, in a retrospective analysis of implants place in post-menauposal woman, ONJ was not observed consequent to implant placement in any of the bisphosphonate users or non-users. In non-users, 163 out of 166 implants were surviving for a cumulative survival rate of 98.19%. In bisphosphonate users, 120 out of 121 implants were surviving for a cumulative survival rate of 99.17%.

Also, a retrospective study was performed in a patient-level database of over 55 million lives and 70 US health plans from 2000 to 2006. Patients with a diagnosis of osteoporosis were categorized based on BP use (IV, oral, or none). Continuous enrollment for at least 6-months pre- and post-index diagnosis was required. The primary outcome was ONJ. Adjusted odds ratios (OR) were calculated controlling for patient demographics, and defined comorbidities. In the three randomized controlled clinical trials the incidence of ONJ was 0% in the BP group and in the placebo group (NS). The retrospective database study identified 423,845 BP treatment-naïve (control) patients, 213, 364 taking oral BPs and 2,321 taking IV BPs. Oral BPs were not associated with increased odds of ONJ relative to the control group where patients utilizing IV BPs were associated with significantly greater adjusted odds of ONJ.

Conclusion:

Oral bisphophonate administration with the concomitant non-surgical (scaling root planning) therapy has been proven to be clinically effective in the management of adult chronic periodontal disease. This in turn is an auxiliary to the management of periodontitis. These results were in agreement with similar controlled human studies. The authors will be looking in the difference in bone density around periodontally involved teeth, in part 2 of this trial.

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Figure 1 a). Study Design

	Recruitment	Baseline	3 Months	6 Months	
History	X		X	X	
Periodontal screening	X	X			
Randomization			X		
SRP		X			
Xray		X	X	X	
Periodontal exam		X	X	X	
Safety Evaluation		X	X	X	
Assessment of the need of additional periodontal therapy					

Figure 1 b) Study Design

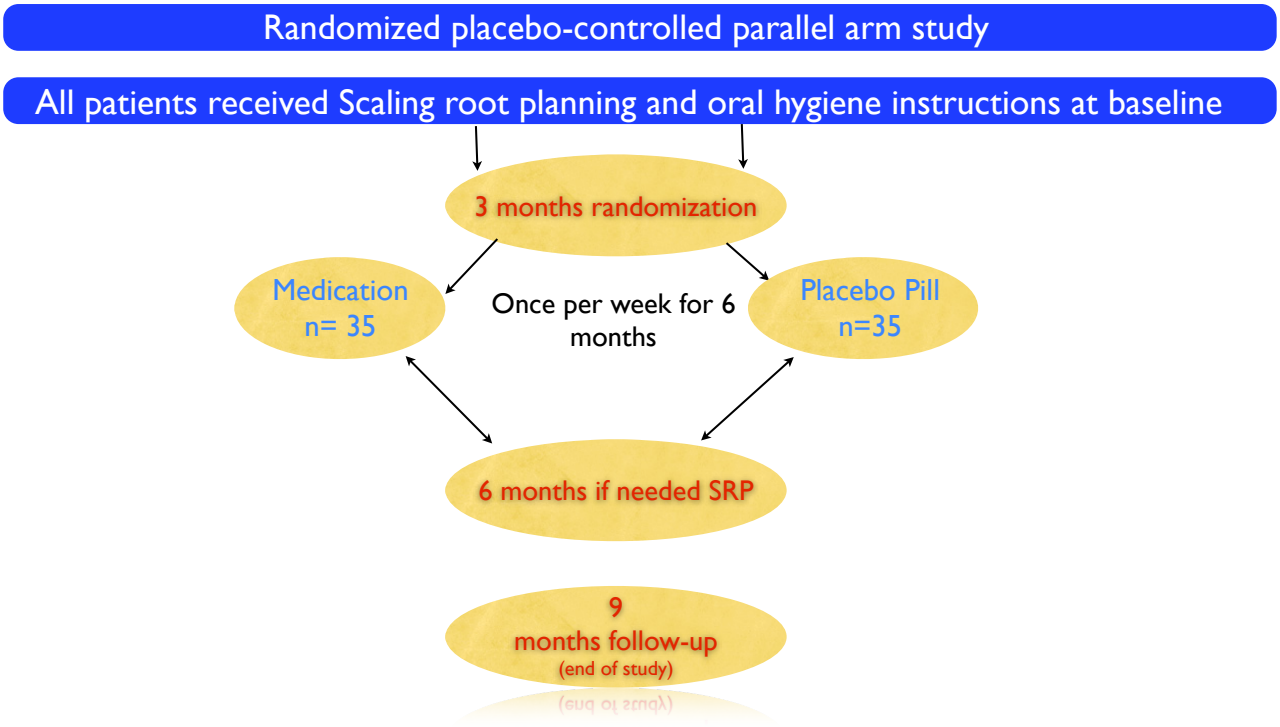

Table 1: Comparison between groups (Patients who completed Study)

	Risendronate group	Placebo Group
Mean age	49.67(±12)	45.2 (±11)
Female	7	3
Male	8	7
Smokers	4	0
Mean Bone Loss Baseline	4.30 mm (±1.53)	3.52mm(±1.00)
Mean PPD Baseline	3.23 mm (±1.35)	3.23mm (±1.29)

Figure 2: Consort Diagram

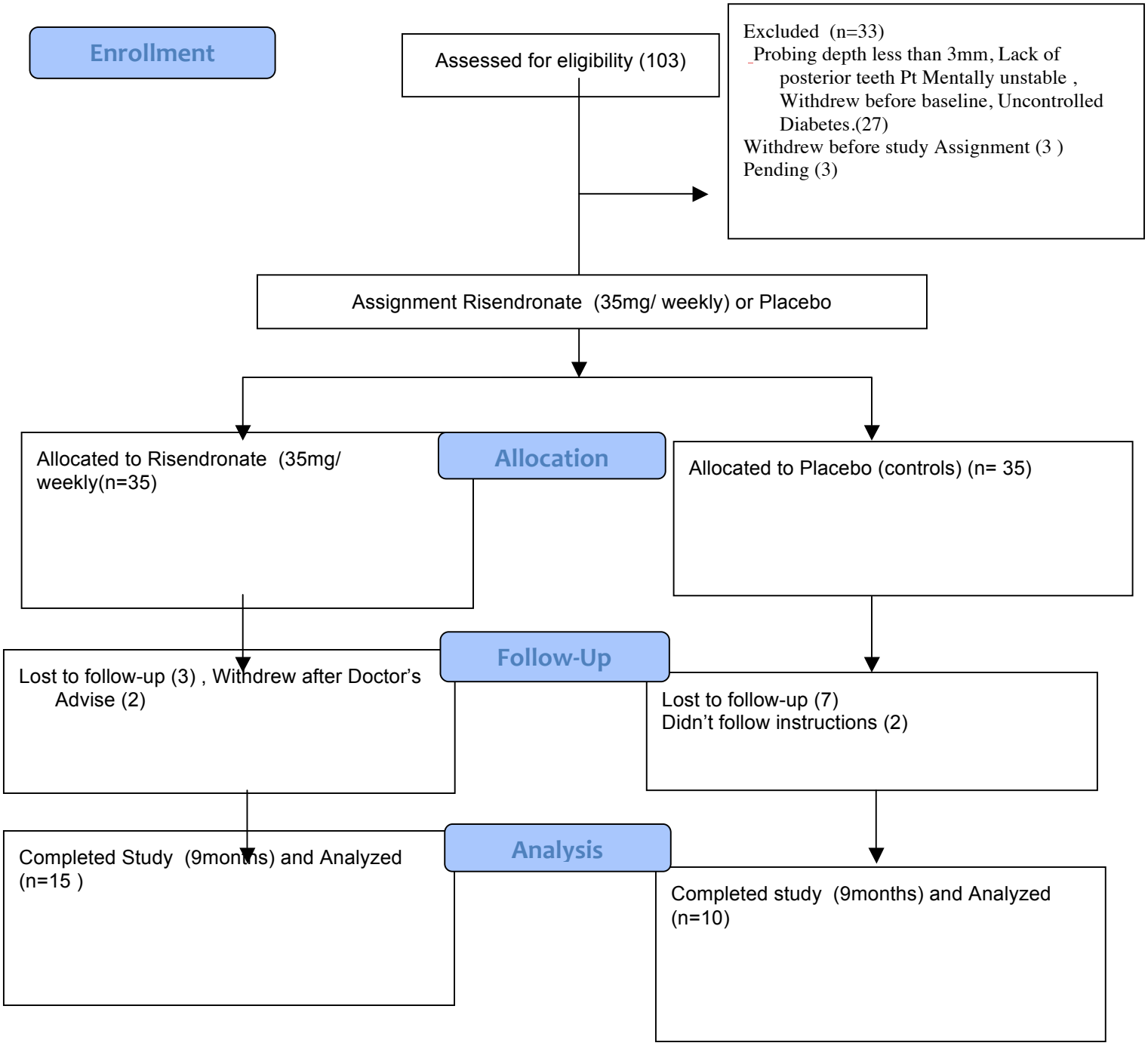

Table 2: Changes in Alveolar Bone Height (Mean Differences Between Baseline and nine months in mm)

	Risendronate	Placebo	F	P
4mm at base	3.85	2.62	9.9	0.004
3.5mm at base	2.82	2.18	6.74	0.011
All Sites	2.25	1.76	5.46	0.02

Figure 3. Mean differences of Alveolar bone height change (in mm).

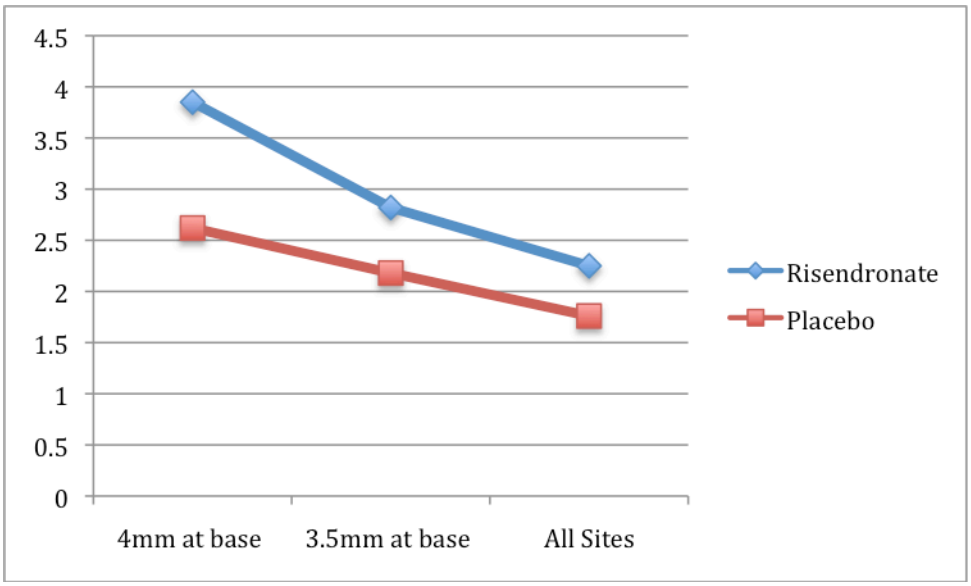

Table 3. Changes in PPD during the study.(in mm)

	PPD	SD
Risendronate Group 0 Month Mean	**3.2363**	**1.3594**
RisendronateGroup 3 Month Mean	**3.0649**	**1.3037**
Risendronate_Group 9 Month Mean	**2.9184**	**1.1238**

	PPD	SD
Test_Group 0 Month Mean	**3.2349**	**1.2958**
Test_Group 3 Month Mean	**3.0279**	**1.4049**
Test_Group 9 Month Mean	**3.0785**	**1.3511**

Figure 4. Mean changes in PPD during the study (mm)

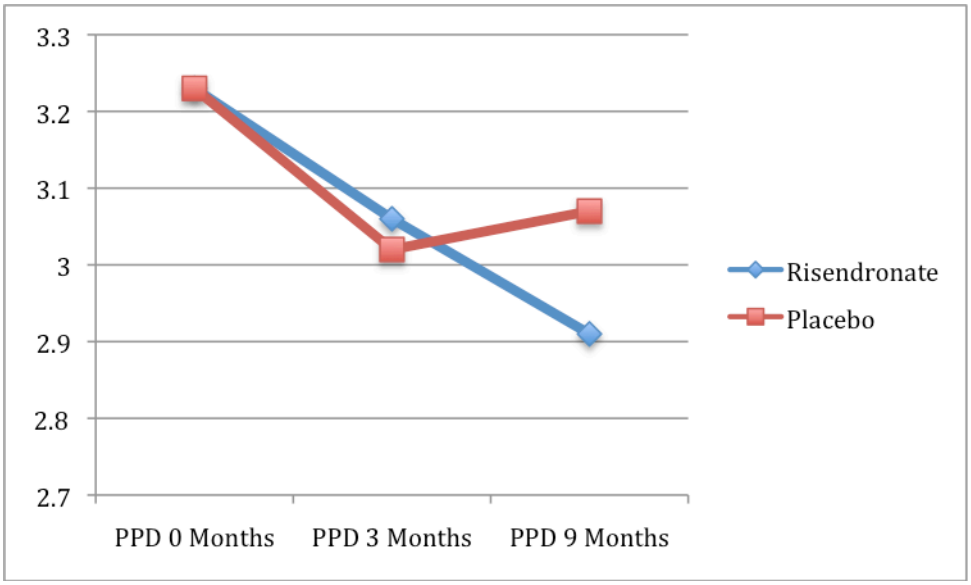

Table 4a) : Adverse Events

	Risendronate Group	Placebo Group
ONJ	0	0
GI disturbance Upper	0	0
GI disturbance Lower	0	0
Cardiovascular	0	0
Endocrinology	0	0
Rheumatology	0	0
Infections	0	0
Neurological	0	0
Unrelated (Enlarged prostate, vaginal polyps)	2	0
Unrelated Iron deficiency	1	0
Unrelated Infections (Bronchitis, Flu,)	2	1

Table 4 b): Severe Adverse Events

	Risendronate Group	Placebo Group
Death	0	0
Hospitalized (not planned)	0	0
Cancer	0	0