

Reclast<sup>®</sup> (zoledronic acid) Injection

**FDA Joint Reproductive Health Drugs Advisory Committee  
and Drug Safety and Risk Management Advisory  
Committee Meeting on the long term use of  
bisphosphonates for the treatment and prevention of  
osteoporosis**

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**List of abbreviations**

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AE	Adverse Event(s)
ASBMR	American Society for Bone and Mineral Research
BMD	Bone Mineral Density
BP	Bisphosphonate(s)
BSAP	Bone Specific Alkaline Phosphatase
BTM	Bone Turnover Marker(s)
CI	Confidence Interval
CT	Computed Tomography
$\beta$ -CTX	C-terminal telopeptide of Type 1 collagen
FDA	Food and Drug Administration
FN	Femoral Neck
FPPS	farnesyl diphosphate synthase
GI	Gastrointestinal
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NNT	Number Needed to Treat
NNH	Number Needed to Harm
ONJ	Osteonecrosis of the Jaw
OP	Osteoporosis
P1NP	n-terminal propeptide of type 1 collagen
PBO	Placebo
PMO	Post-menopausal osteoporosis
pt-yrs	patient-years
SAE	Serious Adverse Event(s)
USPI	United States Prescribing Information

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## 1 Executive Summary

- There are 44 million women and men with osteoporosis (OP) and osteopenia in the US. This population has an increased risk for OP-related fractures which have significant associated morbidity and mortality. OP related fractures are estimated to cost over \$17 billion annually.
- Reclast<sup>®</sup> (zoledronic acid) for infusion, marketed by Novartis Pharmaceuticals Corporation (Novartis), is a third generation bisphosphonate (BP) approved for the treatment and prevention of OP, and the treatment of Paget's Disease of the bone. In OP, intravenous (i.v.) infusion of 5 mg annually provides a durable antiresorptive effect with beneficial effects on fracture risk reduction, increases in bone mineral density (BMD) and markers of bone turnover.
- Reclast is effective in the treatment and prevention of OP.
  - Reclast treatment has been shown to provide significant reductions in morphometric vertebral (70%) and hip fracture (41%), in addition to non-vertebral (25%), clinical (33%), and clinical vertebral (77%) fractures in postmenopausal osteoporotic women over a 3 year course of therapy.
  - In osteoporotic women treated for 3 years with Reclast, 3 years of additional therapy (6 years in total) resulted in a statistically significant increase in femoral neck (FN) BMD and a 49% reduction in the risk of new morphometric vertebral fractures compared with women who stop Reclast therapy after 3 years, suggesting that the protective effect against osteoporotic fractures may persist.
  - Post-hoc analyses of patients treated for 6 years with Reclast provide information on subgroups that may benefit most from continued therapy (hip OP, T-score  $\leq$  -2.5; or a new vertebral fracture while on therapy).
- The long-term safety profile of Reclast therapy (up to 6 years) has been established through evaluation in controlled clinical trials and in post-marketing pharmacovigilance; including evaluation of skeletal events of interest (osteonecrosis of the jaw [ONJ] and atypical subtrochanteric femur fracture). Current labeling describes the reported and potential risks with Reclast therapy and provides recommendations to practitioners regarding continued therapy.
- While treating physicians have the option to interrupt therapy in individual cases based on a benefit/risk evaluation, there is no evidence to support a blanket recommendation of a drug holiday for all patients who receive Reclast therapy. Decisions to continue or interrupt Reclast therapy should be made on a patient-specific basis with consideration of clinical factors and BMD or bone turnover markers (BTM) to guide decision making.

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## 2 Introduction

The Food and Drug Administration (FDA) has convened a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee to “discuss the benefits and risks of long-term bisphosphonate use for the treatment and prevention of osteoporosis, in light of the emergence of the safety concerns of osteonecrosis of the jaw and atypical femur fractures that may be associated with the long-term use of bisphosphonates.” The sponsors of the currently marketed BP products for OP have been invited to participate. Novartis was asked to provide responses to questions posed by the FDA:

- Provide an opinion and discussion of whether the efficacy and safety data support a long-term duration of use (i.e., > 3 years) for Reclast (zoledronic acid) Injection.
- Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment.

This document presents efficacy and safety data from the Reclast post-menopausal osteoporosis (PMO)/osteopenia development program to inform the benefit-risk assessment of Reclast, in the context of the available information on ONJ and atypical subtrochanteric femur fractures from clinical trials and post-marketing surveillance. These data will form the basis of Novartis responses to the questions posed.

### 2.1 Osteoporosis and Osteopenia

OP is a chronic, progressive disorder in which bone resorption exceeds formation, resulting in decreased bone mass and deterioration of the microarchitecture of bone. This results in decreased bone strength and increased susceptibility to fracture. OP is a silent disease until it is complicated by fractures ([NIH 2001](#)).

In the United States, approximately 10 million Americans have OP and another 34 million have low bone mass (osteopenia) and are at risk of developing OP; 80% of these are women. Women with low bone mass have an increased fracture risk (compared with those with normal bone density) unless bone loss is prevented ([NOF 2010](#)).

Over 2 million osteoporotic fractures are reported each year, which is greater than the annual incidence of heart attack, stroke, and breast cancer, combined ([NOF 2008](#), [AHA 2008](#), [ACS 2008](#)). Fractures related to OP will affect approximately 1 of every 2 women and 1 of every 5 men over the age of 50 in the United States. The most common fractures are those of the spine, hip and wrist. Hip fractures result in 10 to 20 percent excess mortality within one year. Over half of women who sustain a hip fracture do not return to their previous functional state and become dependent on others for their daily activities ([Bentler 2009](#), [Cauley 2000](#)). Additionally, hip fractures are associated with a 2.5 fold increased risk of future fractures. Mortality is also increased following spine fractures, which can cause significant complications including back pain, height loss and kyphosis. Multiple thoracic fractures may result in restrictive lung disease, and lumbar fractures may alter abdominal anatomy, leading to abdominal pain, distention and constipation ([NOF 2010](#)).

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Annual US direct medical costs associated with new osteoporotic fractures are over \$19 billion. By the year 2025, these costs are projected to rise by as much as 50%, to over \$25 billion, reflecting an increase in the US population of persons aged 50 years and over (NOF 2010).

Over the past two decades, BP drugs have assumed a significant role in the prevention and treatment of OP because of their demonstrated ability to increase BMD and reduce the risk of fractures and their associated morbidity and mortality.

## 2.2 Reclast (zoledronic acid)

Intravenous Reclast as an annual infusion was developed to offer the opportunity for improved compliance, without the potential for gastrointestinal (GI) irritation associated with oral BP.

Reclast is a third generation BP with a high binding affinity for human mineralized bone. Like other BP, Reclast binds to all bone surfaces with the greatest deposition on surfaces which are in the process of mineralization at the time of infusion. Reclast, as an i.v. infusion, is administered at a lower dose than oral BP (e.g., 70 mg alendronate weekly) where only about 1% of the drug enters the blood stream after each dose due to poor GI absorption (Fosamax<sup>®</sup> United States Prescribing Information [USPI] 2011). After i.v. infusion, peak Reclast blood levels occur at the end of the infusion period followed by a rapid decline in circulating concentrations to <1% of peak levels by 24 hours after dosing. Mean urinary excretion of unmetabolized Reclast is 39% over the 24 hours following infusion, indicating that approximately 61% of the Reclast dose is deposited on the bone surfaces within 24 hours (Reclast USPI 2011).

Delivery of the full annual dose (5 mg) at one time supports a rapid onset of the antiresorptive effect, while the systemic exposure to Reclast at biologically relevant concentrations is limited to a window of approximately 24 hours following annual infusion. With oral BP it may take weeks or months to achieve similar coverage of the bone compared to i.v. Reclast administration (Saag 2007).

Following deposition in the mineralized matrix, BP exert a long-term effect on bone resorption (Fosamax USPI 2011, Actonel<sup>®</sup> USPI 2011, Boniva<sup>®</sup> USPI 2011). During the process of bone resorption, BPs are internalized by fluid-phase endocytosis by the osteoclasts (Thompson 2006, Coxon 2008). Within the osteoclast, BP inhibit the enzyme, farnesyl diphosphate synthase (FPPS), which reduces bone resorption by the osteoclasts and promotes their apoptosis (Russell 2007). The process of bone remodeling represents the main mechanism by which BP are eliminated from the skeleton. The antiresorptive effect of Reclast (and other BP) persists while sufficient drug is left on the bone surface to inhibit osteoclast function whenever bone resorption is initiated. As a result, the duration of the bone-protective effect of Reclast and other BP in a given patient depends on the intensity of bone turnover (bone remodeling), with higher bone turnover resulting in more rapid clearance of the BP and thus a shorter duration of action (Russell 2008).

Based on biomarkers of bone resorption (serum C-terminal telopeptide of Type 1 collagen [ $\beta$ -CTx]) and bone formation (serum n-terminal propeptide of type 1 collagen [P1NP] and bone specific alkaline phosphatase [BSAP]), an infusion interval of 1 year for the 5 mg dose

appears to be appropriate for most postmenopausal osteoporotic patients to maintain the biomarkers of bone turnover within the pre-menopausal range (Black 2007). For postmenopausal patients who are osteopenic, an infusion interval of every other year is recommended due to persistent increases in BMD and changes in BTM beyond 1 year (McClung 2009). It is important to note, however, that once bound to bone, all BP have a long duration of effect (Fosamax USPI 2011; Actonel USPI 2011; Boniva USPI 2011).

Reclast was approved for the treatment of postmenopausal OP in 2007. For this indication it is administered annually as a 5 mg i.v. infusion.

Currently, Reclast is approved in the US for the following indications.

- Treatment of Paget’s disease of bone in men and women (approved 16-Apr-2007)
- Treatment of OP in postmenopausal women (approved 17-Aug-2007)
- Treatment to increase bone mass in men with OP (approved 19-Dec-2008)
- Treatment and prevention of glucocorticoid-induced OP in patients expected to be on glucocorticoids for at least 12 months (approved 13-Mar-2009)
- Prevention of OP in postmenopausal women (approved 29-May-2009)

Zoledronic acid, the active ingredient in Reclast, is also approved as Zometa<sup>®</sup> with a different dose and dosing regimen for use in advanced cancer indications. As the Zometa data does not inform the benefit/risk of Reclast for OP/osteopenia, the Zometa clinical data in cancer patients will not be reviewed in this Briefing Book.

### 3 Efficacy in Reclast Clinical Trial Program for Postmenopausal Osteoporosis and Osteopenia

Supportive data to address the questions posed by the FDA are taken from completed phase III and IIIb trials in adult patients with PMO, incident hip fracture, and osteopenia (summarized Table 3-1).

**Table 3-1** Summary of supportive efficacy and safety data from completed studies

Study	Population	Duration	Primary Objective	Number of Subjects (ITT)
Pivotal Fracture Trial (H2301)	Osteoporotic postmenopausal women	3 years	Reduction of morphometric vertebral and hip fracture	7736 ZA: 3875 Placebo: 3861
Pivotal Fracture Trial Extension 1 (H2301E1)	Osteoporotic postmenopausal women	3 years	% change in femoral neck BMD at Year 6 relative to Year 3	2456 Z6: 616 Z3P3: 617 P3Z3: 1223
Recurrent Fracture Trial (L2310)	Osteoporotic women and men with an incident hip fracture	Event driven: 5 years with a mean follow up of 1.9 years	Reduction of clinical fractures after hip fracture	2127 ZA: 1065 Placebo: 1062
Prevention of Bone Loss (N2312)	Postmenopausal women with	2 years	% change from baseline in lumbar spine BMD	581 ZA: 379

Study	Population	Duration	Primary Objective	Number of Subjects (ITT)
	osteopenia			Placebo: 202
ZA: zoledronic acid (Reclast); Z6: patients treated with ZA for up to 6 years; Z3P3: patients treated with 3 years of ZA followed by 3 years of placebo; P3Z3: patients treated with 3 years of placebo followed by 3 years of ZA				

### 3.1 Reclast Pivotal Fracture Trial in postmenopausal osteoporosis (H2301)

Women with PMO are at a markedly increased risk for fractures of the spine, hip and wrist. Prevention of these fragility fractures is the goal of OP therapy. The Pivotal Fracture Trial Study (H2301) investigated the efficacy and safety of Reclast compared with placebo (PBO) in reducing vertebral and hip fractures over 3 years in PMO patients. The results of this trial have been published in the New England Journal of Medicine (Black 2007) and serve as the basis of the approved labeling for the treatment of PMO.

This trial was a 3-year multicenter, randomized, double-blind, PBO-controlled trial in women with PMO. A total of 7736 women were enrolled in 27 countries. Patients were randomly assigned to receive Reclast or PBO infusions annually for 3 years in addition to daily oral calcium and vitamin D.

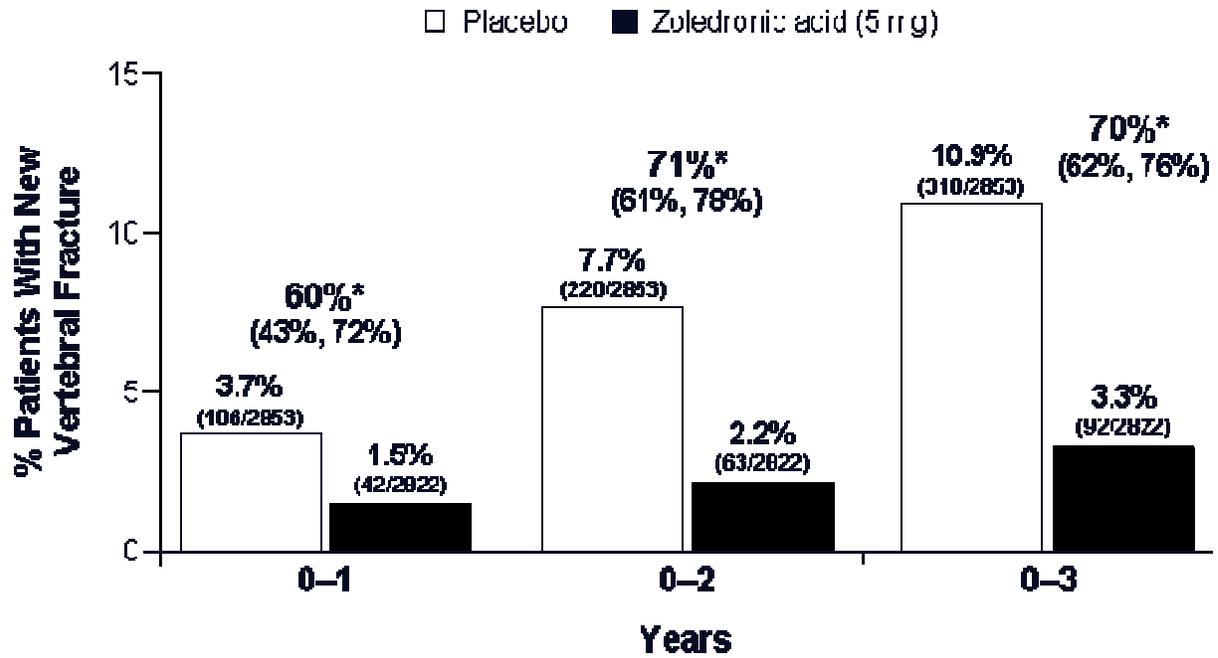
Postmenopausal women between the ages of 65 and 89 with a BMD T-score of -2.5 or less at the Femoral Neck (FN) (with or without evidence of a previous vertebral fracture), or a T-score of -1.5 or less with radiologic evidence of a previous vertebral fracture were studied. The primary efficacy endpoints were new vertebral fractures and hip fracture. Secondary endpoints included non-vertebral fractures, changes in BMD and changes in BTM (P1NP,  $\beta$ -CTx, and BSAP).

Treatment with Reclast was found to reduce the risk of morphometric vertebral fracture (fractures identified by measurement of vertebral height on spine radiograph) by 70% during a 3-year period as compared to PBO (3.3% in the Reclast group vs. 10.9% in the PBO group) (Figure 3-1), and reduced the risk of hip fracture by 41% (1.4% in the Reclast group vs. 2.5% in the PBO group) (Figure 3-2). Non-vertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively ( $p < 0.001$  for all comparisons) compared with PBO group (Figure 3-2).

The number of fractures prevented per 100,000 patient-years (pt-yrs) of treatment with Reclast based on these findings is 2533, 1467 and 367 for morphometric vertebral fracture, any clinical fracture and hip fracture, respectively. The number of patients needed to treat (NNT) to prevent 1 fracture with 3 annual infusions was 13.2, 22.7 and 90.9 for morphometric vertebral fracture, any clinical fracture and hip fracture, respectively (Data on File).

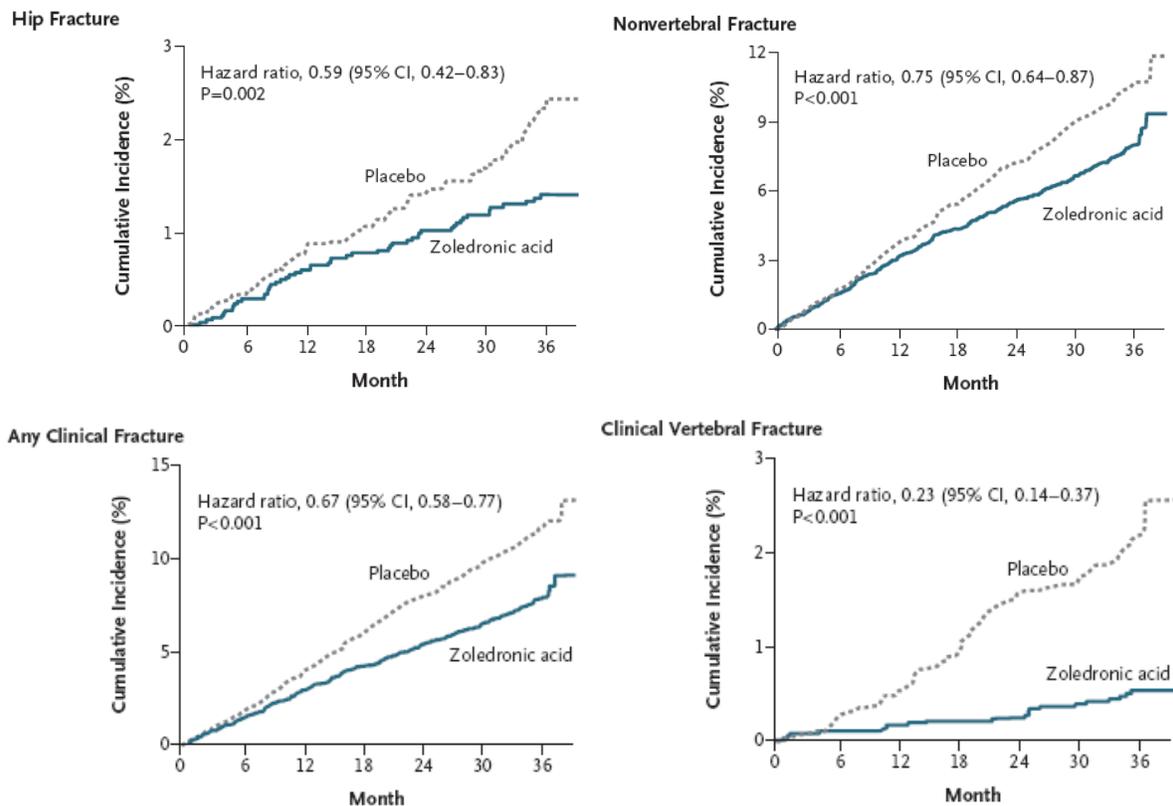
BMD and markers of bone turnover were assessed as surrogate markers of efficacy. Reclast was associated with a significant improvement in BMD. Total hip, lumbar spine and FN BMD increased significantly by 6.0%, 6.7%, and 5.1%, respectively, compared with PBO ( $p < 0.001$  for all comparisons). All 3 biochemical markers of bone turnover decreased significantly in patients in the Reclast group as compared with those in the PBO group ( $p < 0.0001$  for all comparisons), and importantly, the mean values remained within the premenopausal reference range over the 3 year treatment period.

Figure 3-1 Effect of zoledronic acid treatment on the risk of vertebral fractures – Study H2301 (mITT<sup>†</sup>)



<sup>†</sup> mITT included all ITT patients who were evaluable for incident vertebral fractures over the period being analyzed. \*Relative fracture risk reduction (CI)

Figure 3-2 Effect of zoledronic acid treatment on the risk of hip and other clinical fractures over time – Study H2301 (ITT)



In patients with OP treated with antiresorptive agents, reduction in bone turnover can explain part of the observed fracture risk reduction. Lower levels of BTM have been associated with a lower risk of fracture in BP-treated patients. The association between changes in BTM and fracture incidence was assessed in 1132 patients who had P1NP measurements at baseline and 1 year as part of this Pivotal Fracture Trial. In this post hoc analysis, annual injections of Reclast reduced markers into the premenopausal reference range, with a significant response persisting after the third infusion. Clinical fracture risk at 3 years was lower in those with lower levels of P1NP at 1 year. Furthermore, there was no association between low P1NP levels at 1 year and increased fracture incidence (Delmas 2009).

### 3.2 Reclast Pivotal Fracture Trial Extension up to 6 years (H2301E1)

The Reclast Pivotal Fracture Trial study was extended to 6 years, to investigate the long-term effects of Reclast in women with PMO through assessment of the surrogate marker BMD and secondarily on fracture risk reduction.

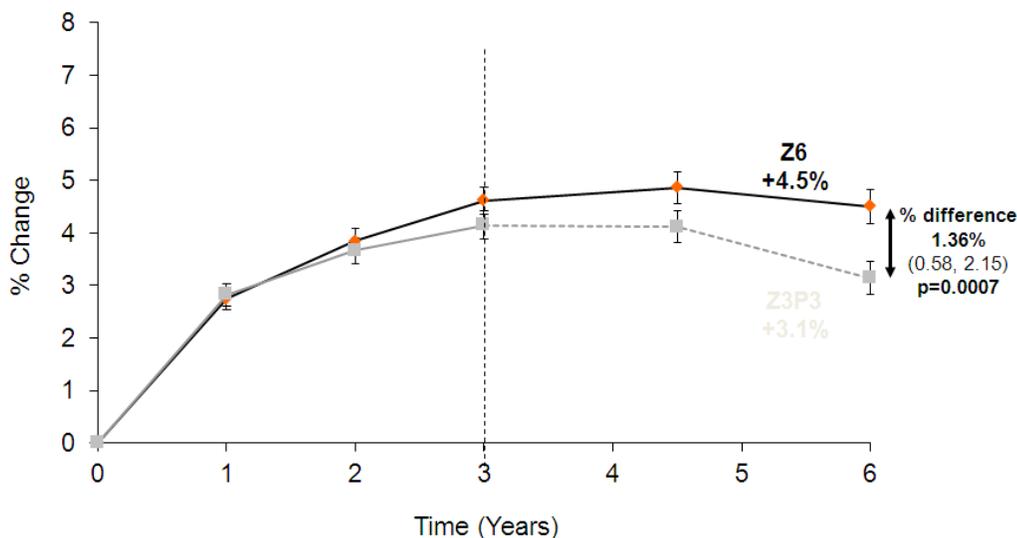
1233 women who received Reclast for 3 years in the Core study (H2301) were re-randomized to blinded treatment with Reclast or PBO for an additional 3 years (zoledronic acid up to 6 years: Z6, n=616; 3 years of zoledronic acid followed by 3 years of PBO: Z3P3, n=617). In order to retain the blind of the Core study, patients who had received PBO for 3 years during the Core study were assigned to receive Reclast in the extension study (P3Z3, n=1223). As

the pre-planned analysis of this study was designed to assess the difference between the Z6 and Z3P3 groups, and as the P3Z3 group was not a randomized study population, only the data for the two randomized treatment groups (Z6 and Z3P3) are provided below.

The primary efficacy endpoint was the percentage change in FN BMD from Year 3-6. Pre-specified secondary endpoints included BMD at other sites, fractures (morphometric vertebral, hip, clinical vertebral and non-vertebral), BTM, and safety parameters.

In the Z6 group, FN BMD increased from baseline to Year 3 and was maintained up to 6 years (Black 2010 ASBMR Oral Presentation). In the group that discontinued Reclast after 3 years (Z3P3) FN BMD showed modest loss (between treatment difference 1.36%), though it remained well above the mean pretreatment BMD from Year 0 of the Core study (Figure 3-3). Similar findings were observed for total hip and lumbar spine BMD.

Figure 3-3 Percentage change from year 0 in femoral neck BMD over 6 years (H2301E1 ITT population)

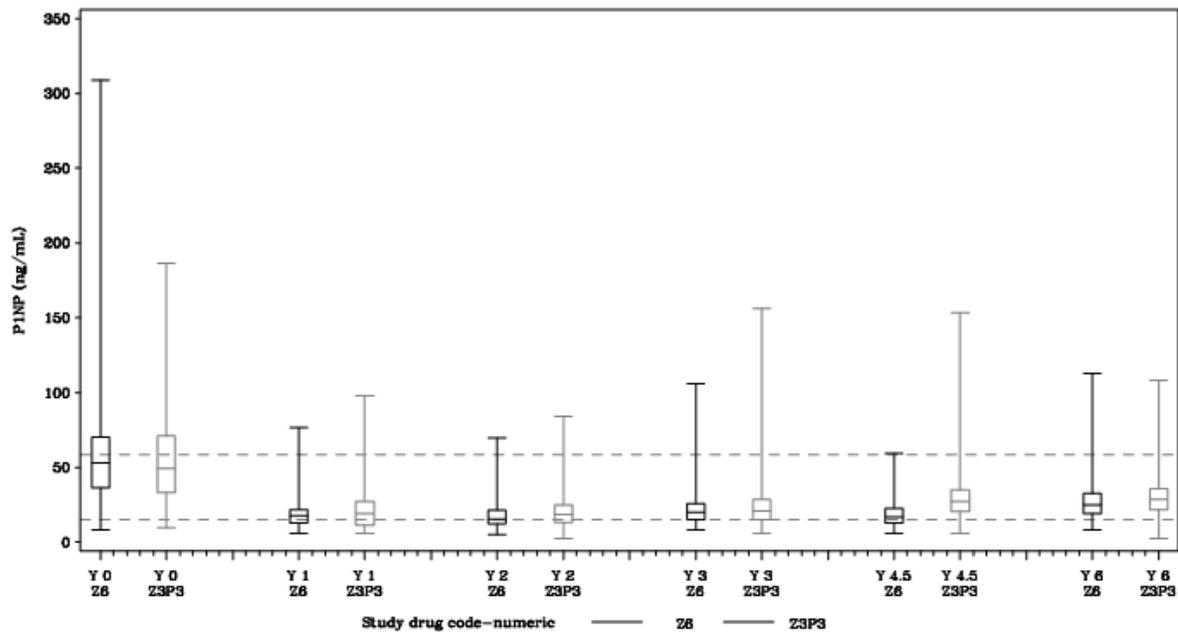


Z6, n=	613	609	608	600	524	450
Z3P3, n=	615	613	606	602	540	467

Values shown are for patients treated with Reclast in the Pivotal Fracture Trial who were subsequently re-randomized to the Z6 and Z3P3 groups. The FN BMD values were not significantly different at re-randomization. Year 4.5 is ITT population, year 6 is mITT population.

During the 3 years of the extension study, the mean P1NP rose slightly in both the Z3P3 (+32.5%) and Z6 (+19%) groups (Figure 3-4). Three years after discontinuation, P1NP remained below pre-treatment levels for the Z6 and Z3P3 groups. The values for most patients in both treatment groups were within the normal pre-menopausal reference range (15.1-58.6 ng/mL per Synarc technical protocol for serum P1NP, dated Mar 1, 2010). The patterns of change were similar for  $\beta$ -CTX and BSAP, but the sample sizes for these markers of bone resorption were too small to draw meaningful conclusions.

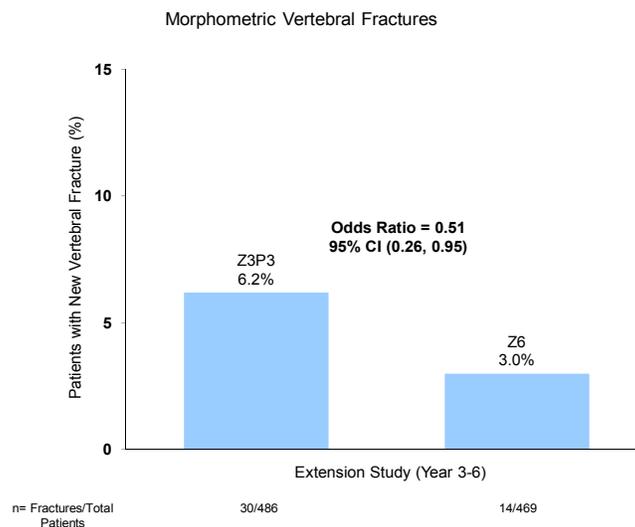
Figure 3-4 P1NP (ng/mL) by visit over 6 years – Study H2301E1 (ITT)



The horizontal reference lines are the lower and upper normal pre-menopausal reference limits (15.1 and 58.6 ng/mL). Min, 1<sup>st</sup> quartile, median, 3<sup>rd</sup> quartile, and max are presented in each plot.

Incident morphometric vertebral fractures have been shown to be associated with significant pain, limited activity, disability and increased risk of future fractures. During the Core study (H2301), the incidence of new morphometric vertebral fractures in the PBO group was 10.9% which was reduced to 3.3% in the Reclast treatment group. In this extension study (H2301E1), the rate of morphometric vertebral fractures was 6.2% in the patients that discontinued Reclast (Z3P3), and 3.0% in the group that continued Reclast (Z6), Z6 vs. Z3P3,  $p=0.035$  (Figure 3-5), suggesting that while some benefit persists even after discontinuing therapy, greater benefit is achieved with continued therapy. The sample size in the extension trial was relatively small and the fracture incidence was low, therefore making it difficult to assess non-vertebral fracture outcomes.

Figure 3-5 Morphometric vertebral fractures, Years 3–6—Study H2301E1 (ITT)



After 3 years of annual Reclast treatment, the Z3P3 group (those who discontinued therapy for up to 3 years) maintained their mean BMD above their Core pretreatment value. Nevertheless, a significant reduction in the risk for morphometric vertebral fractures was observed in patients who continued annual treatment for 6 years as compared with those who discontinued treatment (Figure 3-5). These data demonstrate NNT of 31.3 for prevention of these fractures over the 3 year extension treatment period, representing prevention of 1067 fracture events per 100,000 pt-yrs (Data on File).

Thus, stopping treatment after 3 years of annual Reclast therapy may not be optimal for all PMO patients. To address this issue, Novartis conducted a *post-hoc* analysis to identify the predictors of new vertebral fracture risk and to determine which subgroups of patients may be most likely to benefit from continued therapy (Data on File). The most important predictors of new morphometric fracture risk in the Z3P3 group were FN or total hip T-score at H2301E1 baseline  $\leq -2.5$  [Odds Ratio (95% Confidence Interval [CI]) = 3.3 (1.4, 8.0),  $p=0.008$ ; and 4.01 (1.8, 8.9),  $p=0.0007$ , respectively], and incident morphometric vertebral fracture during the Core study (Odds Ratio 4.74 [1.3, 16.7],  $p=0.0156$ ). Significant beneficial treatment effects (absolute fracture risk reduction and lowest NNT) with continued Reclast in H2301E1 were seen in these high risk subgroups. While it is acknowledged that the sample size for this analysis is small and should be interpreted with caution, the findings are consistent with the OP literature.

### 3.3 Reclast Recurrent Fracture Trial in patients with recent hip fracture (H2310)

Hip fractures are associated with increased morbidity, functional decline, and death in older adults. One source of the excess morbidity in patients with hip fractures is new osteoporotic fractures. Such fractures occur at a rate of 10.4 per 100 patients-years, which is 2.5 times the rate in age-matched persons without previous hip fracture (Colon-Emeric 2003).

Reclast was investigated to assess its impact on reducing clinical fractures in patients who had an incident low trauma hip fracture. In this trial with a median patient follow-up of 1.9 years,

the rate of any new clinical fracture was 8.6% in the Reclast group and 13.9% in the PBO group, correlating to a 35% risk reduction with Reclast (HR [95% CI] = 0.65 [0.50 to 0.84], p=0.001) (Lyles 2007) and extrapolating to the prevention of 2650 fractures per 100,000 pt-yrs of treatment. The rates of new clinical vertebral fracture were 1.7% in the Reclast group and 3.8% in the PBO group (p=0.02), and the rates of new clinical non-vertebral fracture were 7.6% and 10.7%, respectively (p=0.03). There was a non-significant trend in the reduction of recurrent hip fractures (HR=0.70; p=0.18), with a new hip fracture rate of 2.0% in the Reclast group and 3.5% in the PBO group (Table 3-2).

**Table 3-2 Rates of fracture in men and women with an incident hip fracture over median 1.9 years follow-up (H2310)**

Location	Reclast (N=1065) n (%) <sup>1</sup>	Placebo (N=1062) n (%) <sup>1</sup>	Hazard Ratio (95% CI)	p-value	Number of fractures to prevent per 100,000 pt-yrs of treatment	NNT
Any clinical fracture	92 (8.6)	139 (13.9)	0.65 (0.50–0.84)	0.001	2650	18.9
Non-vertebral fracture	79 (7.6)	107 (10.7)	0.73 (0.55–0.98)	0.03	1550	32.3
Hip fracture	23 (2.0)	33 (3.5)	0.70 (0.41–1.19)	0.18	750	66.7
Clinical vertebral fracture	21 (1.7)	39 (3.8)	0.54 (0.32–0.92)	0.02	1050	47.6

<sup>1</sup>For clinical fracture end points the number of subjects with events is provided along with the 24-month Kaplan-Meier estimates of the cumulative event rate

Total hip BMD was assessed as a surrogate marker at the contralateral hip. An increase in total hip BMD was observed in the Reclast group (2.6% at 12 months, 4.7% at 24 months and 5.5% at 36 months) and declined in the PBO group by 1.0%, 0.7%, and 0.9%, respectively.

In this trial of highly co-morbid osteoporotic patients, Reclast was also found to reduce the risk of death by 28% compared to PBO (a first for an OP therapy). This observed mortality benefit was manifested after the first year of treatment, and persisted after adjustment for baseline demographic and prognostic variables. While subsequent fractures were significantly associated with death (HR 1.62, 95% CI 1.09-2.40), they only explained 8% of the survival benefit (Colon-Emeric 2009).

Although osteoporotic fractures (including vertebral fractures) have been shown to be associated with increased mortality, this significant mortality reduction was unexpected in a trial powered to show a reduction in clinical fractures. The pathway and underlying mechanism producing this death benefit remains unknown.

### 3.4 Reclast Prevention of Bone Loss (N2312)

During the onset of estrogen deprivation due to menopause, there is a loss of bone mass resulting from increased bone resorption. Some women have significant bone loss during the perimenopausal period that may progress to osteopenia which is associated with an increased risk of fracture and continuing bone loss resulting in OP.

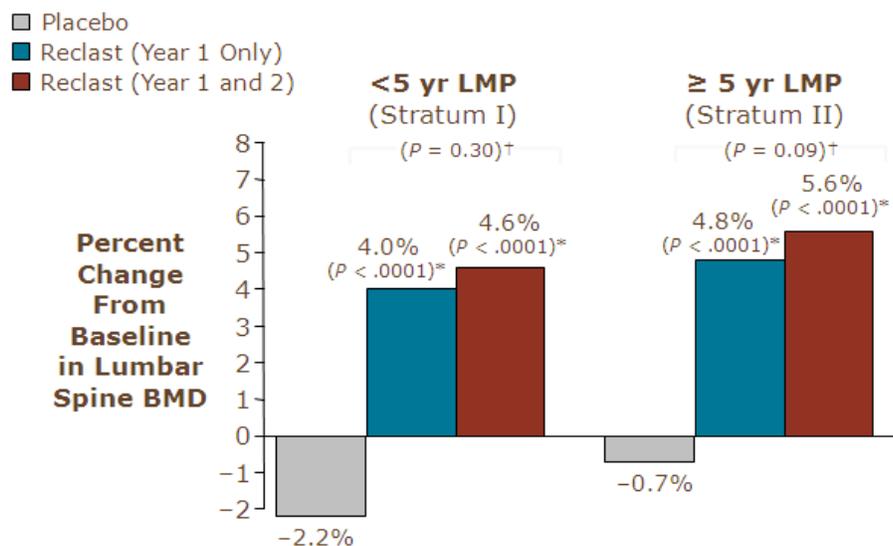
Reclast has been evaluated for the prevention of PMO in a 2 year study that compared a single Reclast infusion or two annual infusions with PBO (McClung 2009). 581 postmenopausal

women with low bone mass (BMD T-scores between -1.0 and -2.5) were enrolled in a two year trial where they were treated with one of 3 treatment regimens: 1) PBO, 2) Reclast at baseline only or 3) Reclast at baseline and 1 year. The objective was to assess the percent change in lumbar spine BMD at 24 months relative to baseline.

In the analysis, women were stratified into 2 groups based on the number of years from menopause (Stratum I: <5 years [n=224] or Stratum II: ≥ 5 years since menopause [n=357]). The results showed that Reclast given once significantly increased lumbar spine BMD relative to baseline at 2 years in both Strata (4.0% in Stratum I and by 4.8% in Stratum II). The PBO group had a decrease in lumbar spine BMD: -2.2% in Stratum I and -0.7% in Stratum II at 24 months. There was also a significant increase in hip BMD in the Reclast group while there was a loss of BMD in the PBO group (Figure 3-6).

The treatment group who received 2 annual infusions of Reclast had a significant increase in lumbar spine and hip BMD relative to PBO which was numerically greater but not significantly different from the group that received a single infusion.

Figure 3-6 Effect of Reclast treatment on lumbar spine BMD in postmenopausal women with osteopenia



LMP = Last Menstrual Period. Stratum I <5 years from menopause; Stratum II ≥ 5 years from menopause (LMP). \* Reclast vs. placebo, † Reclast (Year 1 and 2) vs. Reclast (Year 1 Only).

While no trial with BP in osteopenic patients has been designed to assess fracture end-points (due to the necessary sample size and anticipated length of study to assess the end-point), the increase in BMD with BP treatment is anticipated to reduce the known increased rate of fractures (1.8-fold increase compared with normal BMD; Siris 2001) and delay the progression to OP.

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## 4 Review of Reclast safety data

In the Reclast clinical development program for OP/osteopenia, the most common adverse events (AE) include: pyrexia, myalgia, flu-like illness, headache, and arthralgia. The majority of these symptoms occur within the first 3 days following Reclast infusion. The overall incidence of serious adverse events (SAEs) and discontinuations due to AEs in clinical trials was similar between Reclast and comparator groups as presented in the USPI. After the 3 day post-infusion period, the overall incidence of AEs was comparable to PBO. AEs observed during the clinical program are more fully described in the USPI.

In order to fully evaluate the safety profile of Reclast during the development program, Novartis prospectively incorporated an adjudication program to oversee the evaluation of events of special interest within the clinical trials program. The adjudication program was built utilizing pre-defined Medical Dictionary for Regulatory Activities (MedDRA) preferred AE terms and laboratory parameters which triggered blinded external expert review to assign “relationship” to Reclast use. The events of interest included: ocular, hypocalcemia, renal, maxillofacial, joint-related avascular necrosis and delayed union/nonunion of fractures, arrhythmia and cause of death.

Novartis routinely provides summaries of these events of interest to regulators as part of its on-going post-marketing surveillance regarding Reclast, to which Novartis is committed both in the U.S. and world-wide. To summarize briefly:

- Ocular inflammatory events: Not visually threatening, can generally be treated with topical therapy using either steroids or antibiotics. Consistent with those observed with other BP.
- Hypocalcemia: Typically transient and asymptomatic, with full recovery following supplementation of calcium.
- Renal impairment: Marginal and transient increase in serum creatinine following infusion may occur without long-term effect on renal function ([Boonen 2008](#)). Post-marketing renal reports including renal failure requiring dialysis or with a fatal outcome have been received with a low reporting rate, primarily in patients with pre-existing renal impairment, dehydration before or after the infusion, advanced age or concomitant use of nephrotoxic medications.
- Maxillofacial (includes ONJ): To be discussed in detail in Sections 4.2, 4.3 and 4.7 below.
- Joint-related avascular necrosis and delayed union/nonunion of fractures: No evidence of an increased risk was observed in the clinical trials.
- Atrial fibrillation: One trial in the development program found an imbalance in the incidence of atrial fibrillation SAEs between Reclast and PBO. No plausible mechanism and no evidence of a causal relationship between atrial fibrillation and Reclast has been established ([Camm 2010](#)).
- Cause of death: No evidence of an increased risk was observed in the clinical trials.

A possible association between oral BP and esophageal cancer has been reported ([Wysowski 2009](#)) since the completion of the phase III registration program. Therefore, this event was not prospectively adjudicated. In a review of the Reclast clinical trials database, there is no evidence of an increased risk (2 reports of esophageal cancer in PBO treated patients and no

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reports in Reclast treated patients). Atypical subtrochanteric femur fractures: to be discussed in detail in Sections 4.4, 4.5 and 4.8 below.

## 4.1 Bone safety

This section focuses on the long-term use of Reclast, related to bone safety, and will outline the available information as it relates to ONJ and atypical subtrochanteric femur fractures.

Treatment with first-generation BP such as etidronate raised concerns over potential mineralization defects ([Jowsey 1971](#)). Defective mineralization has not been observed in long-term clinical studies with the nitrogen-containing BP, alendronate, risedronate, and ibandronate, which do not share the same propensity for mineralization defects as etidronate. These studies also reported total absence of other qualitative abnormalities (woven bone, marrow fibrosis, or signs of cellular toxicity) in newly formed bone. Reclast is a third-generation nitrogen-containing BP displaying the highest inhibition of FPPS and greatest affinity for bone mineral to date.

Novartis prospectively assessed bone quality in a substudy of the Pivotal Fracture Trial (H2301) in which 152 patients underwent bone biopsy. Analysis of bone structure by Micro computerized tomography (CT) revealed better preservation of trabecular structure after treatment with Reclast than with PBO. Qualitative analysis revealed presence of tetracycline label in 81 of 82 biopsies from patients on Reclast and all 70 biopsies from PBO patients, indicative of continued bone remodeling. There was no evidence of marrow fibrosis, woven bone or osteomalacia after 3 years treatment with Reclast ([Recker 2008](#)).

In the Extension study (H2301E1), histomorphometry and micro CT data were available for 5 patients (3 in the Z6 group and 2 in the Z3P3 group) at the 6 year timepoint. All biopsies contained double tetracycline labeling, no evidence of osteomalacia, woven bone, cortical trabeculation or marrow fibrosis. The micro CT data revealed preservation of trabecular bone structure.

Yearly i.v. zoledronic acid 5 mg for 3 years resulted in a median 63% reduction of bone turnover with preservation of bone quality and no evidence for adynamic bone.

## 4.2 ONJ Overview

ONJ is a dental event defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks despite proper dental care, in a patient who has not had radiation therapy to the craniofacial region ([Khosla 2007](#); [Recknor 2011](#)). The American Society of Bone Mineral Research (ASBMR) appointed a multidisciplinary Task Force in 2007 to address key questions related to case definition, epidemiology, risk factors, diagnostic imaging, clinical management, and future areas for research related to the disorder. Their report summarized the findings and recommendations of the Task Force focusing initially on ONJ in patients treated with BP. However, ONJ has since been reported in patients treated with denosumab, a RANK-ligand inhibitor that inhibits bone resorption and is also indicated for the treatment of OP. Therefore, reports of ONJ events are not limited to use in patients who have received BP therapy.

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Risk factors for ONJ include: periodontal disease (including gingivitis), mucositis, infectious osteomyelitis, sinusitis, dental abscess, bony tumors and metastases (Khosla 2007). Treatment with chemotherapy and corticosteroids has also been identified as risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (e.g. advanced breast cancer, multiple myeloma) and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ, both in patients receiving i.v. BP therapy and those who have not, involve patients with signs of local infection, including osteomyelitis.

Based on review of both published and unpublished data, the reported incidence rate of ONJ in patients receiving oral BP therapy for OP appears to be very low, with estimates ranging between 1 and 10 per 100,000 patient-treatment years (Khosla 2007).

### 4.3 Reclast clinical trial data and ONJ

In light of reports of a potential association of ONJ and BP therapy, Novartis established a formal prospective program for the evaluation of ONJ during the Reclast clinical trials program. The clinical trial program with Reclast is the only BP program for OP treatment to prospectively adjudicate for ONJ. To objectively and independently assess maxillofacial AEs and to identify possible causal relationships, an adjudication process was established. The blinded, external adjudication committee consisted of 5 independent expert dental specialists who reviewed maxillofacial AEs from all studies. The pre-specified definition of ONJ for purposes of adjudication was “exposed bone with delayed healing despite 6 weeks of appropriate medical care” (Ruggiero 2004), which predates, and is more conservative than, the definition established by the ASBMR Task Force (Khosla 2007).

A list of 60 MedDRA preferred terms was selected by the adjudication committee in order to identify potential cases of ONJ. When a potential case was identified through search of MedDRA terms on the clinical trial AEs database, the clinical site was requested to provide a standardized set of information defined by the adjudication committee. A thorough description of the event with a detailed follow-up of the patient’s medical history, concurrent medical conditions, and relevant source documents was requested for review by the committee in a blinded fashion which then assessed whether each case met the specified criteria for ONJ. Cases adjudicated as “confirmed” would meet the ONJ criteria regardless of whether a duration of 6 or 8 weeks was used as the criterion.

While no reports of ONJ have been received by verbatim terms within the Reclast clinical trials program, there were 4 cases of ONJ confirmed through adjudication, two in the pivotal fracture study (one “probable” case in the Reclast group and one “possible” case in the PBO group) and two in the Reclast Extension Study (one in the Z6 and one in the P3Z3 group). All 4 cases resolved with therapy. Patient narratives for adjudicated events of ONJ are presented in the Appendix. The data represent a reporting rate of 8.8 per 100,000 pt-yrs for the phase III and IIIb trials, which is consistent with the rate of ONJ that has been reported with oral BP use in OP (Khosla 2007). The calculated number needed to harm (NNH) for ONJ is 3783 for patients who receive 3 years of Reclast therapy.

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#### **4.4 Atypical subtrochanteric femur fractures overview**

Atypical subtrochanteric femur fractures have recently emerged as a potential safety signal in patients on long term BP therapy. These fractures have specific radiographic features, and all major features are required to satisfy the case definition of atypical femur fracture. The major features are (Shane 2010):

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Non-comminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Atypical subtrochanteric femur fractures have also been reported in osteoporotic patients who have not been treated with BP, which can confound the evaluation of an association with BP.

#### **4.5 Reclast clinical trial data and “atypical” subtrochanteric femur fractures**

To evaluate available data related to atypical subtrochanteric femur fractures within the Reclast clinical program, a retrospective search of the AE database using the MedDRA preferred terms for hip fracture and femur fracture was conducted for all Reclast phase III and IIIb clinical trials, including those trials of OP in men and glucocorticoid-induced OP. Five reports of subtrochanteric femur fracture were received (2 on PBO and 3 on Reclast). Clinical fractures in the clinical trials program were verified based on either radiograph (X-ray), radiographic report or surgical report. The major features of atypical fractures can only be verified based on review of radiographic images; which were not available for these 5 reports. The 5 reports of subtrochanteric femur fracture thus could not be confirmed or excluded as atypical.

Novartis also commissioned a re-analysis of the Reclast Pivotal Fracture Trial (Black 2010). On interrogation of the trial database, a total of 84 hip or femur fractures were identified for assessment by a blinded external expert radiologist who reviewed all available data including radiographic reports. Of these, 5 subjects who had 6 fractures meeting the pre-specified regional criterion for fracture of the subtrochanteric femur were identified. Three were receiving Reclast (2.8 per 10,000 pt-yrs) and 2 were receiving PBO (1.9 per 10,000 pt-yrs). Although the location of these fractures was subtrochanteric, atypical features (per ASBMR criteria) could not be fully assessed in this retrospective analysis since primary radiographs were not available.

Therefore, there are no confirmed cases of atypical subtrochanteric femur fractures in the Reclast clinical trials program. As a result, a reporting rate for atypical subtrochanteric fractures cannot be determined.

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## **4.6 Post-marketing experience**

To provide additional perspective on the potential risks and benefits of Reclast in the treatment and prevention of OP, Novartis has reviewed its post-marketing database. As of 30-Jun-2011, the worldwide patient exposure to Reclast (including Aclasta, the trade name used outside of the US) was estimated to be over 2.3 million pt-yrs.

Because AE reports in a postmarketing setting are received voluntarily from a population of uncertain size and in many cases are reported with limited information, it is not possible to reliably estimate the frequency of postmarketing events or to reliably establish a causal relationship to drug exposure.

## **4.7 Post-marketing reports of ONJ**

The published incidence of ONJ in OP patients treated with oral BP is estimated to be 1-10 per 100,000 patient treatment-years (Khosla 2007). ONJ has been reported in the Reclast post-marketing setting at a rate of 4.5/100,000 pt-yrs, which is consistent with the published rates for oral BP. The majority of the ONJ reports to date have provided limited information to confirm the diagnosis of ONJ (e.g., lack of information on the occurrence of exposed jaw bone or event duration). The risk factors for ONJ that were identified as part of the review of the Reclast case reports include preceding dental procedure, long-term exposure to steroids, poor oral hygiene, and prior use of other BP.

Novartis will continue to closely monitor ONJ through its pharmacovigilance activities.

## **4.8 Post-marketing reports of “atypical” subtrochanteric femur fractures**

There have been rare post-marketing reports of subtrochanteric or diaphyseal femur fracture after Reclast therapy, as well as rare reports of “atypical” femur fracture. Due to limitations in the information provided with these post-marketing reports of “atypical” femur fracture (e.g., lack of information on the nature of trauma in association with the fractures, unavailability of X-ray films or X-ray reports or unspecified anatomic location for the reports of the "atypical" femur fracture), it is not possible to confirm whether these case reports meet the criteria for “atypical” femur fracture, as defined by ASBMR Task Force (Shane 2010). For the post-marketing reports of subtrochanteric/diaphyseal fracture or "atypical" femur fracture after Reclast therapy, underlying medical conditions (e.g. OP, Paget’s disease of bone) may provide an alternative explanation for these events.

Therefore, there are no confirmed cases of “atypical” subtrochanteric femur fracture in the post-marketing experience with Reclast. Novartis will continue to closely monitor atypical subtrochanteric femur fractures through its pharmacovigilance activities.

## **4.9 Novartis on-going safety evaluation program**

Novartis is committed to the ongoing evaluation of the safety of Reclast and to providing appropriate information to prescribers to allow for its informed use. This includes the targeted adjudication program for events of special interest occurring in clinical studies, as described above, along with post-marketing surveillance to evaluate the safety of Reclast. The current Reclast USPI provides detailed information for prescribers on Contraindications,

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Warnings and Precautions, Adverse Reactions, and appropriate use in patient populations. Novartis is committed to continued dialogue with the FDA to ensure that the Reclast label reflects the available information for the product.

To further evaluate the long-term safety of Reclast especially with regard to rare skeletal events Novartis initiated a 5-year cohort study using health registries in the Scandinavian countries (Denmark, Norway and Sweden) to evaluate the safety of Reclast in relation to oral BP and matched, untreated population controls. The purpose of this ongoing, European Union post-approval commitment study is to further explore the incidence of specific safety-related outcomes including: cardiovascular events, stroke-related events, skeletal events, and ONJ. Denmark, Sweden and Norway were chosen for this study because they have national registries for the recording of prescribed drugs and disease diagnoses that can be cross-referenced. Implementation in these countries could cover a total potential subject population of 18 million people. A report of the 5-year information is expected in 2015.

## **5 Overall benefit/risk of Reclast in light of the questions being posed by FDA**

An integrated evaluation of the benefit/ risk of Reclast is provided to support the answers to the questions posed by the FDA.

### **Overall Benefit/Risk**

In postmenopausal OP, the evidence from clinical trials demonstrates significant reductions in the risk of hip, vertebral and other osteoporotic-related fractures with BP treatment over 3 years of therapy and continued reduction in vertebral fractures up to 6 years. In postmenopausal women with OP at high risk of fracture who were treated with Reclast for 3 years, the numbers of fracture events prevented ranged from 367 per 100,000 pt-yrs for hip fractures (which are associated with 20-25% 1 year mortality) to over 2500 morphometric vertebral fractures (which have long term consequences for functional status, morbidity and risk of higher morbidity fractures). After 3 years of treatment with Reclast, an additional 3 years of treatment prevented over 1000 morphometric vertebral fracture events per 100,000 pt-yrs when compared with patients that stopped Reclast treatment at 3 years. In a population of osteoporotic patients with recent hip fracture, the benefit of Reclast therapy was also demonstrated, correlating to the prevention of over 2500 clinical fracture events per 100,000 pt-yrs. Clinical fracture events are associated with significant increase in disability, morbidity, mortality and decreased quality of life. Importantly, a significant 28% reduction in mortality was observed in the highly co-morbid population studied in the Recurrent Fracture Trial.

In clinical trials, the safety and tolerability of Reclast has been demonstrated up to 6 years. Data from the Reclast clinical trials program and post-marketing reports suggest that the reported rate of ONJ in patients receiving Reclast is consistent with that estimated for the oral BP by the ASBMR Task Force Report: 1 to 10 per 100,000 pt-yrs. Within the clinical trials program and post-marketing data, there is no evidence for increased frequency of ONJ events with longer duration of therapy. The incidence of atypical subtrochanteric femur fractures in patients treated with Reclast for OP is not well established due to its rarity, and the limitations in the availability of the radiographic evidence that is required for unequivocal diagnosis of these events.

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Additionally, the Reclast prescribing information provides information for the practitioner with regard to appropriate use in specific patient populations, based on available data and the known mechanism of the drug, including Contraindications (Section 4 of the Reclast label) and Warnings & Precautions (Section 5 of the Reclast label) including ‘ONJ’ and ‘Atypical Subtrochanteric Diaphyseal Femoral Fractures’.

There are no controlled studies evaluating the effect of a drug holiday on the efficacy or safety of Reclast. In patients with OP treated with antiresorptive agents, reduction in bone turnover explains much of the observed fracture risk reduction. Lower levels of BTM appear to be associated with a lower risk of fracture in BP-treated patients. The association between changes in markers of bone turnover and fracture incidence has been assessed in patients who had P1NP measurements at baseline and 1 year as part of the H2301 Pivotal Fracture Trial. In a *post hoc* analysis of the Pivotal Fracture Trial, annual injections of Reclast reduced markers into the premenopausal reference range, with a significant response persisting after the third infusion with no association between low P1NP levels at 1 year and increased fracture incidence (Delmas 2009). The long-term data obtained as part of the Pivotal Fracture Trial Extension (H2301E1) suggests that there are patients with postmenopausal OP who continue to accrue benefits with Reclast therapy beyond 3 years.

In postmenopausal women with osteopenia Reclast increases and maintains BMD when it is administered every 2 years, a fundamental component for the prevention of OP and osteoporotic fractures.

#### **Novartis Response to Questions Posed by FDA**

- *Provide an opinion and discussion of whether the efficacy and safety data support a long-term duration of use (i.e., > 3 years) for Reclast<sup>®</sup> (zoledronic acid) Injection.*
- *Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment.*

It is Novartis’ position that the overall data support the annual use of Reclast for 3 years and a positive benefit/risk for treatment with Reclast up to six years in the treatment of OP. Data in patients who remain on Reclast for up to 6 years suggest that continued treatment builds and maintains BMD better than in patients who discontinued treatment after 3 years. The second 3 years of Reclast treatment provided additional benefit specific to the occurrence of new morphometric vertebral fracture which are associated with increased risk of fractures. Advice to the practitioner regarding the duration of use provided in Section 1.6 of the Reclast label accurately reflects what is known about the product to date: “*The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis*”.

A *post hoc* analysis from Study H2301 describing the relationship of P1NP and BMD at 1 year post treatment in relation to fracture risk reduction at 3 years, in addition to *post hoc* analyses from Study H2301E1 outlining which patients may best benefit from continued therapy, have demonstrated that the use of BMD or markers of bone turnover are appropriate surrogate markers to help inform the decision to continue or discontinue therapy. This information, in addition to a clinical evaluation of other factors that may impact the risk for future osteoporotic fractures, such as medication use (e.g. glucocorticoids, proton pump

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inhibitors), inactivity, and tobacco and alcohol use, will aid the decision of the practitioner to continue or interrupt Reclast therapy.

It is Novartis' position that the totality of efficacy and safety data with Reclast do not support a blanket restriction on the duration of use or the implementation of a drug holiday for long-term use. Current labeling recommends that the lower-risk population with osteopenia be treated with Reclast infusion every other year and that the higher risk osteoporotic population be treated with annual infusions of Reclast.

Novartis remains committed to ensuring that its products are used safely and effectively and welcomes the opportunity to engage in the discussion of these important topics.

## 6 Conclusions

- Current data support a positive benefit/risk for Reclast for up to 6 years in patients with osteoporosis.
- A decision to continue or interrupt Reclast therapy should be made by the health care provider and patient on a patient-specific basis with consideration of relevant clinical factors and bone mineral density or bone turnover markers
- The existing data do not support a specific limitation on the duration of use of Reclast for all osteoporosis patients.

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## APPENDICES

### Narratives of Adjudicated ONJ cases from Reclast Clinical Trials

#### Reclast pivotal fracture trial (H2301)

**Placebo treatment group:** This patient (0601-00019) in the placebo group presented 6 months after the 3rd infusion with a lesion in the region of the left maxilla that was inflamed and painful to palpation. Osteitis was diagnosed without any clinical evidence of a soft tissue infection. Two debridements on the infected area and antibiotic therapy were performed as treatment for the condition. The time to resolution was approximately 8 months. This case was adjudicated a “possible” case of ONJ.

**Reclast treatment group:** This patient (0311-00020), a 70-year-old insulin-dependent diabetic in the Reclast group who had never had regular dental care. She presented with an abscess in the residual root of a previous extraction 5 months after her 2<sup>nd</sup> infusion. Given her poor dental hygiene and long-standing diabetes, this patient was at high risk for delayed healing and other complications. An additional 12 extractions and curettage were performed. Within a week, the patient became extremely ill and was diagnosed with a periodontal infection. She refused hospitalization. The infection subsequently spread to the mandibular bone, resulting in osteomyelitis. The osteomyelitis resulted in necrosis of part of the mandible, which was confirmed radiographically. The patient was subsequently treated with antibiotics. Resolution of the infection with full healing was confirmed by X-ray. This case was adjudicated a “probable” case of ONJ.

#### Reclast pivotal fracture trial extension (H2301E1)

The extension study had two adjudicated reports of ONJ, one in the Z6 group and the other in the P3Z3 group (patients received placebo for the first 3 years and Reclast during the extension study). The narratives for these cases are presented in below. Both patients made a complete recovery following treatment with antibiotics and dental care.

The first patient (0736-00120), a 77-year-old Asian female in the Z6 group, presented 6 months after her 5<sup>th</sup> Reclast infusion. She was a smoker with a medical history of poor dental hygiene, periodontal disease, and loss of a tooth. Her dental visits occurred on an emergency basis only. She presented with mandibular pain, swelling, pus discharge from the alveolar ridge and numbness of the lower lip. The patient made a complete recovery following treatment with antibiotics, wound debridement and sequesterectomy.

The second patient (0324-00062), a 76-year-old Caucasian female in the P3Z3 group presented 10 months after her 2<sup>nd</sup> infusion. She had a medical history of alcohol use, dental caries, and periodontal disease. The patient presented with mild tooth infection due to an infected tooth socket. She made a complete recovery following treatment with antibiotics and wound debridement.



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**Reclast<sup>®</sup> US Prescribing Information**



System Organ Class	0.4	0.3	3.1	1.2
Musculoskeletal and administration site conditions				
Pain	17.9	4.6	8.7	3.4
Musculoskeletal	8.8	2.7	0.8	0.1
Headache	5.4	1.5	2.1	1.2
Dizziness	5.4	1.0	1.5	0.5
Paresthesia	5.3	2.8	2.2	2.0
Peripheral edema	4.6	4.2	5.5	5.3
Malaise	3.2	1.3	1.5	0.5
Hypertension	0.3	<0.1	2.3	0.3
Chest pain	1.3	1.1	2.4	1.8
Insurgations				
Reactions	2.0	2.4	2.1	1.7

at randomization and placebo at Month 12 ( $n=181$ ) and (3) placebo group at randomization and placebo at Month 24 ( $n=181$ ). All patients received 500 to 1000 mg elemental calcium plus 800 to 800 IU vitamin D<sub>3</sub> daily. The incidence of adverse events was similar for both groups. The incidence of adverse events at Month 12 (0.8%) and (2) placebo at randomization and placebo at Month 24 (0.8%) and (3) placebo at randomization and placebo at Month 24 (0.8%) were similar. The incidence of adverse events was similar for both groups. The incidence of adverse events was similar for both groups. The incidence of adverse events was similar for both groups.

**Table 2. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Placebo (n=152)
Nervous system disorders	14.6	11.4	11.4
Dizziness	7.5	6.1	3.5
Hypertension	5.6	2.2	2.0
Ear and labyrinth disorders	2.0	1.7	1.0
Vertigo	5.1	8.3	6.9
Headache	17.7	11.6	7.9
Nausea	8.1	6.6	7.9
Dizziness	7.6	3.0	4.5
Vomiting	7.6	3.0	4.5
Abdominal pain*	8.6	6.6	7.9
Constipation	2.0	1.1	0.5
Abdominal distension	2.0	0.6	0.0
Skin and subcutaneous tissue disorders	3.0	2.2	2.5
Rash	2.3	1.8	1.9
Alopecia	2.3	1.8	1.9
Pruritus	1.8	1.2	1.5
Erythema	1.8	1.2	1.5
Skin atrophy	1.1	1.6	0.9
Maculopapular rash	5.6	2.8	5.0
Maculopapular rash	8.1	7.2	7.9
Erythema	5.1	3.3	1.0
Necrotic skin	5.1	6.6	5.0
Alopecia	4.0	2.2	1.5
Joint stiffness	3.5	1.1	2.0
Joint swelling	2.0	0.6	0.0
Joint pain	2.0	0.6	0.0
Pain in jaw	2.0	3.9	2.5

**Table 3. Adverse Events Occurring in ≥2% of Men with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=149)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 4. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 5. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	14.6	11.4	11.4
Dizziness	7.5	6.1	3.5
Hypertension	5.6	2.2	2.0
Ear and labyrinth disorders	2.0	1.7	1.0
Vertigo	5.1	8.3	6.9
Headache	17.7	11.6	7.9
Nausea	8.1	6.6	7.9
Dizziness	7.6	3.0	4.5
Vomiting	7.6	3.0	4.5
Abdominal pain*	8.6	6.6	7.9
Constipation	2.0	1.1	0.5
Abdominal distension	2.0	0.6	0.0
Skin and subcutaneous tissue disorders	3.0	2.2	2.5
Rash	2.3	1.8	1.9
Alopecia	2.3	1.8	1.9
Pruritus	1.8	1.2	1.5
Erythema	1.8	1.2	1.5
Skin atrophy	1.1	1.6	0.9
Maculopapular rash	5.6	2.8	5.0
Maculopapular rash	8.1	7.2	7.9
Erythema	5.1	3.3	1.0
Necrotic skin	5.1	6.6	5.0
Alopecia	4.0	2.2	1.5
Joint stiffness	3.5	1.1	2.0
Joint swelling	2.0	0.6	0.0
Joint pain	2.0	0.6	0.0
Pain in jaw	2.0	3.9	2.5

**Table 6. Adverse Events Occurring in ≥2% of Men with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=149)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 7. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 8. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 9. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7
Malaise	7.2	3.9	3.9
Acute phase reaction	3.9	0.0	0.0
Investigations	4.8	1.4	1.4
C-reactive protein increased	4.8	1.4	1.4

**Table 10. Adverse Events Occurring in ≥2% of Patients with Osteoporosis and More Frequently than in the Placebo-Treated Patients**

System Organ Class	5 mg IV Repeated (n=150)	5 mg IV Repeated (n=151)	Active Control (n=150)
Nervous system disorders	15.0	6.1	6.1
Headache	3.3	1.4	1.4
Dizziness	2.0	0.0	0.0
Ear pain	2.0	0.0	0.0
Cardiac disorders	3.3	2.0	2.0
Atrial fibrillation	2.0	0.0	0.0
Paresthesia	6.5	4.7	4.7
Dizziness	7.9	4.1	4.1
Abdominal pain*	2.0	0.0	0.0
Skin and subcutaneous tissue disorders	2.0	2.0	2.0
Maculopapular rash	19.6	5.8	5.8
Pruritus	12.4	10.8	10.8
Erythema	4.8	0.0	0.0
Maculopapular rash	4.8	0.0	0.0
Real and urinary disorders	3.0	0.7	0.7
General disorders and administration site conditions	3.0	4.1	4.1
Fatigue	17.6	6.1	6.1
Pain in jaw	11.8	4.1	4.1
Dizziness	9.8	2.2	2.2
Oribital pain	7.2	0.7	0.7



