

**DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE
AND
REPRODUCTIVE AND UROLOGIC PRODUCTS
ADVISORY COMMITTEE**

**BRIEFING DOCUMENT
AUGUST 2011**

**FOR
NDA 21-455 BONIVA® (ibandronate sodium) Tablets
and
NDA 21-858 BONIVA® (ibandronate sodium) Injection**

**Hoffmann-La Roche Inc.
Nutley, New Jersey**

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GLOSSARY OF ABBREVIATIONS

ACE	Annual cumulative exposure
ASBMR	American Society of Bone Mineral Research
BMD	Bone mineral density
Boniva®	ibandronate
BTM	Bone turnover markers
CI	Confidence interval
FDA	Food and Drug Administration
GQ	Guided questionnaire
IV	Intravenous
LTE	Long-term extension
MedDRA	Medical Dictionary for Drug Regulatory Activities
NNH	Number needed to harm
NNT	Number needed to treat
ONJ	Osteonecrosis of the jaw
PMO	Postmenopausal osteoporosis
q 2 mo	Every two months
q 3 mo	Every three months
Rare	frequency $\geq 1/10,000$ to $< 1/1000$
sCTX	Serum C-terminal peptide of type I collagen
sPINP	Serum procollagen type 1 N-propeptide
US	United States
USPI	United States Package Insert
Very rare	frequency of $\geq 100,000$ to $< 10,000$

1. EXECUTIVE SUMMARY

FDA held teleconferences on April 25, 2011 with sponsors of bisphosphonates approved in the United States (US) for the treatment and prevention of osteoporosis, to notify them of its intention to hold an Advisory Committee Meeting on September 9, 2011. The purpose of the meeting is to discuss the evidence supporting the benefit of long-term bisphosphonate use for the treatment and prevention of osteoporosis in light of potential safety concerns such as osteonecrosis of the jaw (ONJ) and atypical fracture. In these teleconferences FDA requested Sponsors to provide an opinion and discussion on two topics: (1) whether the efficacy and safety data of their drug supported long-term (> 3 years) treatment and (2) whether restriction of use or implementation of a drug holiday may be beneficial for patients requiring long-term treatment.

This section contains a summary of Roche's response to each topic based on a thorough review of Boniva[®] data.

TOPIC #1 Provide an opinion and discussion of whether efficacy and safety data for Boniva support a long-term duration of use (> 3 years).

SPONSOR'S OPINION: Boniva treatment for up to five years is safe and effective for the treatment of postmenopausal osteoporosis and the benefit/risk ratio remains favorable for this duration of treatment, based on our data.

Efficacy and safety of Boniva for approval in the treatment of postmenopausal osteoporosis (PMO) were established based on three-year clinical fracture data and one-year bridging/non-inferiority BMD studies with Boniva oral and IV formulations, which were extended for up to five years' duration.

In the longer-term clinical development program with currently marketed doses, Boniva demonstrated sustained efficacy with a consistent safety profile for up to five continuous years of treatment. There were no confirmed reports of ONJ or atypical fractures in the clinical development program and post-marketing reports remain rare ($\geq 1/10,000$ to $<1/1000$).

EFFICACY DATA:

The efficacy of Boniva observed during the first year of treatment (oral or IV) was maintained during long-term treatment based on the five-year results of bone mineral density (BMD), bone turnover markers (BTMs), bone histomorphometry, and the incidence of clinical fractures. There were no signs of diminution in efficacy during the course of treatment. The key efficacy results are based on findings after five years of continuous treatment with marketed Boniva doses (oral dose of 150 mg monthly or IV dose of 3 mg every 3 months [3 mg q 3 mo]).

- For patients treated for five years with oral or IV Boniva, BMD continuously increased in the lumbar spine and was initially increased and then generally maintained in the total hip compared with baseline.

- The proportion of patients classified as responders for lumbar spine BMD and total hip BMD at five years of treatment was comparable to the proportion of responders after one year of treatment for both the oral and IV formulations.
- In the oral and IV Boniva treatment groups, the decrease in BTM levels of serum procollagen type 1 N-propeptide (sP1NP) and serum C-terminal peptide of type I collagen (sCTX) achieved over the first year remained lowered relative to baseline over the entire five-year treatment period. At no time did median absolute sP1NP or sCTX values fall below the normal premenopausal range among patients treated with either oral or IV Boniva. The five-year bone histomorphometry results showed that newly formed bone was of normal composition, which supported the BTM results.
- Based on results of a meta-analysis of fractures in patients taking oral doses of 150 mg monthly or IV doses of 2 mg q 2 mo or 3 mg q 3 mo, the estimated time to first occurrence of any clinical fracture was significantly longer with either oral or IV doses of Boniva compared with placebo. The rate of first clinical fracture during five years of oral or IV Boniva treatment was similar when analyzed by fracture type and when expressed as fracture rate per 100 patient-years. The median time to first occurrence of any clinical fracture was longer with either oral or IV doses of Boniva than with placebo.

SAFETY DATA

- The overall safety profile in the clinical development program of Boniva after up to five years of continuous treatment with either an oral monthly dose of 150 mg or an IV dose of 3 mg q 3 mo (total estimated exposure of 11,900 patient-years) was similar to the profile obtained after the first year of treatment. No new safety concerns or signals emerged after the first year on treatment.
- There were no confirmed reports of ONJ or atypical fracture in the Boniva clinical development program with up to five years of treatment.
- Spontaneous reports of ONJ or atypical fracture (including literature cases and post-marketing studies) have been rare. The crude reporting rate for ONJ (based on the ASBMR case definition [1]) was 2.1 events per 1,000,000 patients exposed; the crude reporting rate for atypical fracture (meeting all 5 ASBMR Task Force criteria [2]) was 0.3 event per 1,000,000 patients exposed.
- At the present time, there is no definitive agreement on whether an increase in the occurrence of ONJ or atypical fracture is associated with Boniva or other bisphosphonate use. Nevertheless, several risk management tools are currently in place:
 - Roche developed a risk management pharmacovigilance tool in the form of Guided Questionnaires (GQs) that are used to enhance understanding of reported cases of ONJ and atypical fracture. The GQ for ONJ has been in use since 2007 and the GQ for atypical fracture has been in use since 2009.
 - The Warnings and Precautions section of the United States Package Insert (USPI) contains detailed language designed to raise the awareness of the physician to the possible occurrence, nature, and possible risk factors for ONJ and atypical fractures. The USPI states that “Interruption of therapy should be considered, pending a risk/benefit assessment, on an individual

basis” for atypical fractures and that “clinical judgment of the treating physician should guide the management plan of each patient based on an individual benefit/risk assessment” for ONJ. Roche considers these statements consistent with principles of good patient management.

- The patient-directed Medication Guide dispensed with every prescription additionally raises the awareness of patients to the events of atypical fracture and ONJ and refers them to their doctor in the event of manifestation of possible symptoms of these events.
- All communications to physicians from the Sponsor regarding Boniva include information on the risk of ONJ and atypical fractures.
- Roche is committed to the continued collection of and investigation into reported or suspected cases of ONJ and atypical fracture and any safety issue associated with the use of Boniva.

TOPIC #2 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.

SPONSOR’S OPINION: There is no evidence to either support or refute that limiting the duration of use or implementing a drug holiday would benefit patients who are on long-term treatment. All patients on bisphosphonate therapy should have the need for continued therapy reevaluated on a periodic basis as per the current USPI. The treating physician is best placed to make this determination.

The safety profile following long-term treatment was consistent with the safety profile following short-term treatment. Efficacy was maintained during long-term use.

2. BACKGROUND

The stated purpose of the Advisory Committee meeting is 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 ONJ and atypical femur fractures that may be associated with the long-term use of bisphosphonates. Therefore, the main focus of this Briefing Document will be long-term (> 3 years) data of Boniva based on:

- Data from key clinical studies comprising the safety database for the currently marketed Boniva doses of oral 150 mg monthly and 3 mg IV q 3 mo which include core efficacy and safety data with a duration of up to five years and a total estimated patient exposure of 11,900 patient years.
- Data from ADVENT, the Roche pharmacovigilance database, where safety data from the post-marketing setting are collected. These data are presented to complement the clinical safety profile of Boniva that was established in the clinical development program. As of June 2011, an estimated 26,000,000 patients have been exposed to Boniva worldwide.

2.1 Description of Product

Boniva® (ibandronic acid, ibandronate sodium monohydrate, ibandronate) is a nitrogen-containing bisphosphonate with a high affinity for mineralized tissue. The molecule acts

as a potent inhibitor of osteoclast-mediated bone resorption and reduces the generation of new bone remodeling units. Boniva is indicated for the treatment and prevention of PMO. Boniva increases bone mineral density (BMD) and reduces the incidence of vertebral fractures.

2.2 Regulatory History

Boniva is approved in the US for treatment and prevention of PMO (Table 1). The current Boniva USPIs are available at:

<http://www.gene.com/gene/products/information/>

Table 1 US Registration History for Boniva

Indication	Formulation	Approval Date
Treatment and prevention of postmenopausal osteoporosis	Ibandronate 2.5 mg tablets (once daily)	May 16, 2003
Treatment of postmenopausal osteoporosis	Ibandronate 150 mg tablets (once monthly)	May 25, 2005
Treatment of postmenopausal osteoporosis	Ibandronate 3 mg/3 mL prefilled syringes (every 3 months)	January 6, 2006
Prevention of postmenopausal osteoporosis	Ibandronate 150 mg tablets (once monthly)	November 28 2008

3. TOPIC #1 PROVIDE AN OPINION AND DISCUSSION OF WHETHER EFFICACY AND SAFETY DATA FOR BONIVA SUPPORT A LONG-TERM (> 3 YEARS) DURATION OF USE

SPONSOR'S OPINION: Boniva treatment for up to five years is safe and effective for the treatment of postmenopausal osteoporosis and the benefit/risk ratio remains favorable for this duration of treatment, based on our data.

Efficacy and safety of Boniva for approval in the treatment of PMO were established based on three-year clinical fracture data and one-year bridging/non-inferiority BDM studies with Boniva oral and IV formulations which were extended for up to five years' duration.

In the longer-term clinical development program with currently marketed doses, Boniva demonstrated sustained efficacy with a consistent safety profile for up to 5 years of continuous treatment. There were no confirmed reports of ONJ or atypical fractures in the clinical development program and post-marketing reports remain rare.

3.1 Efficacy of Boniva in Clinical Trials

The Boniva clinical development program was completed in 2010.

The clinical trials provided in Table 2, which include those with long-term (> 3 years) treatment, are the basis for the efficacy results presented in this section.

The pivotal studies for the registration of treatment of PMO included studies MF4411 (oral Boniva) and MF4380 (IV Boniva) which were placebo-controlled fracture trials; BM16549 (oral Boniva) and BM16550 (IV Boniva) which were bridging BMD studies from the 2.5 mg daily dose to the 150 mg monthly oral and to the 3 mg q 3 mo IV dosing regimens, respectively (Table 2). These studies constitute the majority (>15,000 patient-years) of the exposure to Boniva. Three of these pivotal studies each had its own long-term extension study as follows, pivotal study (long-term extension study): MF4380 (MF4380F), BM16549 (MA17903), and BM16550 (MA 17904).

Table 2 Long-term Efficacy: Pivotal Registration Trials and Their Long-term Extensions

	CORE STUDIES			
	MF4411 (BONE)	MF4380*	BM16549 (MOBILE)	BM16550 (DIVA)
Duration (yrs)	3	3	2	2
Primary endpoint	Fracture	Fracture	BMD	BMD
Mean Age yrs	68.7	67.0	66.0	66.0
Dose tested	Oral 2.5 mg daily, 20 mg intermittent*	IV 0.5 mg q3mo 1 mg q3mo	Oral 50/50 mg, 100mg, 150 mg monthly	IV 2 mg 2qmo 3 mg q3mo
Comparator	Placebo	Placebo	2.5mg daily oral	2.5mg daily oral
Patients Exposed to Boniva	1954	1911	1583	1382
Total Patient-years of Exposure to Boniva	4775	5041	2832	2600
	LONG-TERM EXTENSION STUDIES			
	(None)	MF4380F*	MA17903 (MOBILE LTE)	MA17904 (DIVA LTE)
Duration (yrs)	---	2	3	3
Dose tested	---	IV 0.5mg q3mo 1mg q3mo	Oral 50/50mg, 100mg, 150mg monthly	IV 2mg 2qmo 3mg q3mo
Total Patients Exposed to Boniva	---	850	719	781

*The doses in Study MF4380 were found to be suboptimal for the treatment of PMO. Prior to its completion, Study MF4380F was discontinued based on the results from Study MF4380.

BONE (MF4411) pivotal fracture trial was a three-year trial investigating antifracture efficacy of oral (2.5 mg daily) and intermittent (20 mg) regimens vs placebo. After three years, daily treatment with 2.5 mg of Boniva reduced the risk of new incident morphometric vertebral fractures by 52.1% in comparison with placebo ($p = 0.0003$), leading to registration of Boniva for the treatment of PMO. In two separate bridging/non-inferiority trials of the marketed regimens of 150 mg monthly and 3 mg q 3 mo (Studies BM16549 and BM16550, see [Table 2](#)), both doses were shown to be non-inferior to the 2.5 mg daily dose as assessed at the primary endpoint of lumbar spine BMD after one year of drug administration. Following demonstration of non-inferiority, additional testing confirmed that both doses were also superior to the 2.5 mg daily dose for BMD at the lumbar spine. Both trials were extended for an additional three years, for a total of five years of treatment. All patients previously treated with the daily oral 2.5 mg dose continued on an intermittent regimen in the 3-year extension phase. A post-hoc meta-analysis of pooled intermittent oral doses of 150 mg monthly and IV doses of 2 mg q 2 mo and 3 mg q 3 mo was performed to assess the long term effect of Boniva on the incidence of clinical fractures over time. A placebo comparison was included in the meta-analysis using the pooled placebo data from fracture trials MF4411 (oral placebo) and MF4380 (IV placebo), because the bridging BMD trials did not have placebo groups.

Data from BMD and BTM are presented for patients who were on oral doses of 150 mg monthly or IV doses of 3 mg q 3 mo continuously for five years.

3.1.1 Bone Mineral Density: Five-year Data

The primary efficacy endpoint of the core studies and their long-term extensions ([Table 2](#)) was change from baseline in mean lumbar spine BMD. Based on the data from patients who received five years of continuous treatment with oral or IV intermittent treatment, there were sustained increases in mean lumbar spine (L2 - L4) BMD relative to baseline, with no evidence of a diminution in efficacy after five years of treatment.

In Study MA17903, there were continuous year-to-year increases in mean lumbar spine BMD (L2 - L4) relative to the Study BM16549 baseline ([Figure 1A.](#)), with a mean relative increase from baseline after five years of treatment of 8.43% (95% CI 7.49, 9.37) ([Table 3](#)). Mean BMD increases observed for total hip, femoral neck, and trochanter relative to the BM16549 baseline after one year were initially increased and then generally maintained for up to five years of treatment.

Results with IV Boniva (3 mg q 3 mo) showed results similar to oral Boniva. There were continuous year-to-year increases in mean lumbar spine BMD (L2 - L4) relative to the Study BM16550 baseline ([Figure 1B.](#)), with a mean relative increase from baseline after five years of treatment of 8.05% (95% CI 7.17, 8.94) in the 3 mg q 3 mo IV group ([Table 3](#)). Mean BMD increases were also observed for total hip, femoral neck, and trochanter relative to the BM16550 baseline after one year, which were generally maintained for up to five years of treatment.

Figure 1 Time Course of Relative Change (% and 95% CI) from Baseline of Mean Lumbar Spine BMD Over 5 Years with Monthly Oral Boniva Dosing (ITT Population)

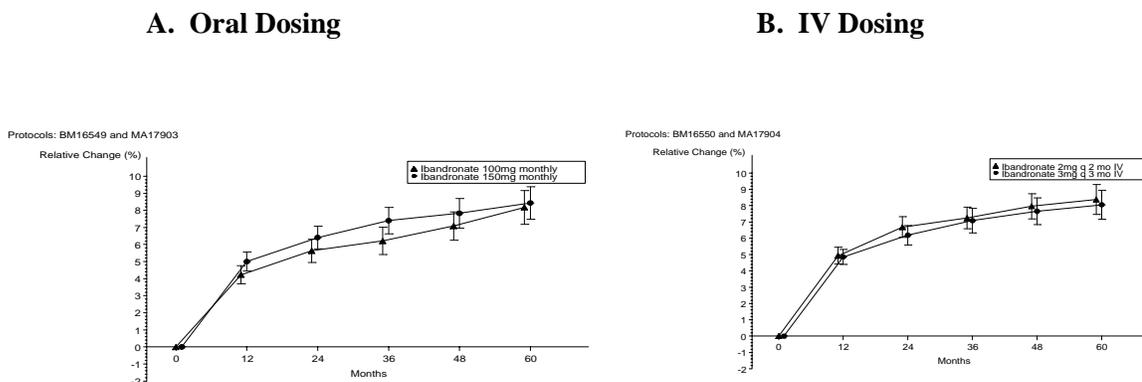


Table 3 Mean Relative Change (%) from Baseline of Lumbar Spine, Total Hip, Femoral Neck, and Trochanter BMD at Years 1 and 5 (ITT Population)

	Mean Relative Change in BMD*			
	150 mg monthly oral Boniva		3 mg IV q 3 mo	
	BM16549 YEAR 1 (N=168)	MA17903 YEAR 5 (N=156)	BM16550 YEAR 1 (N=257)	MA17904 YEAR 5 (N=228)
Lumbar Spine	5.00% (95% CI 4.44,5.56)	8.43% (95% CI 7.49, 9.37)	4.86% 95% CI (4.40, 5.32)	8.05% 95% CI (7.17, 8.94)
Total Hip	2.94% (95% CI 2.55, 3.34)	3.47% (95% CI 2.83, 4.11)	2.60% 95% CI (2.16, 3.04)	2.81% 95% CI (2.09, 3.52)
Femoral neck	1.91% (95% CI 1.37, 2.46)	3.18% (95% CI 2.09, 4.26)	2.52% 95% CI (1.99, 3.05)	3.35% 95% CI (2.52, 4.18)
Trochanter	4.22% (95% CI 3.65, 4.79)	5.96% (95% CI 5.08, 6.83)	4.16% 95% CI (3.38, 4.95)	5.26% 95% CI (4.14, 6.38)

*Relative to the BM16549 (oral) or BM16550 (IV) baseline.

3.1.2 Responder Rate: Five-year Data

In the pooled analysis of the responder rate (defined as the proportion of patients with mean lumbar spine (L2 - L4) or total hip BMD equal to or above the BM16549 baseline values), the proportion of patients classified as responders after five years of treatment with continuous monthly oral doses of 150 mg was 92% for lumbar spine BMD and 87% for total hip BMD. These responder rates after five years of treatment were similar to those seen after one year of treatment (lumbar spine BMD: 93%; total hip BMD: 94%). Similar results were seen with IV intermittent dosing, responder rates at year five for

continuous 3 mg IV q 3 mo were 93% for lumbar spine BMD and 78% for total hip BMD. These responder rates after five years of treatment were similar to those seen after one year of treatment (lumbar spine BMD: 91%; total hip BMD: 83%).

3.1.3 Bone Turnover: Five-year Data

The biochemical markers of bone turnover used in the studies were sP1NP, a marker of bone formation and sCTX.

In patients who received five years of continuous Boniva treatment with either oral (100 mg or 150 mg monthly) or IV (2 mg q 2 mo or 3 mg q 3 mo), median sP1NP and sCTX values decreased relative to baseline. A rapid and pronounced decrease from baseline in median sP1NP values was seen during the first 12 months of treatment -74.5% in the 150 mg oral monthly group, and -62.5% in the 3 mg IV q 3 mo group. Similar decreases were seen in median sCTX (-73.5% and -52.5% for oral and IV, respectively). Over the remaining four years of the study, sP1NP and sCTX values consistently remained below the baseline values for the oral and IV Boniva doses. After five years of Boniva treatment, suppression of bone turnover was still apparent with both intermittent doses, indicated by reduced levels of median sP1NP and sCTX: with 150 mg oral monthly treatment (-61.0% and -39.1%, respectively) and with 3 mg IV q 3 mo (-45.0% and -36.0%, respectively). It is important to note that median absolute values of sP1NP and sCTX achieved after the first year of treatment with either oral or IV Boniva were within the premenopausal range, as defined by Elecsys (ROCHE Diagnostic assay), and were maintained within this range during the entire five-year course of the treatment.

3.1.4 Bone Histomorphometry Results

The bone histomorphometry substudy was conducted in the BM16550 and MA17904 studies. In this substudy, 29 patients underwent paired transiliac bone biopsies at year two (months 22 to 23 in the BM16550 core study) and year five (months 34 to 35 in the MA17904 study). In extension study MA17904, 16/29 of these patients received Boniva 2 mg q 2 mo for three years (seven of these patients had five years of treatment) and 13/29 received Boniva 3 mg q 3 mo for three years (nine of these patients had treatment for five years) following two years of the initial treatment with oral 2.5 mg daily, respectively in the core study.

The histomorphometric analysis of transiliac bone biopsies demonstrated a continued reduction in remodeling, normal composition of newly formed bone, and absence of defects in mineralization after approximately five years of treatment with IV Boniva. These effects were similar with both IV regimens of Boniva treatment as well as comparable to the effect seen in patients on 2.5 mg daily at year two. Furthermore, there was no evidence of a significant further change (reduction) in remodeling rates at five years compared with the rates at two years. This continued suppression of remodeling was sustained over five years of treatment while normal composition of newly formed bone was maintained. This is evidence in favor of the long-term efficacy and safety of intermittent IV therapy with Boniva.

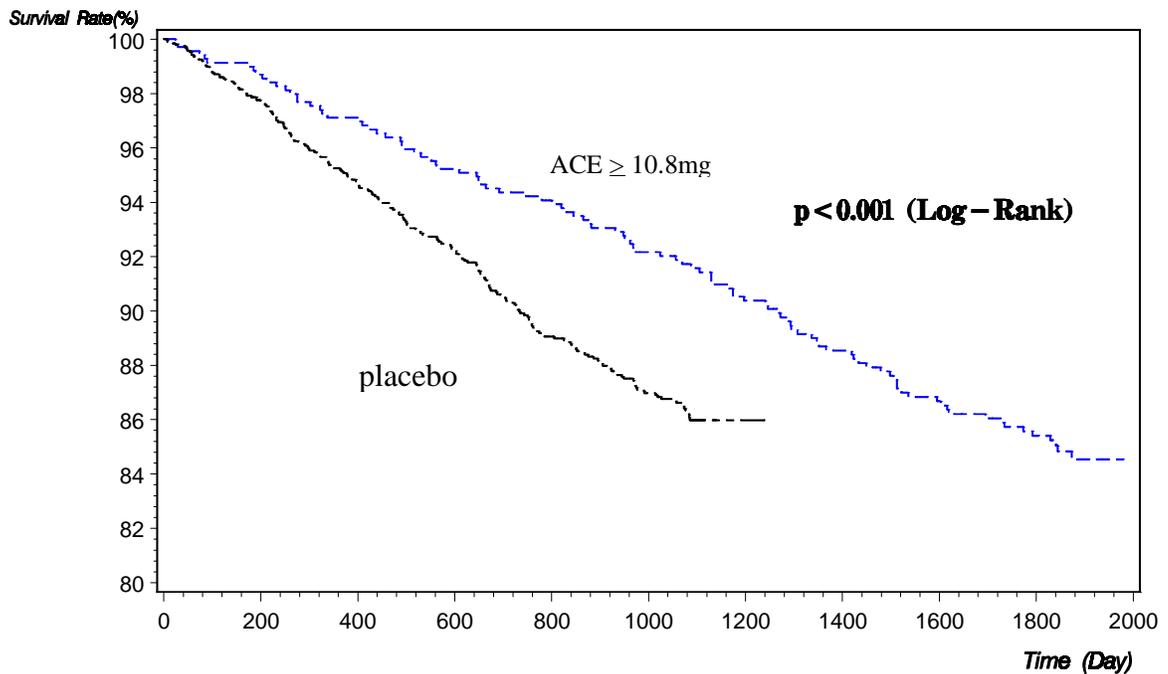
3.1.5 Fractures: Five-year Data

This analysis included 692 patients who received continuous treatment over five years with either monthly oral doses of 150 mg or IV doses of 2 mg q 2 mo or 3 mg q 3 mo.

The doses of Boniva, including marketed doses, had an annual cumulative exposure (ACE)* ≥ 10.8 mg. The 150 mg oral monthly, 2 mg IV q 2 mo, and 3 mg IV q 3 mo doses were pooled and compared with the pooled placebo group. The log-rank test showed that the Kaplan-Meier estimated time to first occurrence of any clinical fracture (Figure 2) was significantly longer with pooled doses of Boniva compared with placebo. This was true for comparisons using either three or five years of data, even though the placebo group ended at three years.

The rate of all clinical fractures over five years of oral or IV Boniva treatment was similar between the various treatment groups when analyzed as fracture rate or per 100 patient-years (Table 4).

Figure 2 Kaplan-Meier Estimated Time to First Clinical Fracture for Pooled Intermittent Doses of Boniva



The high ACE group in Figure 2 includes the following doses: 150 mg oral monthly, 2 mg IV q 2 mo, and 3 mg IV q 3 mo.

*ACE is calculated as the total annual dose multiplied by 0.6% for oral doses which represents the quantity that is systemically absorbed as determined from pharmacokinetic studies. The ACE for IV dosing is the total dose administered, which is 12 mg for 2 mg and 3 mg IV doses [3]. High ACE group includes 3 doses: 150 mg oral monthly, 2 mg IV q 2 mo and 3 mg IV q 3 mo.

Table 4 Incidence of at Least One Clinical Fracture after Five Years of Oral or IV Boniva Treatment (Safety Population)

Boniva regimen	Any clinical fracture, (%)	All clinical fractures per 100 patient- years ^a	ACE (mg)
2 mg IV q 2 mo	15.42	3.37	12
3 mg IV q 3 mo	14.07	3.01	12
150 mg oral monthly	14.77	3.20	10.8
High dose ACE ^b	14.74	3.19	≥ 10.8

The incidence of clinical fractures at 5 years was calculated as the proportion of patients having ≥ 1 fracture over 5 years of treatment.

^a Defined as 100 x the total number of patients with ≥ 1 clinical fracture/total person-years of treatment.

^b High dose ACE group included pooled data from the monthly 150 mg oral (ACE=10.8 mg), 2 mg IV q 2 mo, and 3 mg q 3 mo arms (ACE each =12 mg) . ACE = annual cumulative exposure, IV = intravenous,.

There was a reduction in the estimated proportion of patients with any clinical fracture with the three Boniva regimens compared with placebo, this reduction became more pronounced over time [4]. A similar meta-analysis was performed comparing a high ACE dosing group versus low (5.5 mg, including daily 2.5 mg) which showed that compared with the 2.5 mg daily dose, pooled intermittent doses had a significantly reduced clinical fracture risk [5].

The incidence of all clinical fractures was stable over five years with the pooled oral and IV Boniva regimens, suggesting there was sustained antifracture efficacy (Table 5). Similar trends were observed for all nonvertebral fractures and key nonvertebral fractures (ie, those affecting the clavicle, humerus, wrist, hip, pelvis, and leg) (Table 5).

Table 5 Crude Rate of Fractures by Year in Patients Receiving Continuous Treatment over 5 Years (Safety Population)

ACE ≥ 10.8 mg (pooled 150 mg oral, 2 mg and 3 mg IV) N=692			
	All Clinical Fractures	All Nonvertebral Fractures	Key Nonvertebral fractures*
Year 0 to <1	20/692 (2.89%) (95% CI 0.64, 0.14)	15/692 (2.17%) (95% CI 1.08, 3.25)	11/692 (1.59%) (95% CI: 0.66, 2.52)
Year 1 to <2	21/692 (3.03%) (95% CI 0.76, 0.31)	13/692 (1.88%) (95% CI 0.87, 2.89)	12/692 (1.73%) (95% CI: 0.76, 2.71)
Year 2 to <3	20/692 (2.89%) (95% CI 1.64, 4.14)	13/692 (1.88%) (95% CI 0.87, 2.89)	12/692 (1.73%) (95% CI: 0.76, 2.71)
Year 3 to <4	26/667 (3.90%) (95% CI 2.43, 5.37)	19/667 (2.85%) (95% CI 1.59, 4.11)	16/667 (2.40%) (95% CI: 1.24, 3.56)
Year 4 to 5	21/644 (3.26%) (95% CI 1.89, 4.63)	14/644 (2.17%) (95% CI 1.05, 3.30)	12/644 (1.86%) (95% CI: 0.82, 2.91)

*Key nonvertebral fractures include: clavicle, humerus, wrist, hip, pelvis, and leg.

3.1.6 Summary Regarding Long-term (> 3 years) Efficacy of Boniva

The efficacy of Boniva that began during the early phase of treatment was maintained during long-term treatment. The key efficacy findings that support this statement are based on findings for continuous treatment with either oral (150 mg monthly) or IV (3 mg q 3 mo) Boniva for up to 5 years.

- For patients treated for five years with oral or IV Boniva, mean BMD continuously increased in the lumbar spine and was initially increased and then generally maintained in the total hip compared with baseline.
- The proportion of patients classified as responders for lumbar spine BMD and for total hip BMD at five years of treatment was comparable to the proportion after one year of treatment for both oral and IV formulations.
- In the oral and IV Boniva treatment groups, the decrease in median BTM levels of sP1NP and sCTX achieved over the first year remained lowered relative to baseline over the entire five-year treatment period. At no time did median absolute sP1NP or sCTX values fall below the normal premenopausal range among patients treated with either oral or IV Boniva. The five-year bone histomorphometry results showed that newly formed bone was of normal composition, which supported the BTM results.
- Based on results of a meta-analysis of fractures in patients taking oral doses of 150 mg monthly or IV doses of 2 mg q 2 mo or 3 mg q 3 mo, the estimated time to first occurrence of any clinical fracture was significantly longer with either oral or IV doses of Boniva compared with placebo. The rate of first clinical fracture during five years of oral or IV Boniva treatment was similar with both marketed doses when analyzed by fracture type and when expressed as fracture rate per 100 patient-years.

3.2 Safety of Boniva

3.2.1 Overall Safety Profile of Boniva in the Clinical Development Program

The overall safety profile of Boniva (oral and IV) at year five was comparable to the profile established at year one. In addition, the safety profiles of oral monthly 150 mg and IV q 3 mo Boniva were similar to the safety profile of the 2.5 mg daily dose of Boniva and the 2.5 mg daily dose was shown in an earlier fracture trial to have a safety profile comparable to that for placebo.

3.2.2 Incidence of ONJ in Boniva Clinical Trials

The American Society of Bone Mineral Research (ASBMR) definition for ONJ [1] is as follows:

An area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.

A retrospective search of the clinical development program database was conducted to identify any cases of ONJ that may have occurred during the key Phase III and Phase IIIb trials. The trials included in the search are presented in [Table 6](#). The search was made for the preferred MedDRA term *osteonecrosis*.

- Based on the retrospective search of the clinical development program database, no confirmed cases of ONJ were reported with Boniva treatment for up to five years' duration.

Table 6 Trials Searched in the Clinical Development Trials Database

Study	Baseline condition	Duration (years)	Patients exposed to Boniva (safety population)	Boniva dose	Comparator
MF4411 (BONE, fracture)	PMO	3	1954	2.5 mg daily oral, 20 mg intermittent oral	Placebo
MF4380	PMO	3	1911	2.5 mg daily oral, 0.5 mg q3mo i.v.	Placebo
MF4380F	PMO	2	850	0.5 mg or 1.0 mg i.v. every 3 months	Placebo
BA18492 Prevention of PMO	Osteopenia	1	77 (randomized and safety pop)	150 mg oral monthly	Placebo
MF4499	PMO	2	489	0.5 mg/daily 1.0 mg/daily 2.5 mg/daily	Placebo
MF4500	PMO	2	466	5 mg/weekly 10 mg/weekly 20 mg/weekly	Placebo
Total Number of Placebo-treated Patients:					N =2661
BM16549 (MOBILE)	PMO	2	1583	150 mg monthly oral, 50/50 mg monthly oral, 100 mg monthly oral	Boniva 2.5 mg daily oral
(BM16550 (DIVA)	PMO	2	1382	2 mg q2mo i.v., 3 mg q3mo i.v.	Boniva 2.5 mg daily oral
MA17903 Extension to MOBILE	PMO	3	719	100 mg oral monthly, 150 mg oral monthly	NA
MA17904 Extension to DIVA	PMO	3	781	2 mg q2mo i.v., 3 mg q3mo i.v.	NA

(continued)

Table 6 Trials Searched in the Clinical Development Trials Database (Cont.)

Study	Baseline condition	Duration (years)	Total patients exposed to Boniva (safety population)	Boniva dose	Comparator
MM17835 (MOTION)	PMO	1	872	150 mg oral monthly	Alendronate 70 mg oral weekly
BA20341 Renal safety	PMO with high risk for renal disease	1	532 (and 526 for safety)	3 mg q3mo i.v. injection, same dose infusion	Alendronate 70 mg oral weekly
Total number of Alendronate-treated patients					N = 1124
					(safety population)
Total Number of Boniva-treated Patients			N = 11,610		
Total Estimated Patient-years of Exposure to any Boniva dose = 27,100					

3.2.3 Incidence of Atypical Fracture in Boniva Clinical Trials

The ASBMR Task Force definition of atypical femoral fracture requires the presence of all five of these major features [2]:

- 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, and
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Specifically excluded from the definition were fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and peri-prosthetic fractures.

The ASBMR Task Force report concluded that a causal association between bisphosphonates and atypical femoral fracture has not been established.

A retrospective search of the clinical development program database was conducted to identify any cases of atypical fracture that may have occurred during the key Phase III and Phase IIIb trials listed in Table 6. The search terms used for adverse events in the 12 clinical trials included: femoral neck fracture, femur fracture, and hip fracture. In order to capture events not reported as adverse events, but mentioned in patient narratives or laboratory test results, a free-text search was performed. The following search terms

were used: trochanteric fracture, subtrochanteric fracture, pertrochanteric fracture, atypical fracture, stress fracture, and insufficiency fracture.

Manual review of all fracture cases was performed to assess femur fractures according to ASBMR criteria for atypical fractures [2]. Location of the fracture was assessed based on the reporter preferred term, investigator term, or additional comments. All prior traumas or falls were assessed as low impact, unless a car accident or specific high-velocity trauma was indicated.

Information on all ASBMR features for atypical fractures in the reports of femoral fractures was limited. Based on available data, there were no definitive cases of atypical femur fractures reported in Boniva key Phase III or Phase IIIb trials in the 11,610 patients who received Boniva for up to five years.

3.2.4 Spontaneous Reports from the Roche Pharmacovigilance Database (ADVENT)

The source of information for spontaneous reports of ONJ or atypical fracture was ADVENT, the Roche global pharmacovigilance database. All spontaneous reports and serious adverse events from clinical trials and postmarketing studies (including ibandronate literature case reports) from countries where Roche ibandronate products are marketed are coded onto ADVENT.

ADVENT was searched for spontaneously reported events related to ONJ or atypical fracture. The search also included any serious adverse events reported from post-marketing studies and clinical trials (except for the 12 trials identified in [Table 6](#) and discussed in Sections [3.2.2](#) and [3.2.3](#)).

3.2.4.1 Spontaneous Reports of ONJ

ADVENT was searched for events related to ONJ from June 1, 2008 through May 24, 2011. The search results were adjudicated independently by two Roche physicians. It should be noted that data quality was limited because of the nature of spontaneous and solicited reporting.

Results

A total of 34 of 176 potential cases met the definition of ONJ as per the ASBMR case definition [1]. [Appendix 1](#) presents a schematic diagram of the distribution of the original potential cases of ONJ that were adjudicated. Based on more than 16 million patients exposed to Boniva during the stated time period, this represents a crude reporting rate of 2.1 ONJ cases per 1,000,000 patients exposed in the PMO indication.

For total bisphosphonate use (including previous bisphosphonate use [in 20 out of 34 cases]) the median duration was 2.5 years (range of 0.2 to 7.6 years). The median duration of Boniva treatment was 1.7 years (range of 0.2 to 6.0 years).

Risk factors for ONJ were reported in 20/34 patients, as follows: history of dental intervention in 14 cases and previous use of steroids in 12 cases, with 6 of these cases containing both risk factors. In the remaining 14 patients, no risk factors were reported. In seven of these reports, there were no details about any test performed and/or test result;

therefore, there was insufficient information to make any further medical assessment on their ONJ diagnosis.

The outcome of ONJ at the time of reporting was “unknown” in 10 patients, “resolved/improved” in 13 patients, and “persisting” in 11 patients.

In summary, when assessing these 34 case reports, a possible contributory role of Boniva and other bisphosphonates in the occurrence of ONJ could neither be excluded nor confirmed.

3.2.4.2 Spontaneous Reports of Atypical Fracture

ADVENT was searched cumulatively up to May 24 2011, for spontaneous reports and reports in the clinical development program and postmarketing studies for potential atypical fracture reports. There were no confirmed reports of atypical fractures from clinical development studies or postmarketing studies. The only cases were from spontaneous reports and the literature.

The search results were adjudicated independently by three Roche physicians. They found that eight patients, including six from literature case reports, had femoral fractures that fulfilled all five ASBMR criteria [2]. [Appendix 2](#) presents a schematic diagram of the distribution of the hip and femur fracture cases that were adjudicated by the three Roche physicians.

Of the eight cases, three had Boniva treatment only (duration of treatment: 1.0, 2.0, and 4.3 years). For all eight cases, the median duration of bisphosphonate treatment was 4.0 years with a range of 2.0 to 17.0 years. No additional information was provided about possible risk factors in any of these patients (ie, rheumatoid arthritis, diabetes, cancer, use of corticosteroids, proton pump inhibitors, or any other antiresorptive treatments).

Based on more than 26 million patients exposed to Boniva, the crude reporting rate of atypical fractures that fulfilled all five ASBMR criteria (n=8) was less than 0.3 per 1,000,000. Even in the context of potential under-reporting, this adverse event is very rare ($\geq 1/100,000$ to $<1/10,000$).

In summary, when assessing these eight case reports, a possible contributory role of Boniva and other bisphosphonates in the occurrence of atypical fracture could neither be excluded nor confirmed.

3.2.5 Proactive Actions to Identify Cases of ONJ and Atypical Fractures

Roche created a Guided Questionnaire (GQ) system in an attempt to increase data quality by obtaining better characterization of potential ONJ and atypical fracture cases.

In April 2007, a GQ implemented by the Sponsor used the ASBMR 2007 case definition of ONJ for spontaneous reports of ONJ and certain events that corresponded to the oral and dental region [1]. This GQ, a tool of enhanced pharmacovigilance monitoring, is used within the osteoporosis and oncology indications of ibandronic acid (although not approved in the US, ibandronic acid is indicated for use in adult patients with breast

cancer and bone metastases in other countries, including the European Union, for the prevention of skeletal events such as pathological fractures or bone complications requiring radiotherapy or surgery). The GQ is sent by Roche to reporting Health Professionals and/or Dentists/Oral Surgeons upon receipt of a spontaneous report. The GQ aids to improve data quality and obtain further information about ONJ. In January 2011, a revised GQ was implemented by the Sponsor for spontaneous reports of ONJ and suspicious adverse events in the oral and dental region to further improve data quality and provide further information about ONJ cases.

In November 2009, a GQ was implemented by the Sponsor for spontaneous reports of femur and hip fractures, which may be reports of potential atypical fracture. This questionnaire, is used within the osteoporosis and oncology indications of ibandronic acid and is administered in the same way as the ONJ GQ. In January 2011, this GQ was revised to include the ASBMR Task Force 2010 features.

The following risk mitigation measures are currently in place:

The Warnings and Precautions section of the USPI contains detailed language to raise the awareness of the physician to the possible occurrence, nature, and possible risk factors for events on ONJ or atypical fracture. The USPI states that “Interruption of therapy should be considered, pending a risk/benefit assessment, on an individual basis” for atypical fractures and “clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment”. Roche considers these statements consistent with principles of good patient management.

The patient-directed Medication Guide which is dispensed with every prescription additionally raises the awareness of patients to the events of atypical fracture and ONJ and refers them to their doctor in the event of manifestation of possible symptoms of these events.

In addition, all communications to physicians from the Sponsor regarding Boniva include information on the risk of ONJ and atypical fractures.

3.2.6 Other Adverse Events of Interest: Esophageal Cancer

ADVENT was searched up to July 26, 2011 for cases of esophageal cancer.

In the Boniva clinical development program for PMO, two cases of esophageal cancer were reported, one in study BM16549 and one in study BM16550. Both patients had 50-year histories of smoking (known to be an important risk factor for esophageal cancer). No cases were reported in long-term extension studies MA17903 or MA17904 in which patients were treated with oral 150 mg or 3 mg IV q 3 mo of Boniva for up to five years.

Ten spontaneous case reports of (potential) esophageal cancer were identified in the ADVENT database. Three patients had reports of esophageal tumors. It was unknown whether or not these tumors were malignant. One patient with worsening gastric reflux disease was suspected of having esophageal cancer, however no results of further testing were provided. One patient had a very short latency period and a high likelihood of pre-existing esophageal cancer. Bisphosphonate use and/or drug exposure were minimal (a differentiated adenocarcinoma of gastroesophageal junction was diagnosed 45 days after

one oral dose of 150 mg Bonviva). One patient had a medical history of cancer and hiatal hernia and reflux. The patient was treated with Bonviva for 222 days. She was diagnosed with esophageal cancer 735 days after the start of Bonviva treatment while on lansoprazole therapy (duration of use unknown). Esophageal cancer could not be excluded in four remaining patients, who had no reported risk factors.

In postmarketing studies one case of pre-existing esophageal cancer was reported in a patient on IV Bonviva.

The crude reporting rate of esophageal cancer when Bonviva was used is less than 0.5 events in 1,000,000 patients exposed.

As a risk mitigation measure, the USPI includes language contraindicating oral bisphosphonates in patients with abnormalities of the esophagus that delay gastric emptying and who are unable to stand or sit upright for at least 60 minutes. The wording of the Warnings and Precautions section of the label of the oral bisphosphonates, including Bonviva, was strengthened. In addition, all communications to physicians from the Sponsor regarding Bonviva include information on the risk of esophageal abnormalities.

An association between long-term use of Bonviva and esophageal cancer can neither be excluded nor confirmed based on the available data.

3.2.7 Summary Regarding Long-term (> 3 years) Safety of Bonviva

- The overall safety profile in the clinical development program of Bonviva after up to five years of continuous treatment with either an oral monthly dose of 150 mg or an IV dose of 3 mg q 3 mo (total estimated exposure of 11,900 patient-years) was similar to the profile obtained after the first year of treatment. No new safety concerns or signals emerged after the first year on treatment.
- There were no confirmed reports of ONJ or atypical fracture in the Bonviva clinical development program with up to five years of treatment.
- Spontaneous reports of ONJ or atypical fracture (including literature cases and post-marketing studies) have been rare. The crude reporting rate for confirmed ONJ (per ASBMR case definition 2007) was 2.1 events per 1,000,000 patients exposed, and for atypical fractures (meeting all 5 ASBMR Task Force criteria 2010) the crude reporting rate was 0.3 events per 1,000,000 patients exposed.
- At the present time, there is no definitive agreement on whether an increase in the occurrence of ONJ or atypical fracture is associated with bisphosphonate use. Nevertheless, several risk management tools are currently in place:
 - Roche developed a risk management pharmacovigilance tool in the form of GQs that are used to enhance understanding of reported cases of ONJ and atypical fracture. The GQ for ONJ has been in use since 2007 and the GQ for atypical fracture has been in use since 2009.
 - The Warnings and Precautions section of the USPI contains detailed language to raise the awareness of the physician to the possible occurrence, nature and possible risk factors for these events. The USPI states that “Interruption of therapy should be considered, pending a risk/benefit

assessment, on an individual basis” for atypical fractures and “clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment” for ONJ. Roche considers these statements consistent with principles of good patient management.

- The patient-directed Medication Guide which is dispensed with every prescription additionally raises the awareness of patients to the events of atypical fracture and ONJ and refers them to their doctor in the event of manifestation of possible symptoms of these events.
- In addition, all communications to physicians from the Sponsor regarding Boniva include information on the risk of ONJ and atypical fractures.
- Roche is committed to the continued collection of and investigation into reported or suspected cases on ONJ and atypical fracture and any safety issue associated with the use of Boniva.

4. TOPIC # 2 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

SPONSOR'S OPINION: There is no evidence to either support or refute that limiting the duration of use or implementing a drug holiday would benefit patients who are on long-term treatment. All patients on bisphosphonate therapy should have the need for continued therapy reevaluated on a periodic basis as per the current USPI. The treating physician is best placed to make this determination.

The safety profile following long-term treatment was consistent with the safety profile following short-term treatment. Efficacy was maintained during long-term use.

Considerations for restricting the duration of use or implementing a drug holiday should account for several factors including:

1. The degree of osteoporotic fracture protection afforded by long-term bisphosphonate treatment:

The pooled data from the Boniva oral and IV long-term extension studies have demonstrated the efficacy and safety of Boniva for up to five years and suggest that continued use over a longer period of time would maintain this stable profile.
2. The extent to which fracture protection is attenuated by discontinuation of the drug:

Study MF4348 was a double-blind, placebo-controlled trial of Boniva in PMO patients who were treated for one year with either oral Boniva (0.25, 0.50, 1.0, 2.5, or 5.0 mg daily) or placebo and then followed for one year after discontinuation of treatment. One hundred-forty-one patients completed the first year of the study and 119 women completed the second year. After discontinuation of treatment, BMD at the lumbar spine and proximal femur decreased equally in all groups with a rate of 2% per year on average, a rate which is similar to the normal

postmenopausal bone loss. Twelve months after discontinuation of drug treatment, the bone resorption markers and serum osteocalcin had returned to baseline values.

The Sponsor reviewed published reports on this topic for other bisphosphonates. The most relevant of these was the FLEX study [6]. The results suggest that when considering discontinuation of treatment or implementation of a drug holiday for the management of osteoporosis, the potential loss of benefit needs to be balanced against the potential reduction in risk. In some patients a drug holiday may be appropriate, conversely, high-risk patients may benefit from continued treatment.

An additional report from a large US insurance database showed that longer durations of previous bisphosphonate treatment and greater compliance during treatment conveyed more fracture protection [7].

3. The quantitative levels of various types of risk potentially associated with long-term use of bisphosphonates:

Our knowledge regarding Boniva is presented in Section 3 of this report. In brief, safety as well as efficacy for up to five years of treatment has been demonstrated and rates of atypical fracture and ONJ are very rare based on post marketing reports.

4. The extent to which any risk assumed with long-term therapy diminishes after discontinuation of the drug:

There is limited clinical data to address this key concern of long-term use, either for Boniva specifically, or for other bisphosphonates. The suggestion of a drug holiday implicitly assumes there will be a significant decrease in overall risk following discontinuation of bisphosphonate treatment after long-term use. Empirical data to support a decreased risk are generally lacking (see Section 5 for benefit/risk discussion).

The current USPI reflects the current state of knowledge with regard to atypical fracture, ONJ, and duration of use, and allows flexibility for the treating physician to best provide individualized care for each patient based on their response to the drug and risk factors. The USPI notes that “all patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis” which is consistent with good medical practice. Section 1.2, “Important Limitations of Use” in the current label states:

“The safety and effectiveness of BONIVA for the treatment of osteoporosis are based on clinical data of three years’ duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.”

5. BENEFIT/RISK

In assessing the value of long-term treatment or the need for a drug holiday, both the benefit of treatment and the risk of treatment must be taken into consideration.

BENEFIT: The benefit of treatment with the bisphosphonate class of drugs is prevention of vertebral and nonvertebral fractures. For the purposes of evaluation of benefit of a

given medication, a number needed to treat (NNT) may be of use. For Boniva, the NNT is derived from the pivotal fracture trials where a placebo treatment group was included. From these pivotal fracture trials, (BONE and MF4380), the NNT to prevent 1 vertebral fracture was 22. The NNT to prevent 1 non-vertebral fractures was 52, determined from the meta-analysis performed by Cranney and colleagues [5].

RISK: For the purpose of this discussion, the relevant risks include atypical fractures and ONJ. No cases were observed in the placebo-controlled Boniva pivotal trials, therefore, the number needed to harm (NNH) for these adverse events cannot be calculated for Boniva. The reported atypical fracture incidence rate for osteoporosis patients taking bisphosphonates calculated from three studies was 2.3 per 10,000 patient-years [8]. This incidence was corroborated by a registry study and a population-based study [9, 10]. If one assumes hypothetically, that the highest relative risk of atypical fractures associated with bisphosphonate therapy is 3.0, then the NNH would be 725 patients needed to be treated for three years in order to observe one atypical fracture or 435 patients needed to be treated for five years in order to observe one atypical fracture.. Given that the reported incidence rate of ONJ is even lower than that of atypical fractures, fewer events would be expected and the NNH would be even higher.

In summary, the benefit/risk ratio for Boniva treatment for up to five years remains favorable, based on the available data.

6. CONCLUSIONS

The long-term efficacy and safety data with Boniva treatment support long-term use in patients with PMO.

ONJ and atypical fracture are rare adverse events. No confirmed cases of either ONJ or atypical fracture were observed in the clinical development program in which patients received marketed doses of Boniva for up to five years of continuous treatment. Spontaneous reports of cases have been rare. Currently, there is no agreement on whether an increase in their occurrence is associated with bisphosphonate use. Roche is committed to the continued collection of and investigation into reported or suspected cases of ONJ and atypical fracture as well as any safety issues associated with the use of Boniva.

Interruption of long-term treatment *may* be appropriate for certain patients when their individual risk benefit situation is taken into consideration, but this needs to be assessed on an individual patient basis.

The current USPI reflects the current state of knowledge with regard to atypical fracture, ONJ, and duration of use, and allows flexibility for the treating physician to best provide individualized care for each patient based on their response to the drug and any existing risk factors.

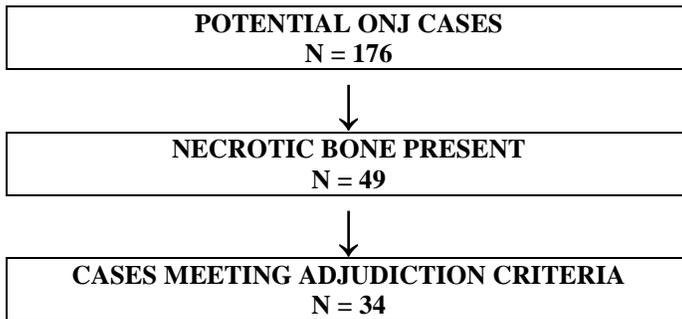
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8. APPENDICES

Appendix 1 Potential ONJ Cases in the ADVENT Database



Appendix 2 Potential Atypical Fracture Cases in the ADVENT Database

