

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

1.3.2 Efficacy

Data from two identical randomized, double-blind, active-controlled, non-inferiority (vs. risedronate) trials provide sufficient evidence to support the efficacy of a single 5 mg intravenous infusion of zoledronic acid in the treatment of Paget's disease of bone. The primary efficacy endpoint in these trials was a comparison of the proportion of patients in each treatment group who either had normalization or a reduction of at least 75% from baseline of their serum bone-specific alkaline phosphatase at the end of 6 months. At Month 6, 96% of the subjects treated with zoledronic acid and 74% of the subjects treated with risedronate achieved a therapeutic response (95% CI for difference 14%, 30%).

1.3.3 Safety

The principal safety concerns that emerged from the pivotal Paget's trials were hypocalcemia, and to a lesser extent, hypophosphatemia. Asymptomatic reductions in serum levels of calcium and phosphorus have been observed in pagetic patients treated with oral alendronate and risedronate, but by comparison, the risk appeared to be greater and occur more rapidly following treatment with 5 mg intravenous zoledronic acid.

At Day 10 of the trials, 32 of the 151 (21%) patients who received zoledronic acid vs. 5 of the 156 (3.0%) who received risedronate, had serum calcium levels below 2.1 mmol/L. Twenty-eight of the 157 (18%) subjects who received zoledronic acid compared with 2 of the 159 (1.3%) treated with risedronate developed serum phosphorus levels below 0.71 mmol/L (2.1 mg/dl) at Day 10. Four of the zoledronic acid subjects and none of the risedronate subjects developed markedly low serum calcium levels (< 1.87 mmol/L) at Day 10.

Although all patients in the two pivotal trials were instructed to take 500 mg bid of daily supplemental calcium and 400 to 1000 IU of daily supplemental vitamin D, the sponsor did not have data to verify if, when, or how much of the supplements were actually taken. Absent this information, it was not possible to judge how effective supplemental calcium and/or vitamin D are in reducing the risk for hypocalcemia and hypophosphatemia, and left unanswered the question of the safety of the proposed dosing regimen.

In their response to the March 2005 approvable letter, Novartis provided information on the amount of supplemental calcium and vitamin D patients took during the two Paget's trials. These data were obtained from questionnaires filled out by investigative-site personnel after the trials were completed. Novartis states that only information from source documents was used to complete the questionnaires. Data on calcium and vitamin D supplementation were obtained from 98% of the patients.

Twenty-four subjects reportedly took < 1000 mg/day of supplemental calcium, 100 took 1000 mg/day, and 27 took > 1000 mg/day of supplemental calcium. The mean percent changes in serum calcium from baseline to Day 10 were -12.0%, -7.0%, and -9.0% in the three groups, respectively.

Of the group that took less than 1000 mg per day, 50% had Day 10 serum calcium levels < 2.1 mmol/L. Seventeen percent of the patients who received 000 mg or more per day of calcium had serum calcium levels < 2.1 mmol/L at Day 10. Of the 63 zoledronic acid subjects who reportedly took less than 800 IU of daily vitamin D, 22 (35%) had a Day 10 serum calcium < 2.1 mmol/L. Of the 82 patients who purportedly took \geq 800 IU of daily vitamin D, 10 (12%) had low serum calcium levels at Day 10.

These data suggest that intake of at least 1000 mg per day of supplemental calcium and/or 800 IU per day of supplemental vitamin D reduces the risk for developing hypocalcemia in pagetic patients treated with a 5 mg intravenous zoledronic acid.

In an analysis of covariance statistical model, treatment with zoledronic acid (vs. risedronate) and low-normal baseline serum calcium level were the two strongest predictors of a Day 10 calcium level < 2.1 mmol/L. Other correlates of lower serum calcium at Day 10 were geographic region (Australia and New Zealand vs. rest of the world), dose of supplemental calcium and vitamin D, low baseline levels of 25OH vitamin D, and high levels of serum alkaline phosphatase and serum phosphate.

Efforts aimed at maintaining normal serum calcium levels following treatment with zoledronic acid, such as ensuring adequate supplemental calcium and vitamin D intake, will minimize increases in PTH and thereby reduce the risk for developing hypophosphatemia, since PTH increases urinary excretion of phosphorus.

In a submission dated 24 January 2006, Novartis provided the Division with interim safety data from the nearly-completed 3-year osteoporosis fracture trial 2301. This study randomized approximately 8000 postmenopausal women to treatment with once-yearly 5-mg zoledronic acid or placebo. There was a statistically significant increase in the incidence of cardiac arrhythmias in the zoledronic acid group compared with the placebo group (5.7% vs. 4.1%; nominal $p=0.0006$). The arrhythmias reported included atrial fibrillation, 1st degree AV block, SV extrasystoles, SV tachycardia, tachycardia, and sick sinus syndrome. Serious arrhythmias were reported in 2.2% of zoledronic acid vs. 1.3% of placebo-treated patients (nominal $p=0.001$). The overall rates of death were 2.8% vs. 2.4% in the active compared with the placebo treatment groups. An increase in serious ophthalmic adverse events was also reported.

These data will be adjudicated by the study's Data Safety Monitoring Board by mid-March 2006. The adjudicated safety data should be reviewed by the Division and factored into zoledronic acid's risk-benefit profile before a final decision is made regarding approval of this NDA.

1.3.4 Dosing Regimen and Administration

Novartis has submitted sufficient evidence that a single infusion of 5 mg zoledronic acid is effective in the treatment of Paget's disease. Information provided in the applicant's complete response to the approvable letter indicates that daily intake of at least ~~2~~ mg bid supplemental calcium and 800 IU supplemental vitamin D attenuates the risk for developing hypocalcemia following treatment with zoledronic acid.

1.3.5 Drug-Drug Interactions

Caution is warranted when administering zoledronic acid concomitantly with drugs that have the potential to lower serum calcium levels, such as loop diuretics, aminoglycosides, and Dilantin. *In-vivo* data do not indicate that zoledronic acid inhibits microsomal CYP450 enzymes.

Special Populations

The dose of zoledronic acid should be reduced in patients with renal insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid 4 mg injection is currently approved for the treatment of hypercalcemia of malignancy and the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

Two pivotal trials were conducted to support the efficacy and safety of 5 mg intravenous zoledronic acid in Paget's disease. Trials 2304 and 2305 were identical multinational, randomized, double-blind, active-controlled, 6-month non-inferiority trials in which 30 mg oral risedronate daily x 60 days was the comparator.

2.6 Other Relevant Background Information

2.6.1 Basis for Approvable Regulatory Action

Novartis was sent an approvable letter on March 18, 2005, for the original submission of this NDA because of concern regarding the incidence of hypocalcemia and hypophosphatemia in Paget's patients treated with a single 5 mg intravenous dose of zoledronic acid.

In analyses of pooled data from studies 2304 and 2305, 21% of the patients who received zoledronic acid, compared with 3% who received risedronate, had serum calcium levels < 2.1 mmol/L at Day 10. Seven patients in the zoledronic acid group and one in the risedronate group had markedly decreased serum calcium levels (i.e., < 1.90 mmol/L) at Day 10. Eighteen percent of the zoledronic acid patients and 1.3% of the risedronate subjects had serum phosphorus levels < 0.71 mmol/L at Day 10.

The Approvable Letter stated in part that, "Before the 5 mg dose of zoledronic acid can be approved for the treatment of Paget's disease, you must provide adequate evidence that administration of supplemental calcium and/or vitamin D to patients treated with zoledronic acid satisfactorily attenuates the risk for hypocalcemia and hypophosphatemia."

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Synopsis of Sponsor's Response to the Approvable Letter

This section provides Novartis's verbatim response to the Division's approvable letter. I provide commentary in boxed, bolded font.

Paget's disease of bone is characterized by high bone turnover, and zoledronic acid by virtue of its anti-resorptive mechanism of action, may result in a clinically significant demand for calcium in this population. This demand can be met by:

- Increasing calcium intake, along with adequate vitamin D supplementation to maximize absorption; and
- A normal parathyroid response which helps to maintain normocalcemia by acutely increasing calcium mobilization from the skeleton and reducing urinary calcium excretion.

It is acknowledged that zoledronic acid 5 mg has a greater effect on serum calcium and phosphate than risedronate 30 mg daily for 2 months. In this response, information is presented that provides elucidation of factors that may impact changes in serum calcium following bisphosphonate administration or that may affect whether a patient's serum calcium falls below the lower limit of the normal reference range following infusion of zoledronic acid 5 mg in Paget's disease. After a brief discussion on the analytical methodology employed, data are presented in relation to whether or not a patient experienced a decline in serum calcium such that their Day 10 level was below the LLN (2.10 mmol/L or 8.4 mg/dL).

Data are presented in relation to their impact on the change in corrected serum calcium. The key variables that are discussed include;

- Baseline serum calcium
- Baseline SAP
- Baseline serum vitamin D
- Baseline serum phosphate
- Dose of calcium supplementation
- Dose of vitamin D supplementation
- Regional effects

Information on the dosage of vitamin D and calcium supplementation prescribed to patients was obtained from source data collected from study sites by a standard questionnaire and from adverse events reported by the investigator during the trial. The questionnaire was sent to all study centers and the data on approximately 98% of the patients was collected. All calcium and vitamin D supplementation data utilized in the analyses was obtained from data that existed in the source documentation prior to database lock even though the questionnaire was not sent to all study centers until after clinical database lock.

Telephone interviews were conducted with the principal investigators and study coordinators to better understand the cases of hypocalcemia, with a focus on co-morbidities that could influence

the risk of developing hypocalcemia. This information was not utilized in any of the inferential analyses.

In order to understand factors predictive of “hypocalcemia” (corrected serum calcium < LLN on Day 10) the data were examined in two general ways. In the first approach, descriptive statistics and logistic regression models were used to identify factors predictive of a patient going below the LLN. In the second approach, descriptive statistics and analysis of variance/covariance models were used to identify factors predictive of decreases in corrected serum calcium.

Models were constructed using the laboratory parameters and calcium/vitamin D dosing variables as continuous variables wherever possible. Dichotomization was performed related to calcium and vitamin D supplementation in the logistic regression due to the relative low frequency of events of hypocalcemia.

There is an inherent limitation in the analysis of factors predicting the “event” of hypocalcemia in that some patients presented at baseline near the threshold LLN for serum calcium, where even small changes result in an event. The modeling of changes in corrected serum calcium is the preferred method to explain the biochemical changes that have occurred due to the greater level of sensitivity to associate risk factors with the outcome variable of interest.

In addition to treatment (zoledronic acid, risedronate), the following variables were used in model development and understanding of the factors that contribute to changes in corrected serum calcium:

- Region (Australia/New Zealand, USA/Rest of World)
- Study (CZOL446H2304, CZOL446H2305)
- Dose of calcium supplementation (continuous divided by 100; < 1000 mg/day, ≥ 1000 mg/day)
- Dose of vitamin D supplementation (continuous divided by 100; < median (800 IU), ≥ median (800 IU))
- Baseline SAP (continuous with log-transformation; < 400 U/L, ≥ 400 U/L)
- Baseline vitamin D level (continuous with log-transformation; < median (60 pmol/mL), ≥ median (60 pmol/mL))
- Baseline corrected serum calcium level (continuous; < median (2.37 mmol/L), ≥ median (2.37 mmol/L))
- Baseline phosphate level (continuous; < median (1.135 mmol/L), ≥ median (1.135 mmol/L))

In performing the retrospective analyses, similar procedures to what would have been utilized if the analyses were prospectively defined were used. Thus, if factors are to be dichotomized, the values used to create subgroups should either have some historical basis or be driven by their ability to help explain any two-factor interactions that may exist within the data. This is the reason why observed medians or protocol-specified values were used as the cutpoints to categorize the biochemical and calcium/vitamin D dosing variables used in the statistical models.

A systematic evaluation of factors predictive of patients falling below the LLN was performed.

The number of patients falling below the lower limit of normal (LLN) is 21.2% and 21.8% for zoledronic acid patients with respect to uncorrected and corrected serum calcium compared to 2.6% and 7.1% respectively for risedronate. Because of this larger treatment effect of zoledronic acid, the focus of subgroup differences will be within the zoledronic acid only.

The relationship between levels of the subgroup variables and the incidence of patients falling below the LLN is presented in following Table.

INCIDENCE OF ZOLEDRONIC ACID-TREATED PATIENTS < LLN NORMAL FOR CORRECTED SERUM CALCIUM AT DAY 10 BY SUBGROUPS

Variable	Subgroup	Zoledronic Acid		P-value (1)
		n/N	(%)	
Baseline SAP (U/L)	< 400	13/96	(13.5)	0.0019
	≥400	19/51	(37.3)	
Dose of calcium supplementation (mg/day)	< 1000	11/22	(50.0)	0.0016
	≥1000	21/123	(17.1)	
Dose of Vitamin D supplementation (IU/day)	< 800	22/63	(34.9)	0.0021
	≥800	10/82	(12.2)	
Region	Australia/New Zealand	21/43	(48.8)	<0.0001
	USA/Rest of World	11/104	(10.6)	
Baseline Phosphate	< Median (1.135)	10/78	(12.8)	0.0095
	> Median (1.135)	22/69	(31.9)	
Baseline Corrected Serum Calcium Category (mmol/L)	< Median (2.37)	21/76	(27.6)	0.1136
Baseline Vitamin D (pmol/mL)	> Median (2.37)	11/71	(15.5)	0.1202
	< Median (60)	10/66	(15.2)	
	> Median (60)	22/81	(27.2)	

(1) P-value is calculated based on a Chi-square test with continuity correction to evaluate the within-treatment difference for the two subgroups within the zoledronic acid treatment group.

There is an approximate twofold or higher incidence of patients falling below the LLN within the zoledronic acid group for individuals who:

- Had a baseline SAP of ≥ 400 U/L
- Received a dose of calcium supplementation < 1000 mg/day
- Received a dose of Vitamin D < 800 IU/day
- Were from Australia/New Zealand
- Had a baseline serum phosphate level ≥ to the median level of 1.135 mmol/L
- Had a baseline corrected serum calcium < the median level of 2.37 mmol/L

Alkaline Phosphatase

For patients who had a baseline SAP \geq 400 U/L, the risk of falling below the LLN was nearly threefold (37.3%) greater compared to patients who were $<$ 400 U/L at Day 10 (13.5%). This difference may be attributed to the greater change in bone resorption for patients with higher baseline SAP following bisphosphonate therapy.

Supplemental Calcium

The study protocols recommended that 1,000 mg of supplemental calcium be taken daily, but variability in the prescribed dose across study sites was evident. The incidence of corrected serum calcium below the LLN is almost three-fold greater in the zoledronic acid treated group receiving less than the protocol recommended 1,000 mg daily. The incidence $<$ LLN for uncorrected serum calcium corroborate these results where 45.5% of subjects who received less than 1000 mg/day are $<$ LLN compared to 17.3% for subjects who received \geq 1000 mg/day ($p = 0.0072$). Therefore, a daily calcium intake of \geq 1,000 mg results in a substantial reduction in the incidence of low serum calcium. This result is supported by the more than twofold greater incidence rate of corrected serum calcium below the LLN for risedronate-treated patients who received $<$ than 1000 mg daily of calcium supplementation.

Supplemental Vitamin D

The study protocols recommended that patients receive at least 400 IU/day of vitamin D. The median dose of vitamin D received was 800 IU/day. When receiving less than 800 IU/day, the incidence of corrected serum calcium below the LLN is almost three-fold greater (34.9%) relative to those subjects who received at least 800 IU/day (12.2%). This difference is more than four-fold greater with respect to uncorrected serum calcium, 38.1% when receiving $<$ 800 IU/day versus 9.3% when receiving \geq 800 IU/day.

These differences suggest that adequate doses of vitamin D supplementation also reduce the risk of experiencing corrected serum calcium below the LLN. However, since calcium and vitamin D are commonly provided in fixed combinations, it is difficult to determine if this represents an independent effect of supplemental vitamin D.

Geographical Region

There was a pronounced regional effect whereby 21/32 (65.6%) of the zoledronic acid-treated patients with Day 10 corrected serum calcium $<$ LLN were from New Zealand and Australia, yet only 43/147 (29.3%) of the zoledronic acid-treated patients in the study with corrected serum calcium at baseline and Day 10 were from this region.

- In the Australia/New Zealand region, 21/43 patients (48.8%) in the zoledronic acid group were $<$ LLN on Day 10, versus 11/104 patients (10.6%) in USA/Rest of World
 - In the risedronate treatment group, 7/42 patients (16.7%) from New Zealand/Australia were $<$ LLN at Day 10 compared to 4/112 (3.6%) in the USA/Rest of World
 - ~~performed calcium measurements in regional laboratories.~~
- All patient samples from the New Zealand/Australia region were analyzed in Australia.

- Mean baseline values for corrected serum calcium were approximately 0.09 mmol/L lower in New Zealand/Australia compared to the rest of the world, consistent with the lower normal range identified by _____ for this region of the world.

These findings suggest an inherent difference in baseline values and possibly the response of patients in the Australia/New Zealand region compared to the ROW. Differences might be related to a lower amount of calcium in the diet. There may be less emphasis on the importance of daily vitamin D and calcium supplementation in this region, which is reflected by 18 of 24 zoledronic acid patients from the primary analysis population who received less than the recommended 1000 mg of daily supplemental calcium originating from either Australia or New Zealand.

There were 11 (10.6%) zoledronic acid patients with corrected serum calcium < LLN at Day 10 from USA/ROW. The experience in New Zealand and Australia is not representative of the experience in the USA/ROW. In the USA/ROW, the majority of patients with corrected serum calcium < LLN were just below 2.1 mmol/L which has minimal clinical significance and does not reflect an increased risk of developing serious adverse events. Larger declines in serum calcium can occur from insufficient oral calcium intake, conditions where intestinal absorption of nutrients are impaired, or parathyroid disease secondary to surgical resection. Therefore, mitigation of the risk of hypocalcemia will depend on identification of patients with predisposing disorders of calcium homeostasis, and, most importantly, ensuring administration of appropriate oral calcium and vitamin D intake.

Baseline Serum Phosphorus

The incidence of corrected serum calcium < LLN at Day 10 is approximately 2.5 times more likely when the baseline phosphate level is \geq the median level of 1.135 mmol/L (31.9%) versus those < the median level of 1.135 mmol/L (12.8%) at baseline.

Baseline Serum Calcium

The risk of being < LLN with respect to baseline corrected serum calcium is approximately 1.8 times greater when the baseline level is < the median baseline level (2.37 mmol/L). This risk increases greatly in the lower quartile (\leq 2.30 mmol/L) where the incidence rate was 40.5% (17/42). This subgroup includes many of the patients from Australia/New Zealand who were lower than the remainder of the population with respect to their baseline corrected serum calcium.

In comparing to the uncorrected baseline serum calcium (median baseline level 2.39 mmol/L) results, the incidence of uncorrected serum calcium < LLN at Day 10 is approximately 2.5 times more likely to fall below the LLN (29.9%) when a patient has an uncorrected serum calcium level below the median at baseline than if a patient is \geq median level (12.2%). It should be also noted that the four cases observed below the LLN for risedronate-treated patients all occurred in patients below the median level at baseline.

Baseline Serum Vitamin D

There is no significant association with baseline 25-hydroxy Vitamin D levels on the incidence of corrected serum calcium < LLN. There are 12% fewer patients with corrected serum calcium < LLN who are below the median level of 60 pmol/mL relative to patients \geq median level (27.2%). Further difficulties in interpreting this relationship exist when examining the incidence of falling below the LLN with respect to baseline quartiles of 25-hydroxy Vitamin D levels where the lowest incidence rate occurs in the 2nd quartile (2/33, 6.1%) and the highest incidence occurs within the 3rd quartile (13/43, 30.2%). The lack of an association between baseline 25-hydroxy Vitamin D levels may be related to other factors, such as baseline serum calcium and the dose of supplemental calcium which may exert a greater effect on whether the calcium level falls below the LLN than the baseline serum 25-hydroxy vitamin D level.

REVIEWER COMMENT: Despite the reported findings that baseline level of 25OH vitamin D did not predict a low serum calcium level at Day 10, vitamin D is critical to calcium homeostasis and all patients treated with zoledronic acid should be vitamin D sufficient to maximize calcium balance.

Logistic Regression Models to Identify Risk Factors for Day 10 Corrected Serum Calcium Below the LLN

The simple, dichotomized presentation of the effect of baseline corrected serum calcium presented above does not fully utilize the range of serum calcium values. A more robust approach to understanding risk factors utilizing baseline corrected serum calcium and the other biochemical parameters as continuous variables is presented in this section.

In order to develop an improved understanding of the data, a series of logistic regression models were fitted based on whether or not a patient was below the LLN for corrected serum calcium at Day 10 following treatment with zoledronic acid or risedronate. In the first model that was fitted, treatment, baseline vitamin D level (continuous), and baseline uncorrected serum calcium levels (continuous) were utilized as explanatory variables. This model demonstrated that treatment and low baseline uncorrected serum calcium were strong risk factors for increasing the likelihood of a patients falling below the LLN at Day 10 (both $p < 0.0001$). There was no relationship between baseline vitamin D level and a patient falling below the LLN at Day 10.

With the risk of a hypocalcemia event known to be higher in the zoledronic acid treatment group, an additional logistic regression model was fitted for zoledronic acid patients only looking at the effect of baseline uncorrected serum calcium (continuous) and baseline SAP (continuous). This model demonstrated that low baseline uncorrected serum calcium and high baseline SAP were both significant risk factors (all $p < 0.025$) for increasing the chance of a zoledronic acid-treated patient falling below the LLN at Day 10.

Novartis was encouraged by the Division to investigate the effects of additional risk factors on changes in serum calcium/serum calcium < LLN through statistical modeling. To more thoroughly investigate risk factors associated with patients falling below the LLN at Day 10, an

additional logistic regression model was constructed that included study, treatment, calcium dose (< 1000 mg/day, ≥ 1000 mg/day), vitamin D dose (< 800 IU/day, ≥ 800 mg/day), baseline vitamin D level (continuous, log-transformed), region (Australia/New Zealand, USA/Rest of World), baseline corrected serum calcium (continuous), baseline SAP (continuous, log-transformed), and baseline phosphate (continuous). The estimates of the different risk factors in this logistic regression model have been adjusted for the effects of the other variables presented in the model.

A summary of the model results is provided in the following Table.

**RISK FACTORS FOR THE OCCURRENCE OF LOW SERUM
 CALCIUM (<2.1 MMOL/L) AT DAY 10**

Factor	Odds ratio (1)	95% CI for odds ratio	P-value
Study	0.825	(0.367, 1.852)	0.6408
Treatment	4.267	(1.879, 9.690)	0.0005
Calcium Dose	0.528	(0.216, 1.292)	0.1621
Vitamin D Dose	0.466	(0.192, 1.134)	0.0924
Baseline vitamin D level (2)	0.517	(0.136, 1.968)	0.3335
Region	2.711	(1.116, 6.589)	0.0277
Baseline corrected serum calcium	0.002	(<0.001, 0.171)	0.0061
Baseline SAP (2)	1.983	(0.924, 4.255)	0.0787
Baseline Phosphate	11.223	(0.874, 144.103)	0.0634

Source: (1) An odds ratio > 1 for biochemical parameters and dosing variables implies that increasing values for an individual patient are more likely to lead to low serum calcium at Day 10 and an odds ratio < 1 for biochemical parameters and dosing variables implies that decreasing values for a risk factor for an individual patient is more likely to experience a low calcium at Day 10. (2) Variable is log-transformed in the model

In summary, both the descriptive statistics and the results of the logistic regression model are consistent in demonstrating that region, baseline corrected serum calcium, baseline SAP, and baseline phosphate are the most predictive factors in increasing the odds of having a corrected serum calcium < LLN at Day 10.

Patients with > 0.4 mmol/L Decrease in Serum Calcium on Day 10

The mean decrease in corrected serum calcium in the 32 patients with uncorrected serum calcium below the LLN at Day was 0.33 mmol/L, compared with a 0.15 mmol/L mean decrease in the patients above the LLN on Day 10. There were five patients in whom the decrease exceeded 0.4 mmol/L, and two of these patients were symptomatic.

Among these five patients, four did not take their calcium supplements as prescribed and two had an underlying disease that negatively affected calcium absorption or calcium homeostasis. Other details about these subjects are provided below.

Patient 0504 00002

The patient with the greatest drop in corrected serum calcium from the USA, who also had the lowest serum calcium at Day 10, is an extreme example of failure of the physiological mechanisms responsible for maintaining serum calcium following bisphosphonate administration. This individual had significant hypoparathyroidism as a consequence of previous thyroid surgery and was unable to mount an appropriate PTH response to counteract the decline in serum calcium. In addition, this subject did not take any calcium supplementation.

Patient 0401 00233

Patient was from New Zealand, did not take calcium supplements.

Patient 0601 00083

Patient was from the United Kingdom, did not take calcium supplements.

Patient 0102 00114

Subject was from Australia, discontinued calcium supplementation, but the precise timing is unknown. This patient also discontinued from the study and therefore a study close out visit was performed at the day 10 visit.

Patient 0501 00145

Patient was from the USA, was deemed to have malabsorption of oral calcium and other nutrients secondary to extensive small bowel resection.

Analysis of Covariance Model to Identify Risk Factors for the Change in Corrected Serum Calcium at Day 10

An analysis of covariance model (linear model) was fitted to investigate the relationship between different risk factors on the change in corrected serum calcium at Day 10 relative to baseline. All factors that may explain the patient-patient variability in the changes in corrected serum calcium regardless of level of statistical significance were included. To maximize the sensitivity to detect changes, all biochemical parameters, and dosing variables were used as continuous variables in the model along with treatment, region, and study. The exact form of each of the risk factors that were included in the analysis of covariance model were as follows:

- Treatment (Zoledronic acid, risedronate)
- Study (Study 2304, Study 2305)
- Calcium dose (continuous, divided by 100)
- Vitamin D dose (continuous, divided by 100)
- Baseline SAP (continuous, log-transformed)
- Baseline corrected serum calcium (continuous)
- Baseline Vitamin D level (continuous, log-transformed)
- Baseline phosphate level (continuous)
- Region (Australia/New Zealand, USA/Rest of World)

The two dosing variables (Calcium and Vitamin D dose) were divided by 100 so that the parameter estimates would reflect changes that are more likely to occur in a clinical practice based on the formulations of calcium and vitamin D available which are often available in multiples of 100. Baseline SAP and baseline vitamin D levels were log-transformed to lessen the influence of some of outlying baseline values which when transformed are approximately normally distributed.

CHANGE IN CORRECTED SERUM CALCIUM AT DAY 10 MODEL SUMMARY

Explanatory Variable	Estimate	Standard Error	P-value
Study	0.024	0.0131	0.0710
Treatment	-0.105	0.0125	<0.0001
Calcium dose (1)	0.013	0.0031	<0.0001
Vitamin D dose (1)	0.013	0.0031	<0.0001
Baseline vitamin D level (2)	0.053	0.0182	0.0040
Region	-0.031	0.0159	0.0509
Baseline corrected serum calcium	-0.387	0.0710	<0.0001
Baseline SAP (2)	-0.044	0.0139	0.0016
Baseline phosphate	-0.085	0.0414	0.0411

Note: All p-values are from F-test statistics constructed from Type III Sums of Squares.

(1) Values for this variable are divided by 100 for use in the model.

(2) Values for this variable are log-transformed for use in the model.

Key findings include:

- Every 100 mg increase in the dose of supplemental calcium decreases the magnitude of change of corrected serum calcium at Day 10 by 0.013 mmol/L.
- The difference between an individual receiving no calcium supplementation and receiving the recommended daily dose of ≥ 1000 mg/day calcium is a 0.13 mmol/L difference in corrected serum calcium at Day 10 which is similar to the effect of zoledronic acid on the change in corrected serum calcium during this time period.
- Every 100 IU increase in the dose of Vitamin D decreases the magnitude of change of corrected serum calcium at Day 10 by 0.013 mmol/L.
- Every 0.1 mmol/L increase in the corrected serum calcium at baseline resulted in a 0.039 mmol/L greater decrease in corrected serum calcium at Day 10.
- Every one unit increase on the log scale in baseline SAP (2.718 fold increase on the original scale) results in a 0.044 mmol/L greater decrease in corrected serum calcium at Day 10. In other words, an increase in baseline SAP from 200 to 544 U/L resulted in a 0.044 mmol/L greater decrease in corrected serum calcium at Day 10.
- Every one unit increase on the log scale in baseline 25-hydroxy vitamin D level (2.718 fold increase on the original scale) results in a 0.053 mmol/L lesser decrease in corrected serum calcium at Day 10. For example, if baseline 25-hydroxy vitamin D level increases from 60

pmol/mL to 163 pmol/mL, this would result in a 0.053 mmol/L lesser decrease in corrected serum calcium at Day 10. In fitting models separately to patients who received less than 1000 mg/day and patients who received ≥ 1000 mg/day it can be shown that baseline 25-hydroxy vitamin D levels only influence changes in corrected serum calcium in patients who received ≥ 1000 mg/day of calcium, consistent with physiological principles. In the group of patients who received less than 1000 mg/day, for which the changes in corrected serum calcium are the greatest, the clinical benefit of adequate calcium supplementation overshadows the modest influence of vitamin D status.

- Subjects from Australia/New Zealand had a 0.031 mmol/L greater decrease in corrected serum calcium at Day 10 when adjusting for all other factors.

Effect of anticonvulsant therapies on change in serum calcium

It was requested in email correspondence with the FDA on June 8, 2005 to provide information on changes in serum calcium in patients who were receiving concomitant anticonvulsant therapy. A search of the data provided as part of NDA #21-817 revealed five zoledronic acid treated patients from the two Phase III Paget's disease studies who received these medications during the course of their clinical studies. The mean reduction in serum calcium and corrected serum calcium at Day 10 was 0.25 and 0.22 mmol/L respectively for this group compared to 0.21 and 0.18 mmol/L respectively for patients who did not receive anticonvulsant therapy.

REVIEWER COMMENT: Although only 5 patients who received zoledronic acid were taking concomitant anticonvulsant therapy, there was a trend towards a greater mean reduction from baseline to Day 10 in these patients compared with those not taking an anticonvulsant.

Effect of previous thyroid surgery, hypoparathyroidism, or intestinal malabsorption of calcium on changes in serum calcium

Extensive thyroid surgery often results in removal or damage to the parathyroid glands that may predispose patients to large changes in serum calcium following zoledronic acid administration. For patients with partial hypoparathyroidism, the residual parathyroid tissue may be sufficient to maintain serum calcium levels in the normal range in the absence of any significant demands for calcium. Following bisphosphonate treatment, these individuals may not be able to increase their serum PTH levels appropriately and are thus prone to greater decreases in serum calcium. These subjects are primarily dependent on calcium intake through the GI tract, and do correct their serum calcium levels following intake of relatively larger total amounts of calcium.

Given these conditions, a request was made by the FDA on June 8, 2005 to provide information on changes in serum calcium for patients who had previous thyroid surgery, hypoparathyroidism, or intestinal malabsorption. A search of the past medical history data provided as part of NDA #21-817 revealed 5 zoledronic acid treated patients who met the specified criteria. There was one additional subject who had a thyroidectomy documented in the narratives, but not in the medical history. This subject experienced a significant decrease in corrected serum calcium of 0.91

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mmol/L. The summary statistics provided for this small group can be misleading due to the large heterogeneity in the population.

There were two subjects who had prior intestinal surgery. The subject with Crohn's disease did not have clinically active disease and most likely the surgery was in the ileum. The subject with obesity and removal of the principle areas of calcium resorption had a much larger decline in serum calcium. Although the number of subjects is extremely small, it is likely, that changes in serum calcium will be related to the areas of surgical removal, specifically the duodenum where significant calcium absorption occurs. Likewise, sequelae from surgery to the thyroid are expected to relate to the amount of functioning parathyroid tissue post-operatively.

Based on the above data, it is clear that not all patients with a partial thyroidectomy or previous surgery of the small intestine will experience changes in serum calcium that are different from individuals who have not had these types of surgical procedures. Subjects with removal of the proximal small intestine and those with a history of previous thyroid /parathyroid surgery should be carefully evaluated and counseled prior to bisphosphonate therapy for Paget's disease.

REVIEWER COMMENT: I agree with the company that subjects who have had removal of the proximal small bowel and those with a history of thyroid or parathyroid surgery should be more closely monitored prior to and immediately following dosing with zoledronic acid. This information should be included in the labeling.

Recommendations for clinical management

Clinicians should be aware of predisposing conditions that can be diagnosed by history and physical exam (e.g. previous thyroid / parathyroid surgery) or by biochemical assessment (serum alkaline phosphatase), so that appropriate management including communication with the patient is performed. In order to establish reliable clinical practice guidelines for minimizing the risk of hypocalcemia following zoledronic acid administration, it is important to have consistency of results between the various analysis methods for identifying strong risk factors, and it is important to integrate this data with current principles of calcium regulation. Due to multiplicity from the comparisons made, it is clearly possible that the effects of some of the risk factors examined may achieve a significance level <0.05 by chance alone. For this reason our recommendations are based on risk factors that have demonstrated consistent effects.

Recommendations for the clinical management to minimize the risk of hypocalcemia are listed in order of importance.

Underlying medical conditions

It is clear from the review of the patients' narratives with the greatest decreases in serum calcium that the existence of certain conditions needs to be evaluated prior to the administration of zoledronic acid. These conditions include: parathyroidectomy, hypoparathyroidism, surgery to removal the proximal small intestine, gastric bypass surgery, and celiac disease.

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REVIEWER COMMENT: Concomitant use of loop diuretics and some anticonvulsants (e.g., Dilantin) should also be included in the list of conditions that may predispose a patient to develop hypocalcemia following administration of zoledronic acid.

Calcium and vitamin D supplementation

Adequate calcium and vitamin D supplementation consistently demonstrates a beneficial effect on serum calcium levels. Therefore, unless there are specific contraindications in an individual patient, routine supplementation with at least 1000 mg/day of elemental calcium and 800 IU/day of vitamin D is warranted.

REVIEWER COMMENT: Given that the nadir for hypocalcemia and hypophosphatemia appears to be 7-14 days post-zoledronic acid infusion, compliance with supplemental calcium and vitamin D is of particular importance during the first 2 weeks following drug delivery.

Baseline serum calcium

It is consistently demonstrated that the magnitude of decrease in corrected serum calcium increases as the baseline serum calcium increases. However, this magnitude of change does not necessarily equate to the development of hypocalcemia. The risk of developing hypocalcemia is greater if the patient has baseline serum calcium < 2.37 mmol/L. Adequate calcium and vitamin D supplementation will mitigate this risk.

Baseline SAP

It is consistently shown that higher baseline SAP increases the magnitude of the reduction in serum calcium and increases the risk of hypocalcemia. Therefore, careful consideration should be given in patients with higher bone turnover indicated by a baseline SAP of at least 400 U/L prior to administering zoledronic acid.

Regional Effect

The regional differences for developing hypocalcemia and for the magnitude of change in corrected serum calcium are greater in Australia and New Zealand than in the USA/Rest of World. While some of the regional differences are explained by the lower baseline levels in that region, and reduced calcium and vitamin D supplementation in New Zealand, there is a residual effect that remains. Although the source of the residual effect is not completely understood, a potential source of this effect could be the lesser calcium and vitamin D dietary intake, consistent with the lower normative ranges for serum calcium documented for this region.

Baseline vitamin D

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Although log-transformed baseline vitamin D is a significant risk factor for the change in corrected serum calcium, it is not demonstrated that the magnitude of change in corrected serum calcium or the incidence of hypocalcemia increases as the baseline vitamin D level decreases. The statistical significance is driven by the reduced changes in corrected serum calcium with increasing baseline vitamin D levels in subjects who received >1000 mg of supplemental calcium daily. While the effect of baseline Vitamin D on changes in serum calcium is not robust, it is recommended to ensure adequate calcium and Vitamin D supplementation.

Baseline phosphate

The baseline phosphate has an effect that is quantitatively less than that for an equivalent change in serum calcium. Based on the current data, there are no therapeutic interventions that should be recommended based on serum phosphate levels.

Hypophosphatemia

Pathophysiology and Clinical Consequence

The development of hypophosphatemia is linked to a reduction in bone resorption and a physiologically appropriate parathyroid response following zoledronic acid infusion. Actions of PTH on the kidney include the renal conservation of calcium and inhibition of phosphate reabsorption. This is a transient physiological response that resolves as the secondary hypoparathyroidism is corrected with appropriate calcium supplementation.

Regional Differences

Investigation into the subjects with serum phosphate levels <0.71 mmol/L (LLN defined by), reveals two groups. Twelve of 28 subjects (43%) also had concomitant serum calcium levels <2.1 mmol/L while 16 of 28 (57%) had isolated hypophosphatemia. The geographic distribution of these hypophosphatemia cases differs from the hypocalcemia cases. Of these cases, 15/16 (94%) occurred outside of Australia and New Zealand. The one case in Australia occurred in a patient whose baseline phosphate level was 0.96 mmol/L (approximately 0.20 mmol/L below the mean) declining to 0.68 mmol/L at Day 10. Since most subjects would be expected to have an increase in serum PTH following zoledronic acid administration, in those patients with hypophosphatemia without hypocalcemia, the difference likely resides in the greater oral intake of calcium in those with isolated declines in serum phosphate to below 0.71 mmol/L. The magnitude of the transient reduction in serum phosphate was modest, and without clinical consequences.

REVIEWER COMMENT: Mild-to-moderate hypophosphatemia (i.e., serum levels between 0.49 and 0.71 mmol/L) is generally asymptomatic and without clinical consequence. When serum phosphorus levels drop below 0.49 mmol/L patients may develop muscle weakness and in rare cases rhabdomyolysis and hemolysis. The lowest Day 10 serum phosphorus level in the zoledronic acid group was 0.48 mmol/L. This patient's baseline phosphorus was 0.84 mmol/L. I agree with the company that the magnitude of the

reduction in serum phosphorus following treatment with zoledronic acid appears to be modest and without clinical consequence. The risk for developing clinically significant hypophosphatemia would be reduced by ensuring that pre-dose levels of serum phosphorus are normal, that patients take adequate amounts of supplemental calcium and vitamin D following treatment with zoledronic acid, particularly during the first two to three weeks post-dose, and by checking serum phosphorus levels within seven-to-ten days following drug administration.

7.1.18 Safety Update

A safety update consisting of serious adverse event data from the ongoing extension phases of the two pivotal Paget's trials and blinded narratives for all patients experiencing death, serious adverse events, and renal events from the two osteoporosis trials 2301 and 2310 were provided in the 23 August 2005 submission. The cut-off date for most of this information was 1 March 2005.

The data from the extension phases of the pivotal Paget's trials do not raise concern regarding the overall safety of zoledronic acid. The blinded narratives from the osteoporosis trials provide little useful information regarding the safety of zoledronic acid in the treatment of Paget's disease.

Partially blinded (i.e., Treatment groups A and B) interim data on hypocalcemia from the ongoing osteoporosis treatment trial was also provided in the 23 August 2005 submission.

Forty-nine of 2019 (2.4%) of patients in treatment group A vs. 1 of 2040 (<0.1%) of patients in treatment group B developed a serum calcium level < 2.1 mmol/L within 2 weeks of receiving their first dose of study drug or placebo. Two of 1577 (0.1%) and 1 of 1644 (<0.1%) of patients in treatment groups A and B, respectively, developed low serum calcium levels following the second dose of study drug or placebo. A similar percentage of patients developed hypocalcemia in each group following the third dose.

Twelve of 2019 (0.6%) treatment group A subjects developed serum calcium levels < 2.0 mmol/L following the initial dose of study drug compared with 0/2040 treatment group B subjects.

All 12 of the patients who developed serum calcium levels < 2.0 mmol/L were reportedly asymptomatic. Of the 12 patients, 3 had values below 1.8 mmol/L. Two of the three patients had had previous thyroid surgery and exhibited a drop in their serum calcium without a significant drop in serum phosphate as would have been expected with an intact parathyroid function. The third patient had hypothyroidism and a low baseline serum calcium. A review of underlying medical conditions that could potentially predispose to hypocalcemia among the 12 patients is as follows. A total of 7 of the 12 patients had a previous history of thyroid disease, 4 of them treated by subtotal thyroidectomy.

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Other identified contributing causes for reductions in serum calcium included resection of the majority of the small intestine including the proximal portion where the majority of calcium absorption occurs, and gastric resection, with consequent impairment in calcium absorption due to lack of gastric acid secretion. Some subjects had low albumin levels as a result of chronic or acute illness. Corrected serum calcium values for these subjects were frequently within the normal range. There were 2 subjects with values just below 2.0 mmol/L for whom no explanatory conditions were apparent other than receiving infusion of study drug. All 12 subjects reportedly normalized their calcium levels with ongoing oral calcium and vitamin D intake.

REVIEWER COMMENT: Although the relative risk for developing hypocalcemia is much higher in women with postmenopausal osteoporosis who receive zoledronic acid compared with placebo, the absolute risk of hypocalcemia is much lower in osteoporotic vs. Pagetic patients.

Interim Safety Data from the Zoledronic Acid Pivotal Osteoporosis Fracture Trial

In a submission dated 24 January 2006, Novartis provided the Division with interim efficacy and safety data from the nearly-completed 3-year osteoporosis fracture trial 2301. This study randomized approximately 8000 postmenopausal women to treatment with once-yearly 5-mg zoledronic acid or placebo. Of note, there was a statistically significant increase in the incidence of cardiac arrhythmias in the zoledronic acid group compared with the placebo group (5.7% vs. 4.1%; nominal $p=0.0006$). The arrhythmias reported included atrial fibrillation, 1st degree AV block, SV extrasystoles, SV tachycardia, tachycardia, and sick sinus syndrome. Serious arrhythmias were reported in 2.2% of zoledronic acid vs. 1.3% of placebo-treated patients (nominal $p=0.001$). The overall rates of death were 2.8% vs. 2.4% in the active compared with the placebo treatment groups ($p=NS$).

The Data Safety Monitoring Board overseeing conduct of study 2301 made the following recommendations based on the interim efficacy and safety data:

- The anti-fracture efficacy has been established
- There are some safety issues that are not yet resolved, concerning:
 - cardiovascular mortality
 - cardiac arrhythmias
 - ophthalmic disorders
- Resolution of these concerns will require review of adjudicated data on adverse events, serious adverse events and deaths by the DSMB

During a 2 February 2006 teleconference with Novartis, in which the above data were discussed, the company stated that the adjudication of the cardiac and ophthalmic safety data should be completed by mid-March 2006.

REVIEWER COMMENT: Since the population of postmenopausal women from whom the cardiovascular safety data have emerged is similar in age to the Paget's population and the

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dosing regimens for the two indications are similar as well, it would be prudent to delay approval of this supplement until the cardiovascular and ophthalmic safety data from the osteoporosis fracture trial have been adjudicated by the DSMB and the results reviewed and found acceptable by the Division.

8.7 Postmarketing Risk Management Plan

The major features of Novartis's proposed risk management plan for hypocalcemia are provided below.

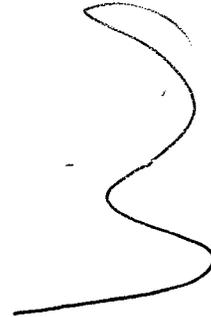
Based on the information presented in this Briefing Book, a minimum of 1000 mg daily of supplemental calcium (elemental) reduces the risk of hypocalcemia in patients with Paget's disease. However, consistent with the recommended daily allowance of calcium for individuals age 65 and over, we recommend all patients with Paget's disease receive a minimum of 1500 mg supplemental calcium daily in divided doses, which will further reduce this risk. This is one component designed to strengthen the language in the Prescribing Information (PRECAUTIONS, Information for Patients, Laboratory Findings sections) and the Patient Product Information. In addition to the labeling, our proposed plan includes enhanced pharmacovigilance activities for hypocalcemia and other risk minimization activities, as follows:

- Expedited reporting of all hypocalcemia adverse events for the first 2 years post-launch and a detailed analysis of hypocalcemia adverse events in the US Periodic Safety Report.

- Patient education materials to reinforce the importance of calcium and vitamin D supplementation via: Patient Prescribing Information (PPI), Patient Brochure, and a consumer web site.

The company is also proposing

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REVIEWER COMMENT: Before this NDA is approved, the Office of Drug Safety will be asked to comment on the likelihood that Novartis's proposed post-approval study would provide meaningful data on the effectiveness of Novartis's risk management plan to minimize hypocalcemia.

9 OVERALL ASSESSMENT

9.1 Conclusions

Novartis has provided sufficient evidence to support the safety of a single infusion of 5 mg zoledronic acid in the treatment of Paget's disease. Patient's taking at least 500 mg bid of supplemental calcium and 800 IU of supplemental vitamin D per day have a notably lower risk of developing hypocalcemia compared with those taking less than these amounts. The risks for hypocalcemia (and hypophosphatemia) would be further reduced if healthcare providers ensure that pre-treatment levels of serum calcium, magnesium (hypomagnesemia can cause hypocalcemia), phosphorus, and 25OH vitamin D are normal. Repeat measurement of serum calcium, magnesium, and phosphorus within seven-to-ten days following drug treatment would also enhance patient safety.

9.2 Recommendation on Regulatory Action

Pending review of adjudicated cardiovascular and ophthalmic safety data from the ongoing osteoporosis trial 2301, this application should be considered approvable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

If approved for Paget's disease, the zoledronic acid labeling should recommend that: 1) patients take at least 500 mg bid supplemental calcium and 800 IU vitamin D per day; 2) serum calcium, phosphorus, magnesium, and 25OH vitamin D be measured prior to dosing; 3) low levels of these parameters be normalized prior to drug administration; and 4) serum calcium, magnesium, and phosphorus levels be measured within seven-to-ten days post-dose. The labeling should also point out that patients with a history of thyroid or parathyroid surgery, resection of the proximal

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small bowel, or significant malabsorption (e.g., celiac disease) are at increased risk for developing hypocalcemia following treatment with zoledronic acid.

9.3.2 Required Phase 4 Commitments

Details of required phase 4 commitments will be provided at the time of this application's approval.

9.3.3 Other Phase 4 Requests

Details of other required phase 4 requests will be provided at the time of this application's approval.

10 APPENDICES

10.2 Line-by-Line Labeling Review

A detailed labeling review will be conducted prior to an approval action.

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2/22/2006 04:36:08 PM
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concur with Dr. Colman

CLINICAL REVIEW

Application Type 21-817

Letter Date 21 September 2004
Stamp Date 24 September 2004
PDUFA Goal Date 21 March 2005

Reviewer Name Eric Colman
Review Completion Date 18 March 2005

Established Name Zoledronic Acid
(Proposed) Trade Name Aclasta
Therapeutic Class Bisphosphonate
Applicant Novartis

Priority Designation P

Formulation Intravenous
Dosing Regimen 5 mg
Indication Paget's disease of bone
Intended Population Patients with Paget's disease

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{NDA 21-817}
{Zoledronic Acid for Paget's disease}

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Reviewer recommends that this application be deemed Approvable.

Through conduct of two identical randomized, double-blind, active-controlled, non-inferiority trials, Novartis has provided sufficient evidence to support the efficacy of a single 5 mg intravenous infusion of zoledronic acid in the treatment of Paget's disease of bone. The applicant has not, however, provided adequate evidence to support the safety of the proposed dosing regimen in this population of patients. Approximately 20% of all of the subjects treated with zoledronic acid developed hypocalcemia or hypophosphatemia within 7 to 14 days post-dosing; whereas, very few subjects treated with risedronate did so during this time frame, or at later time points in the trial when, based on previous studies of risedronate in Paget's patients, one would anticipate nadirs for calcium and phosphorus following daily risedronate dosing.

Because the company does not have data regarding the amounts of supplemental calcium and vitamin D the subjects were provided during the early portions of the studies, nor do they have any data on compliance with the recommended supplementation regimen, it is not possible to assess the effect of calcium and vitamin D intake on the risk for developing low levels of serum calcium and phosphorus.

It is this Reviewer's opinion that the submitted data do not support a favorable balance of benefits to risks for zoledronic acid in the treatment of Paget's disease of bone. If the sponsor is able to demonstrate that a regimen of calcium and vitamin D supplementation prior to and/or during the first 2 to 3 weeks following dosing substantially reduces the risk for hypocalcemia and hypophosphatemia, I believe the benefit-risk profile of zoledronic acid would then be favorable and supportive of regulatory approval.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zoledronic acid, trade name, Zometa, is an intravenously administered bisphosphonate currently approved (4 mg) for the treatment of hypercalcemia of malignancy and bone metastases in patients with certain types of cancer. The current application seeks approval of a single 5 mg dose of zoledronic acid for the treatment of Paget's disease of bone.

The sponsor conducted two identical multinational, randomized, double-blind, active-controlled 6-month non-inferiority studies to examine the efficacy and safety of zoledronic acid to risedronate in the treatment of Paget's disease. Approximately 360 male and female, 42 to 94-year old, primarily Caucasian patients with Paget's disease of bone, confirmed by serum bone-specific alkaline phosphatase levels at least 2 times the upper limit of normal, were randomized 1:1 to treatment with a single 15-minute infusion of 5 mg of zoledronic acid or to 30 mg daily oral risedronate x 2 months. Although all patients were instructed to take 500 mg of supplemental calcium twice a day and 400 to 1000 IU of daily vitamin D, it is unknown how many actually complied with these directives.

About 50% of the patients in the studies had not received drug therapy prior to enrollment. Approximately 45% of the patients had received at least one course of therapy with an oral or intravenous bisphosphonate before taking part in the zoledronic acid trials. Approximately 93% of the subjects in both treatment groups completed the core 6 months of the trials.

1.3.2 Efficacy

The primary efficacy endpoint was a comparison of the proportion of patients in each treatment group who either had normalization or a reduction of at least 75% from baseline of their serum bone-specific alkaline phosphatase at the end of 6 months. Alkaline phosphatase, a marker of bone formation, is the standard parameter used to evaluate the efficacy of drugs used to treat Paget's disease. While this biochemical marker correlates with the severity of the underlying disease, to this Reviewer's knowledge, there is no evidence that normalization of alkaline phosphatase levels with drug therapy prevents serious morbidity such as fractures associated with long-standing Paget's disease. Nonetheless, reduction in alkaline phosphatase following drug treatment often correlates with a reduction in bone pain – a common presenting symptom of the disease – and this biochemical parameter is a reasonable endpoint upon which to base regulatory approval.

Risedronate 30 mg daily for 2 months is currently approved for Paget's disease and this regimen served as the active control in the two zoledronic acid pivotal studies. The non-inferiority

criterion of -0.16 for the difference between treatment groups in the proportion of therapeutic responders was based on the efficacy results from the pivotal studies conducted to support FDA approval of risedronate for the treatment of Paget's disease. The non-inferiority margin of -0.16 allows 75% of the treatment effect demonstrated by risedronate relative to etidronate to be preserved. In other words, -0.16 is approximately 25% of the observed difference between etidronate and risedronate which was minus 0.65.

At Month 6, 96% of the subjects treated with zoledronic acid and 74% of the subjects treated with risedronate achieved a therapeutic response. The point estimate for the difference between groups in response rates was 22% with a 95% confidence interval of 14% to 30%. From a statistical standpoint, these results demonstrate that zoledronic acid was not only non-inferior to risedronate (i.e., lower bound of the 95% confidence interval for the difference between groups was > -16%), but superior as well.

The response rates to treatment with zoledronic acid and risedronate were similar for subjects < 65 years, 65-75 years, or those ≥ 75 years; for male and female patients; and for subjects with baseline serum alkaline phosphatase levels ≤ or > 3 times the upper limit of normal.

The following table provides the primary efficacy outcome by number of pharmacological treatments received prior to enrollment in the zoledronic acid studies. It is clear that patients who received prior drug treatment for their Paget's disease responded more favorably to zoledronic acid than to risedronate. The lowest response rates in the risedronate-treated subjects were seen in those who had previously received treatment with risedronate.

Proportion of Therapeutic Responders by Number of Previous Drug Treatment Cycles					
Subgroup	Zoledronic acid n/N (Proportion)	Risedronate n/N (Proportion)	Difference ¹ (95% CI)	p-value ² for treatment difference	p-value ³ for subgroup interaction
Previous treatment cycles					
None	80/82 (0.98)	65/76 (0.86)	0.12 (0.02, 0.22)	0.0075	0.3553
1	41/45 (0.91)	32/46 (0.70)	0.22 (0.03, 0.40)	0.0098	
2-3	24/24 (1.00)	16/27 (0.59)	0.41 (0.18, 0.64)	0.0005	
>3	24/25 (0.96)	14/22 (0.64)	0.32 (0.06, 0.59)	0.0020	

¹ Difference is zoledronic acid minus risedronate; 95% CI for the difference is based on the normal approximation to the binomial.
² p-value is based on a Mantel-Haenszel test controlling for study for each category.
³ p-value is based on a Breslow-Day test with the subgroup as a controlling factor.

Regarding secondary efficacy endpoints, the relative reductions in serum CTx at Day 10, urine α-CTx at Day 10, and serum alkaline phosphatase at Day 28 were all statistically significantly larger in the zoledronic acid vs. the risedronate groups. Although pain scores decreased from baseline to the end of the studies in both treatment groups, the differences between the zoledronic acid and risedronate-treated patients were not statistically significant.

1.3.3 Safety

The principal safety concerns that emerged from the pivotal Paget's trials were hypocalcemia and hypophosphatemia. Asymptomatic reductions in serum levels of calcium and phosphorus have been observed in Paget's patients treated with oral alendronate and risedronate, but by comparison, the risk appeared to be greater and occur more rapidly following treatment with 5 mg of intravenous zoledronic acid.

At Day 10 of the trials, 32 of the 151 (21%) patients who received zoledronic acid vs. 5 of the 156 (3.0%) who received risedronate, had serum calcium levels below 2.1 mmol/L. Twenty-eight of the 157 (18%) subjects who received zoledronic acid compared with 2 of the 159 (1.3%) treated with risedronate developed serum phosphorus levels below 0.71 mmol/L (2.1 mg/dl) at Day 10. Four of the zoledronic acid subjects and none of the risedronate subjects developed markedly low serum calcium levels (< 1.87 mmol/L) at Day 10.

At Day 63, a time point where one would more likely see low levels of serum calcium and phosphorus in patients treated with daily risedronate, 2.4% of the zoledronic acid subjects and 4.8% of the risedronate subjects had low serum calcium levels; 0.6% of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

Although all patients in the two pivotal trials were instructed to take 500 mg of supplemental calcium twice daily and 400 to 1000 IU of daily vitamin D, the sponsor does not have data to verify if, when, or how much of the supplements were actually taken. Absent this information, it is not possible to judge how effective supplemental calcium and/or vitamin D are in reducing the risk for hypocalcemia and hypophosphatemia, and leaves open to debate the question of the safety of the proposed dosing regimen.

Renal injury, defined as an increase in serum creatinine > 0.5 mg/dl, has been observed in patients, primarily those with cancer, treated with one or more doses of intravenous zoledronic acid. There was no compelling evidence from the Paget's trials that a single 5 mg infusion of zoledronic acid administered over 15 minutes adversely affected renal function when compared with patients treated with 30 mg daily risedronate for 2 months.

Although not a serious safety issue, more zoledronic acid than risedronate-treated subjects reported symptoms consistent with an acute-phase like reaction. These symptoms included influenza-like illness, pyrexia, rigors, and myalgia. By and large, these symptoms occurred soon after administration of zoledronic acid and resolved spontaneously within 72 hours.

1.3.4 Dosing Regimen and Administration

Novartis has provided ample evidence that a single infusion of 5 mg zoledronic acid is effective (i.e., lowers serum alkaline phosphatase levels) in the treatment of Paget's disease. However, the large percentage of patients who developed hypocalcemia and hypophosphatemia within 10 days following dosing raises concern about the safety of this regimen in this population of patients. While it is reasonable to assume that appropriate use of supplemental calcium and vitamin D

prior to and following administration of zoledronic acid will ameliorate or at least attenuate the development of low serum calcium and phosphorus levels, the sponsor does not have empiric evidence to support this claim.

1.3.5 Drug-Drug Interactions

Caution is warranted when administering zoledronic acid concomitantly with drugs that have the potential to lower serum calcium levels, such as loop diuretics or aminoglycosides. *In-vivo* data do not indicate that zoledronic acid inhibits microsomal CYP450 enzymes.

1.3.6 Special Populations

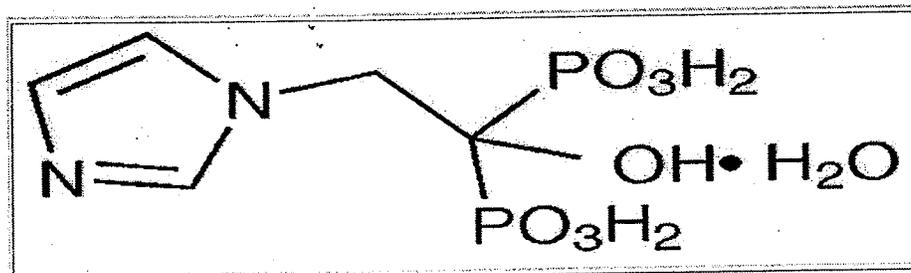
The dose of zoledronic acid should be reduced in patients with renal insufficiency.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, trade named Zometa, is a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zometa, 4 mg intravenous injection, is approved for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

2.2 Currently Available Treatment for Indications

The following drugs are approved for the treatment of Paget's disease of the bone:

Actonel Tablets (Procter and Gamble)

Risedronate Sodium

Aredia for Injection (Novartis)

Pamidronate Disodium

Didronel Tablets (Procter & Gamble Pharmaceuticals)

Etidronate Disodium

Fosamax Oral Solution (Merck)

Alendronate Sodium

Fosamax Tablets (Merck)

Alendronate Sodium

Miacalcin Injection (Novartis)

Calcitonin-Salmon

All of the above drugs, with the exception of Miacalcin are bisphosphonates; Miacalcin is a salmon calcitonin product that, like the bisphosphonates, slows bone resorption through inhibition of osteoclast function.

2.3 Availability of Proposed Active Ingredient in the United States

Zoledronic acid, 4 mg intravenous injection, is approved for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

2.4 Important Issues With Pharmacologically Related Products

The principal safety concern with the intravenous bisphosphonates is renal toxicity. The approval of 4 mg intravenous Zoledronic acid for the treatment of hypercalcemia malignancy was delayed due to concerns about renal injury, i.e., increases in serum creatinine. The dosing regimen was changed to prolong the infusion of drug to 15 minutes.

The following language appears in the Warnings section of the approved labeling for Zometa:

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES.

BECAUSE SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT:

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine >3.0 mg/dL were excluded.
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine >400 mmol/L or >4.5 mg/dL were excluded.

Bisphosphonates, including Zometa[®] (zoledronic acid) Injection, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. In clinical trials, the risk for renal function deterioration (defined as an increase in serum creatinine) was significantly increased in patients who received Zometa over 5 minutes compared to patients who received the same dose over 15 minutes. In addition, the risk for renal function deterioration and renal failure was significantly increased in patients who received Zometa 8 mg, even when given over 15 minutes. While this risk is reduced with the Zometa 4-mg dose administered over 15 minutes, deterioration in renal function can still occur. Risk factors for this deterioration include elevated baseline creatinine and multiple cycles of treatment with the bisphosphonate.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for bone metastases should have the dose withheld if renal function has deteriorated. Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

4.2 Tables of Clinical Studies

The following table provides the basic characteristics of the 4 studies conducted in patients with Paget's disease. In addition to these 4 studies, data from an ongoing, partially-blinded study (2301) of approximately 7700 in postmenopausal women with osteoporosis provide important safety information for this review.

Study	Study objective, population	Patients	Study Duration	Medication, Dosing scheme	Type of control
Large efficacy trials					
2304	phase III, double-blind, randomized safety & efficacy in Paget's disease	172	6 months	1 x 5 mg Zoledronic acid (15 min i.v. infusion) 30 mg risedronate /day (60 days)	active control
2305	phase III, double-blind, randomized safety & efficacy in Paget's disease	185	6 months	1 x 5 mg Zoledronic acid (15 min i.v. infusion) 30 mg risedronate /day (60 days)	active control
Large dose-ranging trial					
002	phase II, double-blind, randomized dose-ranging trial in Paget's disease	176	3 months	1 x 50, 100, 200, or 400 µg Zoledronic acid , 1 x placebo (60 min i.v. infusion)	placebo control
Small dose-ranging trial					
001	phase I, open-label, rising dose trial in Paget's disease	16	14 days	1 x 24, 72, 216, or 400 µg Zoledronic acid (60 min i.v. infusion)	no control

4.3 Review Strategy

The studies that provide the majority of the data upon which this reviewer is basing a decision regarding the balance of benefits to risks of zoledronic acid in the treatment of Paget's disease are the phase 2 study 002, the phase 3 studies 2304 and 2305, and the ongoing phase 3 study 2301.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to inspect the larger of several North American clinical sites. In a recently completed consult, DSI reported no major violations with the sites inspected.

4.5 Compliance with Good Clinical Practices

The trials appear to have been conducted in accordance with the accepted ethical standards.

4.6 Financial Disclosures

1. Compensation made to the investigator in which the value of compensation could be affected by study outcome.

None reported.

2. A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement.

None reported.

3. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.

None reported.

4. Any equity interest in a publicly held company that exceeds \$50,000 in value.

None reported.

5. Significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigator or the investigators' institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

~~_____~~ Amount under negotiations.

~~_____~~ stipend for research fellow.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See review by Dr. Sandra Suarez for details of the pharmacokinetics data.

As described in the approved, zoledronic acid labeling, single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2(\alpha)}$ 0.24 hours and $t_{1/2(\beta)}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination

phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2(\text{gamma})}$ of 146 hours. The area under the plasma concentration versus time curve ($\text{AUC}_{0-24\text{h}}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $\text{AUC}_{0-24\text{h}}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36 , respectively.

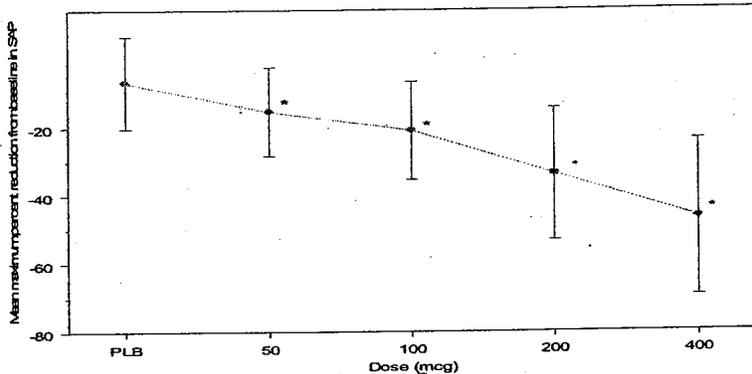
Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C -zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

In 64 patients with cancer and bone metastases on average (\pm s.d.) $39 \pm 16\%$ of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes ($n=5$) to 15 minutes ($n=7$) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean \pm SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng \times h/mL vs 420 ± 218 ng \times h/mL). The difference between the AUC means was not statistically significant.

5.2 Pharmacodynamics

In the phase 2 study 002, intravenous dose of 50 ug, 100 ug, 200 ug, and 400 ug zoledronic acid or placebo were administered over 60 minutes to patients with Paget's disease. The pharmacodynamic marker relevant to Paget's disease of bone and measured in this study was serum alkaline phosphatase (SAP). The mean (SD) for maximum percent reductions from baseline in SAP is shown in the following figure (taken from Dr. Suarez's review).



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Over the range studied, there is a direct relationship between dose of zoledronic acid and suppression of SAP. It is noteworthy that there are no pharmacodynamic data for doses of zoledronic acid between 400 ug to < 5 mg.

See section 7.2.3 of this review for an additional discussion of the dose-response data.

5.3 Exposure-Response Relationships

See section 5.2.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is proposing that zoledronic acid be indicated for the treatment of Paget's disease of bone in men and women.

6.1.1 Methods

Studies 2304 and 2305, randomized, double-blind, active-controlled 6-month trials, provide the efficacy data upon which this Reviewer determined the efficacy of zoledronic acid in the treatment of Paget's disease of bone. The two studies were conducted under identical protocols, as described below.

6.1.2 General Discussion of Endpoints

As with drugs previously approved for the treatment of Paget's disease of bone, the primary efficacy endpoint in the zoledronic acid studies was serum bone-specific alkaline phosphatase (SAP). Specifically, the efficacy endpoint was defined as the proportion of patients in the zoledronic acid and risedronate comparator group who either had normalization or a reduction of at least 75% from baseline of their SAP at the end of six months. While the level of SAP

correlates directly with the severity and extent of disease in patients with Paget's, there is no evidence that this Reviewer is aware of which indicates that normalization of SAP with bisphosphonate therapy prevents the morbid outcomes such as fractures or retards progression of the underlying disease. Nonetheless, SAP is an important marker that physicians follow to evaluate patients' clinical status and is a reasonable parameter upon which to base regulatory approval.

6.1.3 Study Design

The pivotal studies were randomized, double-blind, active-controlled 6-month trials comparing the efficacy of a single 5 mg dose of zoledronic acid administered during a 15-minute intravenous injection to 30 mg qd x 60 days of orally administered risedronate, the approved regimen of this bisphosphonate for Paget's disease. Each individual trial was powered to test whether zoledronic acid was non-inferior to risedronate. Non-inferiority was considered if the lower bound of the two-sided 95% confidence interval for the difference between zoledronic acid and risedronate in the proportion of responders exceeded -0.16.

The non-inferiority criterion of -0.16 for the difference of proportions was based on the efficacy results from the pivotal studies conducted to support FDA approval of risedronate for the treatment of Paget's disease. The non-inferiority margin of -0.16 allows 75% of the treatment effect demonstrated by risedronate relative to etidronate to be preserved. In other words, -0.16 is approximately 25% of the observed difference between etidronate and risedronate which was minus 0.65.

If non-inferiority was demonstrated, superiority was then tested using a logistic regression model with treatment and baseline SAP (above or below 3xULN) as explanatory variables. The secondary efficacy variables were:

- Relative change in serum CTX (bone resorption marker) at Day 10;
- Relative change in urine α -CTX (bone resorption marker) at Day 10;
- Relative change in serum SAP (bone formation marker) at Day 28;
- Change in BPI-SF pain severity over time;
- Change in BPI-SF pain interference over time;
- Proportion of subjects who achieved normalization at Day 28;
- Time to first therapeutic response.

The principal analysis for the primary efficacy variable was performed on the modified intent-to-treat (MITT) population. The MITT population was defined as all randomized patients with both a baseline and at least one post-baseline SAP measurement.

Patients in the pivotal trials who met the definition of a therapeutic response at the end of the core study (Day 182/Month 6) were asked to participate in the extended observation period, for follow-up every 6 months to measure SAP until levels returned to within 20% of baseline. The extended observation period is ongoing, and results are based on available data as of a cut-off

date of approximately 3 months prior to submission of this NDA (18-Jun-2004). For the majority of patients, follow-up occurred within 1 year of the end of the core period. The median follow-up time was 6 months; the maximum was 547 days. Data are provided for the time to first loss of therapeutic response, time to first partial disease relapse, and time to first disease relapse.

Elemental calcium (500 mg) and vitamin D₂ was to be taken by mouth with food (twice daily) beginning at least five days prior to administration of zoledronic acid and during the trial. Since calcium may interfere with the absorption of risedronate, it was to be taken at a different time of day. Calcium carbonate was the preferred form of calcium. If calcium carbonate was not well tolerated, another form of oral calcium was acceptable. In addition, each patient took multiple vitamin supplements containing between 400 and 1000 IU of vitamin D daily; the actual amount varied and was determined by the investigators.

Inclusion and exclusion criteria included the following:

Inclusion criteria

- Male or female patients 30 years and above at the time of entry into the trial who have Paget's disease of bone. Females of child-bearing potential may have been enrolled if they had a negative serum pregnancy test prior to study entry and if they agreed to use acceptable methods of contraception during the study.
- Confirmed diagnosis of Paget's disease of the bone (i.e., by x-ray, magnetic resonance imaging, computerized tomography, radioisotope imaging, etc.).
- Serum alkaline phosphatase level at least two times the upper limit of the normal reference range.
- A normal or not clinically significantly abnormal ECG result during the past 6 months.
- Washout period for other therapies prior to trial drug administration at Visit 2: 90 days for calcitonin and 180 days for any bisphosphonate.
-

Exclusion criteria

- Treatment with any investigational drug within the past 30 days.
- History of noncompliance to medical regimens and patients who are considered unreliable.
- Any disease or therapy which would interfere with the procedures or data collection trial.
- Severe liver disease that would affect alkaline phosphatase levels such as hepatitis, primary biliary sclerosis, and cirrhosis.
- History of any of the following: hypersensitivity to bisphosphonates, clinically upper gastrointestinal disorders that could interfere with compliance, urticaria disease with continuing clinically significant abnormality, diabetic nephropathy retinopathy.
- WBC < 3.5 x 10³/mm³, platelets < 125 x 10³/mm³ or any other clinically significant laboratory abnormality.
- Calculated creatinine clearance < 30 mL/min at baseline or urine protein level without evidence of contamination or bacteruria.
- Evidence of vitamin D deficiency (serum 25(OH) D of <15 ng/mL).

- Patients with allergies to tetracycline or any of its derivatives were to be the bone biopsy procedure.
- Active primary hyperparathyroidism.
- Patients with a new diagnosis or active treatment for any malignancy less than 12 months prior to study entry.

The baseline demographic and disease characteristics of the zoledronic acid and risedronate groups were generally well-matched, as shown in the following two tables.

Baseline Demographic Characteristics – Studies 2304 and 2305 (ITT)				
	Study 2304		Study 2305	
	Zoledronic Acid n=90	Risedronate n=82	Zoledronic Acid N=92	Risedronate n=93
Sex – n (%)				
Male	62 (68.9)	61 (74.4)	62 (67.4)	57 (61.3)
Female	28 (31.1)	21 (25.6)	30 (32.6)	36 (38.7)
Race – n (%)				
Caucasian	84 (93.3)	80 (97.6)	84 (91.3)	84 (90.3)
Black	6 (6.7)	2 (2.4)	3 (3.3)	3 (3.2)
Other	0 (0.0)	0 (0.0)	5 (5.4)	6 (6.5)
Age (years)				
Mean (SD)	70.4 (10.25)	72.1 (9.91)	71.3 (9.42)	68.2 (11.15)
Median	72.0	74.0	72.5	70.0
Range	42.0 – 94.0	44.0 – 87.0	45.0 – 92.0	34.0 – 88.0
Age – n (%)				
<65 years	25 (27.8)	17 (20.7)	21 (22.8)	29 (31.2)
≥65 years	65 (72.2)	65 (79.3)	71 (77.2)	64 (68.8)
Weight (kg)				
Mean (SD)	78.5 (16.44)	78.8 (14.74)	76.7 (13.25)	78.4 (17.06)
Median	77.6	77.7	78.0	77.3
Range	39.8 – 132.7	48.0 – 121.1	49.5 – 110.0	44.2 – 133.0

Baseline Disease Characteristics – Studies 2304 and 2305 (ITT)				
	Study 2304		Study 2305	
	Zoledronic Acid	Risedronate	Zoledronic Acid	Risedronate
	(N=90)	(N=82)	(N=92)	(N=93)
Baseline SAP (U/L)				
Mean (SD)	424.5 (335.35)	423.0 (267.35)	431.0 (308.11)	427.4 (348.56)
Median	329.0	321.0	342.5	301.0

Baseline Disease Characteristics – Studies 2304 and 2305 (ITT)

	Study 2304		Study 2305	
	Zoledronic Acid (N=90)	Risedronate (N=82)	Zoledronic Acid (N=92)	Risedronate (N=93)
Range	229.0 - 2822.0	214.0 - 1971.0	230.0 - 2338.0	222.0 - 2377.0
Baseline SAP – n (%)				
< 3xULN	47 (52.2)	45 (54.9)	46 (50.0)	56 (60.2)
≥3xULN	43 (47.8)	37 (45.1)	46 (50.0)	36 (38.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Creatinine Clearance at Baseline (mL/min)				
Mean (SD)	86.8 (36.51)	84.5 (36.34)	84.2 (28.75)	89.2 (30.26)
Median	77.7	79.2	81.6	88.2
Range	30.6 -217.8	29.4 -228.0	(36.0 - 180.0)	(34.2 - 192.6)
Creatinine Clearance at Baseline – n (%)				
< 30 mL/min	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
30 to < 40 mL/min	3 (3.3)	2 (2.4)	2 (2.2)	1 (1.1)
40 to 50 mL/min	10 (11.1)	7 (8.5)	8 (8.7)	9 (9.7)
> 50 mL/min	77 (85.6)	72 (87.8)	82 (89.1)	83 (89.2)
Last Paget's Disease Therapy Before Randomization - n (%)				
Bisphosphonates	39 (43.3)	39 (47.6)	50 (54.3)	52 (55.9)
Oral	23 (25.6)	28 (34.1)	33 (35.9)	35 (37.6)
IV	13 (14.4)	10 (12.2)	14 (15.2)	16 (17.2)
Clodronate	3 (3.3)	1 (1.2)	3 (3.3)	1 (1.1)
Other	2 (2.2)	2 (2.4)	6 (6.5)	5 (5.4)
None	49 (54.4)	41 (50.0)	36 (39.1)	36 (38.7)
Washout for Bisphosphonates – n (%)				
<180 days	1 (1.1)	0 (0.0)	2 (2.2)	2 (2.2)
180 to < 365 days	4 (4.4)	1 (1.2)	5 (5.4)	3 (3.2)
≥365 days	34 (37.8)	38 (46.3)	43 (46.7)	47 (50.5)
25(OH)D	Zoledronic Acid (2304 & 2305)		Risedronate (2304 & 2305)	
Mean (SD) (nmol/L)	62 (22)		68 (50)	
Mean (ng/ml)	25		27	

Approximately 93% of the subjects in each treatment group completed the 6-month trials. The most common reasons for failure to complete the studies were adverse event (1.1% -2.4%)

protocol violations (0.0% - 3.3%), withdrew consent (1.1% - 3.3%), and lost to follow up (0.0% - 2.4%).

6.1.4 Efficacy Findings

In general, the results of the efficacy outcome analyses were similar for the two pivotal studies; therefore, pooled data from both trials will be provided in this section.

Primary Efficacy Outcome: At Day 182, 169/176 (96%) of the patients in the zoledronic acid group and 127/171 (74%) of the patients in the risedronate group achieved a therapeutic response ($p < 0.001$). The point estimate of the difference between groups in response rates was 22% with a 95% CI of 14%, 30%. From a statistical standpoint, these results demonstrate that zoledronic acid was non-inferior to risedronate (i.e., lower bound of the 95% confidence interval for the difference between groups was above -16%), as well as superior.

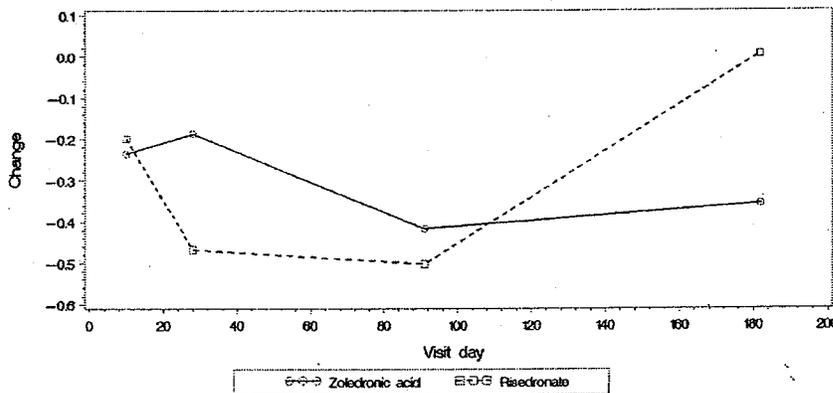
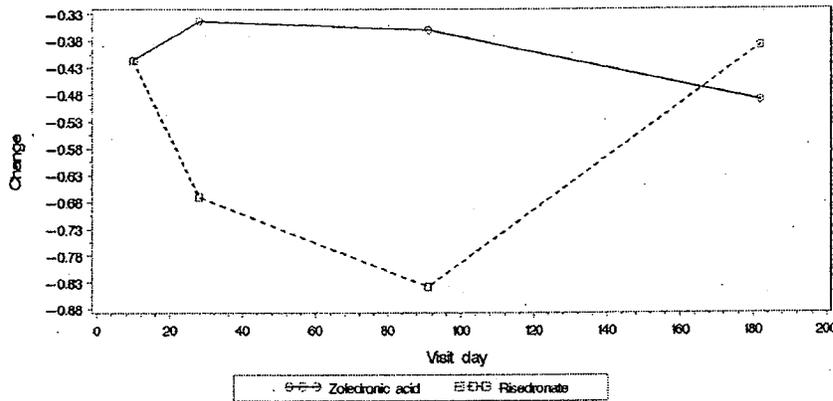
Eighty-nine percent of the zoledronic acid subjects and 58% of the risedronate subjects had normalization of SAP levels by Day 182. Seven percent of the zoledronic acid and 16% of the risedronate subjects had > 75% reduction in SAP excess only at Day 182.

In the Paget's registration trials for risedronate, 77% of patients treated with 30 mg x 2 months had normalization of their SAP levels by Day 180.

Secondary Efficacy Outcomes: The relative changes in serum CTX at Day 10, urine α -CTX at Day 10, and serum SAP at Day 28 were all statistically significantly greater in the zoledronic acid compared with the risedronate group.

Although the within-treatment differences for the changes in scores for BPI-SF pain severity and pain interference were statistically significant (all $p < 0.05$); the between-treatment comparisons for the changes in scores for BPI-SF pain severity and pain interference were not statistically significantly different (p-values 0.3 and 0.9, respectively).

The following two figures depict the pattern of change in the pain severity (top panel) and pain interference (bottom panel) measures for the two treatment groups.



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The proportion of patients who had a normalization of SAP by Day 28 was 13/176 (7%) in the zoledronic acid group and 1/170 (0.5%) in the risedronate group ($p < 0.001$).

The median time to first therapeutic response was 63 days in the zoledronic acid group and 107 days in the risedronate group ($p < 0.001$).

Long-Term Assessment of Efficacy: Following the core 6-month trial, subjects who achieved a therapeutic response and were willing to continue in the study were followed and had their SAP levels checked at 6-month intervals to assess long-term efficacy. At the initiation of the extended observation studies blinding was continued. After database lock for studies 2304 and 2305, the treatment codes were made available to the investigators. The extended observation period continues as of the filing of this NDA. Three parameters, defined below, were used to evaluate long-term efficacy:

- First loss of therapeutic response: the occurrence of a SAP level no longer meets the criteria of a therapeutic response.
- First partial disease relapse: an increase in SAP of at least 50% from the SAP measurement at month 6 and at least 1.25 x UNL

- First disease relapse: the occurrence of a SAP level that was within 20% of the baseline SAP value.

For the majority of patients, follow-up occurred within one year of the end of the core study period. The median follow-up time was 6 months.

The evaluations of long-term efficacy included 113 patients from the zoledronic acid group and 82 from the risedronate group. To date, 21 of the risedronate-treated subjects and one of the zoledronic acid-treated patients lost therapeutic response during the extended observation period (p=0.001). Eleven patients in the risedronate group and one in the zoledronic acid group experienced a partial disease relapse (p=0.01). One risedronate subject and none of the zoledronic acid subjects experienced a relapse of disease.

Efficacy Analyses in Demographic and Disease Subgroups: The primary efficacy outcome variable was assessed by number of previous Paget's treatment cycles, age, gender, race, baseline SAP, last Paget's therapy, and the presence or absence of pain at screening.

Number of Previous Treatment Cycles: The mean number of previous treatment cycles was approximately 1.5 for both groups. Roughly 45% of the patients entered the trial without any previous pharmacological treatment for Paget's. An additional 25% from each group received 1 treatment cycle prior to study entry. About 15% received 2-3 previous treatment cycles and approximately 13% received more than 3 treatment cycles. The following table provides the results of the primary efficacy analysis by previous treatment cycles.

Primary Efficacy Outcome by Number of Previous Treatment Cycles					
Studies 2304 and 2305 Combined					
Subgroup	Zoledronic acid n/N (Proportion)	Risedronate n/N (Proportion)	Difference ¹ (95% CI)	p-value ² for treatment difference	p-value ³ for subgroup interaction
Previous treatment cycles					
None	80/82 (0.98)	65/76 (0.86)	0.12 (0.02, 0.22)	0.0075	0.3553
1	41/45 (0.91)	32/46 (0.70)	0.22 (0.03, 0.40)	0.0098	
2-3	24/24 (1.00)	16/27 (0.59)	0.41 (0.18, 0.64)	0.0005	
>3	24/25 (0.96)	14/22 (0.64)	0.32 (0.06, 0.59)	0.0020	

¹ Difference is zoledronic acid minus risedronate; 95% CI for the difference is based on the normal approximation to the binomial.
² p-value is based on a Mantel-Haenszel test controlling for study for each category.
³ p-value is based on a Breslow-Day test with the subgroup as a controlling factor.
 Studies: 2304, 2305

Comment: It is clear from the above data that the largest differences in response rates between the zoledronic acid and risedronate groups are in the subjects who received previous pharmacological treatment prior to study entry.

Age: The response rates for those < 65 years, 65-74 years, and \geq 75 years were 100%, 97%, and 93% for the respective zoledronic acid groups and 82%, 78%, and 66% for the respective risedronate groups.

Gender: The response rate for females was 97% and 95% for males in the zoledronic acid group and 74% and 75% for the females and males in the risedronate group, respectively.

Race: There were too few patients other than Caucasians to perform meaningful analyses by race.

Baseline SAP: The response rates for those with baseline SAP levels < 3xULN were 97% in the zoledronic acid group and 75% in the risedronate group. For those patients with baseline SAP levels \geq 3xULN, the response rates were 95% and 74% for those in the zoledronic acid and risedronate groups, respectively.

Last Paget's Therapy: For those patients whose last Paget's therapy was an oral bisphosphonate, the response rate was 96% for the zoledronic acid-treated subjects and 55% for the risedronate subjects. For those whose previous therapy was an intravenous bisphosphonate, the response rates were 88% and 81% for the zoledronic acid and risedronate participants, respectively. For those who received clodronate previously, 100% of the subjects treated with zoledronic acid and risedronate responded. For patients who had not been previously treated for Paget's, the response rates were 98% and 86%, respectively, for the zoledronic acid and risedronate groups.

Symptomatic Pain at Screening: Of the patients who did not report pain at screening, 100% of the zoledronic acid and 82% of the risedronate-treated subjects responded. For the roughly 60% of all patients who did have pain at screening, 94% of the zoledronic acid subjects and 70% of the risedronate patients responded to therapy.

6.1.5 Clinical Microbiology

See review by Dr. John Metcalfe

6.1.6 Efficacy Conclusions

Novartis has provided substantial evidence to support the efficacy of a single 5 mg intravenous dose of zoledronic acid in the treatment of Paget's disease. This dosing regimen was statistically significantly more efficacious than therapy with 2 months of 30 mg daily risedronate. The data provided in this application also indicate that a single 5 mg dose of zoledronic acid provides a greater duration of therapeutic response than dose the risedronate regimen. Although both drugs reduced pain scores, the differences between groups were not statistically significant.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This integrated review of safety focuses on the results from the two pivotal Paget's disease trials, 2304 and 2305. Ancillary safety evaluations come from phase 1 and 2 Paget's disease studies, two phase 2 osteoporosis trials, and from one ongoing phase 3 osteoporosis study. Study 2301 is a randomized, placebo-controlled trial of more than 7000 postmenopausal women, and as such, safety data from this study, while partially blinded (treatment groups are designated A and B), will be the focus of the safety assessment from the ancillary data.

Regarding nomenclature, the following abbreviations will be used throughout this review:

- 1) Paget's Studies = the two pivotal Paget's disease studies 2304 and 2305, as well as the phase 1 and 2 studies 001 and 002.
- 2) Studies 2304 and 2305 = the two pivotal phase 3 Paget's disease studies 2304 and 2305.
- 3) Study 2301 = the ongoing postmenopausal osteoporosis fracture trial involving more than 7000 women.

Note: In study 2301, at baseline all subjects had their creatinine clearance (CrCl) calculated using the Cockcroft equation. If a subject's CrCl was less than 30 ml/min, they were excluded from the study. Prior to each dose (Month 12 and 24), serum creatinine, CrCl, and body weight were measured and patients were not to receive study drug if the CrCl was below 30 ml/min. As of the cutoff date for this submission, all of the subjects in each group received infusion #1 and roughly 51% of the subjects in each group had received a second infusion.

7.1.1 Deaths

Paget's Studies: There were four deaths - all occurred in study 002. The causes of death were listed as: DVT, pneumonia, esophageal cancer, and MI.

Study 2301: The incidence of deaths as of the cutoff date were 1.1% and 0.8% in treatment groups A and B, respectively.

7.1.2 Other Serious Adverse Events

Paget's studies: There were a total of 28 SAEs; 7 occurring in the 2 earlier trials using sub therapeutic doses of zoledronic acid, 9 occurring in zoledronic acid 5 mg group, 11 occurring in the risedronate group, and 1 occurring on placebo in Protocol 002. There was no suggestion that one particular SAE occurred at a greater frequency with zoledronic acid use than with risedronate or placebo.

Study 2301: The incidence of SAEs was 12.5% in treatment group A and 11.5% in group B. Although the overall frequency of SAEs was slightly higher (1%) in treatment group A, there

was no suggestion that any specific SAE associated with any particular organ class occurred more frequently with treatment A. A higher frequency of SAEs (≥ 5 patient difference) with treatment A vs. treatment B were observed for the following organ classes: cardiac disorders (2.4% vs. 2.2%), with ≥ 5 patient difference seen for atrial fibrillation (16 vs. 8 patients), acute myocardial infarction (8 vs. 2 patients) - [note for preferred term "myocardial infarction" the frequency was higher in treatment group B (21 patients) than in treatment group A (12 patients)], gastrointestinal disorders (2.2% vs. 1.6%), a difference of ≥ 5 patients seen for vomiting (11 vs. 5 patients) and upper abdominal pain (6 vs. 1 patients); general disorders and administrative site conditions (0.9% vs. 0.6%), a difference of ≥ 5 patients being seen for pyrexia (9 vs. 2 patients) and asthenia (8 vs. 3 patients); infections and infestations (2.4% vs. 1.9%), a difference of ≥ 5 patients seen for acute bronchitis (7 vs. 1 patients); metabolism and nutritional disorders (0.5% vs. 0.3%); musculoskeletal and connective tissue disorders (1.4% vs. 1.2%) a difference of ≥ 5 patients seen with arthralgia (9 vs. 3 patients), myalgia (5 vs. 0 patients); nervous system disorders (2.3% vs. 1.8%) with a difference of ≥ 5 patients seen for cerebrovascular accident (17 vs. 10 patients); psychiatric disorders (0.3% vs. 0.1%) A lower frequency of SAEs (≥ 5 patients) with treatment A vs. treatment B was observed for the following organ classes: endocrine (0.05% vs. 0.2%); hepato-biliary disorders (0.3% vs. 0.7%); neoplasms (1.5% vs. 1.7%); respiratory, thoracic and mediastinal disorders (0.7% vs. 0.9%).

Of the 485 SAEs in treatment group A and 446 SAEs in group B, the majority occurred more than 30 days after study drug infusion, with 90 and 59 SAEs occurring within 30 days for treatment group A and B, respectively.

The number of SAEs occurring within the first 3 days after study drug administration was low in both groups (31 [0.8%] in treatment group A, 14 [0.4%] in group B), with no SAE related to a specific preferred term occurring in more than 0.13% of patients in either group. The small difference in overall frequency was accounted for by a slightly higher number of SAEs of pyrexia (5 vs. 2 patients); myalgia (4 vs. 0 patients); arthralgia (3 vs. 0 patients); and dizziness (3 vs. 0 patients).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Paget's Studies: There was a very low incidence of patient drop outs ~ 4% or less for the zoledronic, risedronate, and placebo groups.

7.1.3.2 Adverse events associated with dropouts

Paget's Studies: Eight zoledronic acid and 2 risedronate patients discontinued from the studies due to an adverse event; all took place in the two phase 3 trials. The Preferred Terms reported in the zoledronic acid groups included peripheral edema, pyrexia, vomiting, dyspepsia, asthenia, abdominal pain, and hypocalcemia (n=1). The Preferred Terms reported in the risedronate groups

included hypocalcemia (n=1) and confusional state. The majority of these adverse events occurred within 10 days of receiving the initial dose of study medication.

7.1.3.3 Other significant adverse events

Renal Abnormalities

Because zoledronic acid has been associated with renal injury (i.e., increases in serum creatinine), a specific evaluation of renal-related adverse events was conducted by Novartis.

Paget's Studies: There were 2 patients with reports of renal-related AEs in the zoledronic acid groups (creatinine clearance decreased and urinary retention) and 3 patients in the risedronate group (hematuria x 2 and renal impairment).

Renal abnormalities (defined as urine protein >2+ on dipstick and /or serum creatinine increase by >0.5 mg/dL) occurred in four zoledronic acid subjects, two risedronate subjects, and none of the placebo patients. Review of the case narratives for these reports does not provide strong support for a causal relationship between the events and use of either drug.

Study 2301: No cases of urine protein >2+ on dipstick and /or serum creatinine increase by >0.5 mg/dL have been reported for patients in Treatment groups A or B.

Upper GI Abnormalities

Bisphosphonates, primarily oral formulations, have been linked in post-approval assessments with an increased incidence of upper GI AEs.

Paget's Studies: Upper GI AEs occurred in 18.6% and 16.3% of patients in the zoledronic acid 5 mg and risedronate groups, respectively. Other than small differences in the incidence of nausea (higher for zoledronic acid 5 mg) or upper abdominal pain (higher for risedronate) between the groups, the individual upper GI AEs were evenly distributed across study groups.

7.1.4 Other Search Strategies

Because bisphosphonates, particularly intravenously-administered ones, are associated with symptoms consistent with an acute phase reaction, special attention was paid to the following adverse events reported within a few days of zoledronic acid administration: pyrexia, influenza-like symptoms, arthralgia, fatigue, rigors, and myalgia.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

According to Novartis, the investigational sites were instructed to ask patients at every visit after screening whether or not they had any adverse events to report.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and use of preferred terms appears to have been appropriate.

7.1.5.3 Incidence of common adverse events

Studies 2304 and 2305: The incidence of adverse events was 83% vs. 77% in the zoledronic acid and risedronate groups, respectively.

7.1.5.4 Common adverse event tables

Paget's Studies: The following table provides the common adverse events ($\geq 5\%$ incidence) in patients from the Paget's Studies.

Adverse Events that Occurred in at Least 5% of Patients in any Group from the Paget's Studies				
	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	146 (82.5)	133 (77.3)	120 (76.4)	29 (82.9)
Adverse events				
Headache	19 (10.7)	17 (9.9)	16 (10.2)	4 (11.4)
Influenza-like illness	19 (10.7)	10 (5.8)	10 (6.4)	0 (0.0)
Arthralgia	16 (9.0)	19 (11.0)	25 (15.9)	9 (25.7)
Nausea	16 (9.0)	11 (6.4)	7 (4.5)	2 (5.7)
Bone pain	15 (8.5)	8 (4.7)	14 (8.9)	3 (8.6)
Dizziness	15 (8.5)	7 (4.1)	4 (2.5)	3 (8.6)
Pyrexia	15 (8.5)	3 (1.7)	3 (1.9)	0 (0.0)
Fatigue	14 (7.9)	7 (4.1)	16 (10.2)	1 (2.9)
Rigors	14 (7.9)	2 (1.2)	4 (2.5)	0 (0.0)
Influenza	13 (7.3)	8 (4.7)	0 (0.0)	0 (0.0)
Myalgia	13 (7.3)	7 (4.1)	3 (1.9)	0 (0.0)
Pain in extremity	13 (7.3)	13 (7.6)	17 (10.8)	6 (17.1)
Diarrhea	11 (6.2)	10 (5.8)	1 (0.6)	3 (8.6)
Nasopharyngitis	11 (6.2)	14 (8.1)	6 (3.8)	2 (5.7)
Constipation	10 (5.6)	9 (5.2)	1 (0.6)	1 (2.9)
Dyspepsia	9 (5.1)	6 (3.5)	2 (1.3)	0 (0.0)
Fall	9 (5.1)	5 (2.9)	0 (0.0)	0 (0.0)
Lethargy	9 (5.1)	1 (0.6)	3 (1.9)	1 (2.9)

Adverse Events that Occurred in at Least 5% of Patients in any Group from the Paget's Studies

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg	Risedronate	Zoledronic acid 24-400 µg	Placebo
Back pain	7 (4.0)	12 (7.0)	22 (14.0)	3 (8.6)
Edema peripheral	5 (2.8)	1 (0.6)	3 (1.9)	5 (14.3)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	2 (5.7)
Cough	4 (2.3)	8 (4.7)	4 (2.5)	2 (5.7)
Paraesthesia	4 (2.3)	0 (0.0)	3 (1.9)	2 (5.7)
Hot flush	3 (1.7)	1 (0.6)	1 (0.6)	2 (5.7)
Upper resp. tract inf.	3 (1.7)	6 (3.5)	10 (6.4)	3 (8.6)

7.1.5.5 Identifying common and drug-related adverse events

Paget's Studies: Based on existing data for intravenously administered bisphosphonates, the following adverse events are biologically plausibly related to zoledronic acid use: influenza-like illness, nausea, bone pain, pyrexia, rigors, influenza, myalgia, and lethargy.

The following table provides the adverse events that occurred with an incidence of at least 2% in either group and were suspected by the investigators to be "drug-related."

Adverse Events that with an Incidence of at least 2% Patients in Either Group and Thought to be Drug-Related by the Study Investigators

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	92 (52.0)	43 (25.0)	65 (41.4)	16 (45.7)
Adverse events				
Influenza-like illness	16 (9.0)	9 (5.2)	4 (2.5)	0 (0.0)
Pyrexia	13 (7.3)	1 (0.6)	3 (1.9)	0 (0.0)
Rigors	13 (7.3)	1 (0.6)	4 (2.5)	0 (0.0)
Headache	12 (6.8)	6 (3.5)	7 (4.5)	2 (5.7)
Myalgia	11 (6.2)	6 (3.5)	3 (1.9)	0 (0.0)
Nausea	10 (5.6)	3 (1.7)	6 (3.8)	1 (2.9)
Bone pain	9 (5.1)	2 (1.2)	8 (5.1)	2 (5.7)
Fatigue	9 (5.1)	3 (1.7)	12 (7.6)	0 (0.0)
Arthralgia	7 (4.0)	3 (1.7)	16 (10.2)	3 (8.6)
Lethargy	7 (4.0)	1 (0.6)	1 (0.6)	1 (2.9)
Influenza	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	6 (3.4)	4 (2.3)	2 (1.3)	0 (0.0)
Hypocalcemia	5 (2.8)	1 (0.6)	0 (0.0)	0 (0.0)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	0 (0.0)
Diarrhea	4 (2.3)	0 (0.0)	1 (0.6)	1 (2.9)
Dyspepsia	4 (2.3)	4 (2.3)	0 (0.0)	0 (0.0)
Dyspnea	4 (2.3)	0 (0.0)	1 (0.6)	0 (0.0)
Back pain	3 (1.7)	2 (1.2)	13 (8.3)	1 (2.9)

**Adverse Events that with an Incidence of at least 2% Patients in Either Group
 and Thought to be Drug-Related by the Study Investigators**

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid 24-400 µg n (%)	Placebo n (%)
Paraesthesia	2 (1.1)	0 (0.0)	3 (1.9)	1 (2.9)
Body temperature increased	1 (0.6)	2 (1.2)	4 (2.5)	0 (0.0)
Hot flush	1 (0.6)	0 (0.0)	1 (0.6)	2 (5.7)
Night sweats	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.9)
Chest wall pain	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Flushing	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Muscle cramp	0 (0.0)	1 (0.6)	4 (2.5)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.9)
Pain in extremity	0 (0.0)	2 (1.2)	11 (7.0)	3 (8.6)

7.1.5.6 Additional analyses and explorations

Paget's Studies: The following adverse events occurred with a greater incidence in the zoledronic acid vs. the risedronate groups during the first three days after zoledronic acid administration: influenza-like symptoms, myalgia, pyrexia, fatigue, headache, nausea, and arthralgia.

Study 2301: The following table provides a summary of important partially-blinded safety information from Study 2301, an ongoing trial of over 7000 postmenopausal women with osteoporosis.

**Number (%) of Subjects Who Died, Had Other Serious or Clinically Significant AEs or Discontinued
 Because of Them - Ongoing Study in Post-Menopausal Osteoporosis - 2301**

	Treatment A n=3876	Treatment B n=3866
	n (%)	n (%)
Serious or significant AEs	2789 (72.0)	2265 (58.6)
Death	44 (1.1)	31 (0.8)
SAEs	485 (12.5)	446 (11.5)
Discontinuation due to SAEs	69 (1.8)	52 (1.3)
Discontinuation due to non-serious AEs	27 (0.7)	15 (0.4)
Lab abnormalities leading to premature discontinuation	1 (0.0)	2 (0.1)
AEs causing concomitant medication taken	2466 (63.6)	2147 (55.5)
AEs due to IV study drug administration (1)	1248 (32.2)	239 (6.2)
Renal AEs leading to deterioration of renal function	37 (1.0)	26 (0.7)
Hypocalcemia* (numbers from 12-day safety update)	7 (0.2)	0 (0.0)

Source: (1) Adverse events classified in this group are any occurrences of pyrexia, myalgia, arthralgia, bone pain, and influenza-like illness occurring within 3 days of study drug infusion.

* There was no standard definition of hypocalcemia, but patients were not to be dosed if their serum calcium level went below 8.0 mg/dl. Of the 5 patients in treatment group A who had a Day 10 serum calcium value, two were below normal. Four of the 7 patients did not have serum calcium levels drawn, even though they were recorded as having hypocalcemia (based on symptoms).

A total of 37 subjects in treatment group A and 26 in treatment group B had AEs related to deterioration in kidney function. Nineteen of treatment group A and 7 of treatment group B subjects developed increases in serum creatinine (120-day safety update). In the majority of these cases, the increases in serum creatinine occurred soon after receiving the study drug. Most of the increases were transient. Two of the 19 patients in Treatment group A received intravenous fluids in response to their increased creatinine levels. Six (0.15%) and 5 (0.13%) of the patients in treatment groups A and B, respectively, had renal impairment. Five (0.13%) and 4 (0.10%) of the treatment group A and B subjects, respectively, developed acute renal failure. And one treatment group A subject and none of the treatment group B subjects developed azotemia.

7.1.6 Less Common Adverse Events

Some of the less common adverse events that occurred with a greater incidence in the zoledronic acid groups compared with the risedronate groups include peripheral edema (2.8% vs. 0.6%), asthenia (2.3% vs. 0.6%), paraesthesia (2.3% vs. 0.0%), and hot flush (1.7% vs. 0.6%)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Studies 2304 and 2305: The following laboratory parameters were obtained during the pivotal studies:

- Hematology at Baseline and Day 182: hematocrit, hemoglobin, platelet count, RBC, WBC, percent basophils, eosinophils, neutrophils, monocytes and lymphocytes
- Biochemistry at Baseline, Days 10, 63, 182: glucose, creatinine, BUN, total protein, AST, ALT, GGT, alkaline phosphatase, sodium, potassium, uric acid, chloride, phosphate, magnesium, albumin, calcium, bicarbonate, calculated creatinine clearance (Cockcroft-Gault equation)
- Urinalysis at Baseline and Days 10 and 182: protein, pH, specific gravity

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two pivotal Paget's disease studies were active-controlled with risedronate.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Studies 2304 and 2305: Changes in hematology parameters from baseline to Day 182 are reported for the zoledronic acid and risedronate groups.

For the biochemistry parameters, comparisons between zoledronic acid and risedronate were made at post-infusion Days 10, 63, and 182. While the Day 182 values are provided below, this Reviewer examined the other time points, and provide comments if clinically meaningful changes between groups were noted.

The baseline values for the following parameters were not statistically significantly different between the two treatment groups.

- Basophils: The mean changes from baseline to Day 182 were 0.0% and 0.1% in the zoledronic acid and risedronate groups, respectively.
- Platelets: The mean changes from baseline to Day 182 were 1.7 10E9/L and -1.9 10E9/L in the zoledronic acid and risedronate groups, respectively.
- Eosinophils: The mean changes from baseline to Day 182 were 0.3% and 0.1% in the zoledronic acid and risedronate groups, respectively.
- Lymphocytes: The mean changes from baseline to Day 182 were 1.1% and 0.5% in the zoledronic acid and risedronate groups, respectively.
- Monocytes: The mean changes from baseline to Day 182 were 0.1% and 0.3% in the zoledronic acid and risedronate groups, respectively.
- Neutrophils: The mean changes from baseline to Day 182 were -1.5% and 0.9% in the zoledronic acid and risedronate groups, respectively.
- WBC: The mean changes from baseline to Day 182 were 0.1 10E9/L in each group.
- RBC: There were no changes in the mean values for this parameter in either group.
- Hematocrit: There were no mean changes in either group from baseline to Day 182.
- Hemoglobin: The mean changes from baseline to Day 182 were -0.6 g/L and -1.5 g/L in the zoledronic acid and risedronate groups, respectively.
- Albumin: The mean changes from baseline to Day 182 were -0.1 g/L and -0.3 g/L in the zoledronic acid and risedronate groups, respectively.
- BUN: The mean changes from baseline to Day 182 were 0.2 mmol/L in each group.

- Serum Calcium: There were no changes in the mean values for this parameter in either group at the Day 182 time point. At Day 10 post-infusion, the mean changes were -0.2 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Chloride: The mean changes from baseline to Day 182 were 0.7 mmol/L and 0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Creatinine Clearance: At Day 10, the mean changes were 5.4 ml/min and -0.6 ml/min in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were -9.0 ml/min and -2.0 ml/min in the zoledronic acid and risedronate groups, respectively.
- Serum Creatinine: At Day 10, the mean changes were -4.4 umol/L and -0.1 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were 3.7 umol/L and 1.1 umol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Glucose: The mean changes at Day 182 were 0.1 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum Magnesium: There were no changes in the mean values for this parameter in either treatment group, at any of the post-infusion time points.
- Serum Phosphate: There were no changes in the mean values for this parameter in either group at Day 182.
- Serum Potassium: The mean changes at Day 182 were 0.0 mmol/L and -0.1 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Serum iPTH: The mean changes at Day 182 were 0.7 pmol/L and 0.2 pmol/L in the zoledronic acid and risedronate groups, respectively.
- AST: The mean changes at Day 182 were -3.6 U/L and -1.9 U/L in the zoledronic acid and risedronate groups, respectively.
- ALT: The mean changes at Day 182 were 0.7 U/L and 0.5 U/L in the zoledronic acid and risedronate groups, respectively.
- Serum Sodium: The mean changes at Day 182 were -0.5 mmol/L and 0.8 mmol/L in the zoledronic acid and risedronate groups, respectively.
- Total Protein: The mean changes at Day 182 were 0.1 g/L and -0.3 g/L in the zoledronic acid and risedronate groups, respectively.

- Serum Uric Acid: At Day 10, the mean changes were -31.1 umol/L and -11.1 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 63, the mean changes were -13.0 umol/L and -14.0 umol/L in the zoledronic acid and risedronate groups, respectively. At Day 182, the mean changes were -7.1 umol/L and -4.7 umol/L in the zoledronic acid and risedronate groups, respectively.

Comment: When Novartis was asked to provide data on changes in serum levels of LDH and total bilirubin, they responded that bilirubin was not measured "due to the lack of any signal in the previous studies and no known mechanism for liver toxicity for the class of bisphosphonates or zoledronic acid." Review of the summaries of data from the trials of patients with cancer and hypercalcemia of malignancy do not suggest that treatment with zoledronic acid was associated with an increased risk for clinically significant elevations of serum bilirubin compared with treatment with placebo or pamidronate. The lack of data on serum LDH from previous trials of zoledronic acid and from the Paget's studies is probably not important given the availability of data on hepatic transaminases.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Studies 2304 and 2305: Definitions of high and low laboratory parameters can be found in the Appendix.

- Platelets: At Day 182, 2 (1.3%) of the zoledronic acid and 1 (0.7%) of the risedronate subjects who had normal baseline platelet levels had high levels.
- Eosinophils: At Day 182, 1 (0.6%) of the zoledronic acid and 4 (2.6%) of the risedronate subjects who had normal baseline eosinophil levels had high levels.
- Hematocrit: At Day 182, 3 (1.9%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline hematocrit levels had low levels.
- Hemoglobin: At Day 182, 3 (1.9%) of the zoledronic acid and 6 (3.9%) of the risedronate subjects who had normal baseline hemoglobin levels had low levels.
- Lymphocytes: At Day 182, 3 (1.9%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline lymphocyte levels had low levels.
- Neutrophils: At Day 182, 7 (4.4%) of the zoledronic acid and 1 (0.7%) of the risedronate subjects who had normal neutrophil levels had high levels.
- RBC: At Day 182, 2 (1.3%) of the zoledronic acid and none of the risedronate subjects who had normal baseline RBC levels had low levels.
- WBC: At Day 182, 4 (2.5%) of the zoledronic acid and 3 (2.0%) of the risedronate subjects who had normal baseline WBC levels had high levels. One (0.6%) of the zoledronic acid subjects and 1 (0.7%) of the risedronate subjects who had normal baseline WBC levels had low levels at Day 182.
- BUN: At Day 10, none of the zoledronic acid and 2 (1.3%) of the risedronate subjects who had normal baseline BUN levels had high levels. At Day 63, 5 (3.0%) of the zoledronic acid and 5 (3%) of the risedronate subjects who had normal baseline BUN levels had high levels. Numbers similar to those at Day 63 were noted at Day 182 for both treatment groups.

- Creatinine Clearance: At Day 10, 7 (4.5%) of the zoledronic acid and 10 (6.3%) of the risedronate subjects who had normal baseline creatinine levels had low levels. At Day 182, none of the zoledronic acid and none of the risedronate subjects who had normal baseline levels had low creatinine clearance values.
- Creatinine: At Day 10, none of the subjects in either group who had normal baseline values for serum creatinine had high values. Of the 3 subjects in the zoledronic acid group who had high baseline serum creatinine values, 2 had high values at Day 10. One risedronate subject had a high baseline creatinine level, which remained high at Day 10. At Day 63, 2 (1.2%) of the zoledronic subjects and 1 (0.6%) of the risedronate subjects who had normal baseline creatinine values had high values. Of the 4 zoledronic acid subjects who had high baseline creatinine values, 3 had high levels at Day 63. One risedronate subject who had a high baseline creatinine also had a high value at Day 63. At Day 182, 2 (1.2%) of the zoledronic acid subjects and 1 (0.6%) of the risedronate subjects who had normal baseline creatinine levels had high levels.
- Calcium: At Day 10, 32 (20%) of the zoledronic acid and 4 (2.5%) of the risedronate subjects who had normal serum calcium levels at baseline had low levels. At Day 63, 4 (2.4%) of the zoledronic acid and 8 (4.8%) of the risedronate subjects who had normal baseline calcium levels had low levels. At Day 182, none of the subjects in either group had low serum calcium levels.
- Magnesium: At Day 10, 1 (0.6%) of the zoledronic acid and none of the risedronate subjects who had normal baseline magnesium levels had low levels. At Day 10, 10 (6.4%) of the zoledronic acid and 5 (3.1%) of the risedronate subjects who had normal baseline values had high serum magnesium levels. At Day 63, none of the subjects in either group who had normal baseline values had low levels. Six (3.6%) of the zoledronic acid and 4 (2.4%) of the risedronate subjects with normal baseline magnesium levels had high levels at Day 63. At Day 182, 9 (5.4%) of the zoledronic acid and 2 (1.3%) of the risedronate subjects with normal baseline levels had high levels.
- Phosphate: At Day 10, 28 (18%) of the zoledronic acid and 2 (1.3%) of the risedronate subjects with normal baseline values had low levels.
- iPTH: At Day 91, 18 (12%) of the zoledronic acid and 20 (13%) of the risedronate subjects with normal baseline iPTH levels had high levels. At Day 182, 5 (3.2%) of the zoledronic acid and 4 (2.6%) of the risedronate subjects with normal baseline values had high values.
- AST: At Day 10, 4 (2.7%) of the zoledronic acid and 10 (6.5%) of the risedronate subjects with normal baseline values had high values. At Day 63, none of the zoledronic acid and 7 (4.3%) of the risedronate subjects with normal baseline values had high values. At Day 182, 1 (0.6%) of the zoledronic acid and 3 (1.9%) of the risedronate subjects with normal baseline values had high values.
- ALT: At Day 10, 8 (5.3%) of the zoledronic acid and 5 (3.2%) of the risedronate subjects who had normal baseline values had high values. At Day 63, 5 (3.0%) of the zoledronic acid and 7 (4.2%) of the risedronate subjects who had normal baseline values had high values. At Day 182, 7 (4.2%) of the zoledronic acid and 8 (5.1%) of the risedronate subjects with normal baseline values had high values.

- Uric Acid: At Day 10, 2 (1.3%) of the zoledronic acid and 5 (3.1%) of the risedronate subjects who had normal baseline values had high values.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Previous clinical trials demonstrated that treatment with a single 4 mg infusion of zoledronic acid caused reductions in serum concentrations of calcium and phosphate, and increases in serum creatinine, with nadirs observed 9-11 days post-infusion. In this section, focus is paid to the "notably" low serum calcium and phosphate and high serum creatinine levels observed during Studies 2304 and 2305.

Serum Calcium: Five zoledronic acid and one risedronate-treated subject developed a serum calcium level < 1.87 mmol/L at any time during the two trials.

Serum Phosphate: None of the patients in either group developed a serum phosphorus level that was notably low.

Serum Creatinine: One zoledronic acid and none of the risedronate-treated subjects developed a serum creatinine > 221 umol/L at any time during the two trials.

7.1.7.4 Additional analyses and explorations

This section provides additional analyses of low serum calcium and phosphorus levels and high serum creatinine levels.

Serum Calcium

Studies 2304 and 2305: The following table shows the serum calcium levels at various time points during the studies for the 32 zoledronic acid and the 4 risedronate subjects who had normal baseline serum calcium levels and then developed a calcium concentration < 2.1 mmol/L at or near Day 10 post-dose.

The absolute and relative risks of hypocalcemia at Day 10 post-dose for the zoledronic acid and risedronate groups were: 32/151 (21%) vs. 5/156 (3.0%); RR = 6.6 (2.8, 19.4)

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**Demographic Characteristics of the Subjects who Developed
 Low Serum Calcium Levels At or Near Day 10 Post-Infusion**

Subject	Country	Age	Sex	Race	Calcium Baseline	Calcium Day 10	Calcium Day 29	Calcium Day 63	Calcium Day 92	Calcium Day 182
Zoledronic Acid Group										
005	Aus	75	F	W						
062	Aus	78	M	W						
071	Aus	84	M	W						
183	Aus	79	M	W						
012	Aus	73	M	W						
120	Aus	70	M	W						
155	Aus	51	M	W						
175	Aus	83	F	W						
204	Aus	56	M	W						
258	Aus	66	M	W						
303	Aus	70	M	W						
297	Aus	55	M	W						
061	Can	68	M	V						
179	Can	62	M	W						
083	GBR	80	F	W						
235	GBR	47	F	B						
086	NZL	78	M	W						
088	NZL	73	M	W						
187	NZL	72	M	W						
232	NZL	72	M	W						
233	NZL	73	F	W						
293	Aus	68	M	W						
114	Aus	84	F	W						
094	Aus	51	M	W						
349	ESP	71	F	W						
026	GBR	76	M	W						
075	NZL	77	M	W						
142	NZL	78	F	W						
303	NZL	63	M	W						
145	USA	64	F	W						
002	USA	78	M	W						
181	ZAF	74	F	O						
Risedronate Group*										
039	Aus	76	M	W						
152	Aus	78	F	W						
261	Aus	72	F	W						
239	ZAF	73	F	O						

Lower limit of normal for serum calcium is 2.1 mmol/L

The actual day the calcium level was drawn may vary ± a few days

*An additional patient who received risedronate developed a serum calcium of 5.4 mg/dl during the Day 9-11 visit. Because the blood was analyzed at a local lab, the information was not included in the above table.

The vast majority of the patients in both groups who developed low serum calcium levels were reportedly without symptoms and few received specific interventions to correct their low levels.

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 {NDA 21-817}
 {Zoledronic Acid for Paget's disease}

Study 2301: Six (0.2%) of the subjects from treatment group A and 1 from treatment group B (<0.1%) developed serum calcium levels < 1.87 mmol/L.

Serum Phosphorus

Studies 2304 and 2305: The following table shows the serum phosphorus levels at various time points during the studies for the 18 zoledronic acid and the 2 risedronate subjects who had normal baseline serum phosphate levels and then developed a phosphate concentration < 0.71 mmol/L at or near Day 10 post-dose.

The absolute and relative risks of hypophosphatemia at Day 10 post-dose for the zoledronic acid and risedronate groups were: 28/157 (18%) vs. 2/159 (1.3%); RR = 14.2 (4.1, 108.6)

Demographic Characteristics of the Subjects who Developed Low Serum Phosphorus Levels At or Near Day 10 Post-Infusion

Subject	Country	Age	Sex	Race	PO4 Baseline	PO4 Day 10	PO4 Day 29	PO4 Day 63	PO4 Day 92	PO4 Day 182
Zoledronic Acid Group										
012	Aus	73	M	W						
204	Aus	56	M	W						
258	Aus	66	M	W						
303	Aus	70	M	W						
004	Can	58	M	W						
010	Can	60	M	W						
061	Can	68	M	W						
099	Can	64	M	W						
102	Can	82	M	W						
113	Can	58	M	W						
083	GBR	80	F	W						
235	GBR	47	F	B						
093	GBR	72	M	W						
291	GBR	88	M	W						
088	NZL	73	M	W						
233	NZL	73	F	W						
274	USA	84	M	W						
114	Aus	84	F	W						
094	Aus	51	M	W						
212	Aus	61	M	W						
201	ESP	70	M	W						
369	FRA	77	F	B						
204	GBR	88	F	W						
347	GBR	75	M	W						
075	NZL	77	M	W						
137	USA	76	F	W						
353	USA	77	M	W						
235	ZAF	71	M	O						
Risedronate Group										
096	AUS	65	M	W						
288	AUS	58	M	W						

Lower limit of normal for PO4 is 0.71 mmol/L
The actual day the calcium level was drawn may vary \pm a few days

Most if not all of the subjects who developed low serum phosphorus concentrations spontaneously normalized their levels.

Serum calcium and phosphorus levels at Day 63: In the trials that served as the basis of approval of risedronate for Paget's disease, the regimen of 30 mg per day x 2 months led to nadirs in serum calcium and phosphorus levels at or near Day 56. This suggests that the nadir for serum calcium and phosphorus levels in the subjects treated with risedronate in the zoledronic acid studies should have occurred near the Day 63 time point.

Of the subjects who had normal serum calcium levels at baseline, 4 (2.4%) of the zoledronic acid subjects and 8 (4.8%) of the risedronate subjects had low serum calcium levels at Day 63. Of the subjects who had normal serum phosphorus levels at baseline, 1 (0.6%) of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

In the pivotal Paget's studies for alendronate, in which 40 mg was administered daily for 6 months, serum calcium and phosphorus were measured at Months 1, 3 and 6. The nadirs for these two minerals appeared to have occurred at the Month 1 time point. The mean reductions in serum calcium and phosphorus at Month 1 were -0.45 mg/dl and -0.47 mg/dl, respectively. In the zoledronic acid trials, the Day 10 mean reductions in serum calcium and phosphorus were -0.8 mg/dl and -1.7 mg/dl, respectively. Further, approximately 19% of the alendronate treated subjects developed serum calcium levels below 8.5 mg/dl, compared with approximately 32% of the zoledronic acid subjects. One (1.5%) of the alendronate patients developed a serum calcium level below 8.0 mg/dl vs. 12 (8%) of the zoledronic acid-treated participants.

Study 2301: A total of 40 (1.1%) of the subjects in Treatment group A and 10 (0.3%) of the subjects in Treatment group B developed serum phosphorus values below 0.71 mmol/L at Day 10 (120-day safety update).

Comment: The above data indicate that a significantly greater percentage of patients treated with zoledronic acid compared with risedronate developed mostly asymptomatic hypocalcemia and hypophosphatemia within the first two weeks post-dosing. Given the potent antiresorptive action of a single 5 mg infusion of zoledronic acid compared with daily oral doses of other bisphosphonates, these findings are not surprising. Novartis states that to the best of their knowledge, of the 32 patients who developed low calcium levels at Day 10, 3 patients received specific interventions in an attempt to increase their low levels (e.g., instructed to take calcium supplements after it was discovered that they were not taking as directed). The rest of the subjects presumably normalized their serum calcium and phosphorus levels spontaneously.

Unfortunately, Novartis does not have data regarding the specific amounts of daily calcium or vitamin D the subjects actually took. Without this information it is not possible to determine if the increased frequency of hypocalcemia and hypophosphatemia in the

zoledronic acid-treated patients was related to poor compliance with, or inadequate doses of, the calcium and vitamin D supplements, or whether the results are simply due to the antiresorptive potency of the drug.

Renal Abnormalities and Adverse Events

Studies 2304 and 2305: As discussed in the below paragraphs, there were 5 reported adverse renal events, two occurring in the zoledronic acid 5 mg group and three in the risedronate group.

One patient (0455/00109) in the zoledronic acid 5 mg group had a clinically notable increase in serum creatinine, defined as a post-baseline value that increased by at least 0.05 mg/dl. Creatinine for this patient had been above the normal range at screening (189 µmol/L) and remained high for the following two visits (200- 212 µmol/L, Days 13 & 63). The high levels were attributed to congestive heart failure as well as to the treatment course, especially diuretics and ACE-inhibitors. Creatinine had decreased by the time of the first visit of the extension observation period. See Appendix for details of this case.

One patient (0452/00213) in the 5 mg zoledronic acid group had urinary retention which was moderate in severity, and related to a progression of urethral stenosis stemming from previous prostate surgery for benign prostatic hypertrophy. There was no evidence of renal compromise in this patient. This event did not require the patient to be discontinued from the study.

Three patients in the risedronate group had AEs associated with renal deterioration: hematuria in two patients and renal impairment in one. For the two patients with hematuria, both events were mild in severity, and did not require patients' discontinuation from the study. For the patient with renal impairment (0605/00199), the event was serious, and moderate in severity. The patient had several other serious AEs and was discontinued from the study as a result of the AE of confusion.

The following table provides the number and percentage of subjects in each group who developed at least +1 urinary protein (by dipstick) at any time post-baseline.

Baseline CrCl ml/min	Subjects Who Developed +1 or greater Urinary Protein by Dipstick					
	Zoledronic Acid			Risedronate		
	N	n	%	N	n	%
< 40	5	0	0	4	0	0
40 - 50	18	0	0	15	0	0
> 50	148	12	8.1	150	10	6.7
All Subjects	171	12	7	169	10	5.9

Study 2301: Three (0.1%) of the subjects in treatment group A and 2 (<0.1%) of the subjects in treatment group B developed serum creatinine values > 221 µmol/L. Ten (0.5%) and 7 (0.3%) had an increase in serum creatinine > 0.5 mg/dl 9-11 days post-infusion #1. A total of 12 of treatment group A subjects vs. 6 of treatment group B subjects had an increase in serum creatinine > 0.5 mg/dl 9-11 days post-infusion #2 (120-day safety update). The largest increase

in either group was 0.8 mg/dl and most increases were followed by lower serum creatinine values upon follow up assessments. Six (0.3%) of treatment group A subjects and 3 (0.1%) of treatment group B subjects had > 2+ protein urine on dipstick 9-11 days post-infusion #1. A total of 4 (0.3%) of treatment group A subjects vs. 1 (0.1%) of treatment group B subjects had > 2+ protein urine on dipstick 9-11 days post-infusion #2. Only one of the patients in Treatment group A and none in group B had an abnormal level of protein in their 24-hour urine sample. The narrative for this patient, as provided by Novartis, is provided below.

Patient ID USA/580/00042 – 84-year-old female from Treatment group A. The patient had a 3+ urine protein dipstick result at her MV5A visit (taken 4 Dec 03). The patient had 2+ urine protein dipstick results on all her previous lab visits. A local 24 h urine collection, performed on 15 Dec 04 confirmed the proteinuria suspicion (900mg protein /24h urine collection were reported). The patient had been advised to see a nephrologist. There was no change in health status and patient did not report any symptoms consistent with an acute phase reaction before or after the infusion. The patient had not developed a disease during the screening period. In the opinion of the investigator a relationship between the event and the study medication is possibly suspected. The nephrologist suspects hypertensive nephrosclerosis; he pointed out that the proteinuria by dipstick is quite variable depending upon the concentration of the urine. A renal ultrasound had also been performed and was reported as “essentially normal”. A recheck of renal function was planned. The patient herself reported no complaints, except some back discomfort.

The following table provides the number (%) of patients with renal adverse events from Study 2301.

Number (%) of Subjects with Renal Function AEs – Ongoing Study 2301		
	Treatment A	Treatment B
	n (%)	n (%)
Subjects studied		
Total no. of subjects studied	3876	3866
Total no. of subjects with deterioration of renal function AEs	37 (0.95)	26 (0.67)
Deterioration of renal function AEs		
Blood creatinine increased	12 (0.31)	4 (0.10)
Creatinine renal clearance decreased	11 (0.28)	10 (0.26)
Renal impairment	6 (0.15)	5 (0.13)
Proteinuria	5 (0.13)	4 (0.10)
Renal failure acute	4 (0.10)	3 (0.08)
Azotemia	1 (0.03)	0 (0.00)
Glomerulonephritis acute	1 (0.03)	0 (0.00)
Nephritis	1 (0.03)	0 (0.00)
Oliguria	1 (0.03)	0 (0.00)

Eye Abnormalities

Paget's Studies: There were more eye abnormalities in subjects treatment with zoledronic acid compared with those treated with risedronate or placebo – see Table in Appendix for listing of actual events.

Study 2301: There have been 10 cases of eye pain and 5 cases of uveitis in treatment group A and there have been 3 cases of eye pain and no cases of uveitis in group B.

Comment: Bisphosphonates including pamidronate, clodronate, and alendronate have been linked to the development of various eye abnormalities including uveitis and scleritis. Whether zoledronic acid poses a greater risk for eye abnormalities such as uveitis than other bisphosphonates is unknown at this time and would probably require a large head-to-head trial to accurately answer the question.

Osteonecrosis

Studies 2304 and 2305: no cases of osteonecrosis of the jaw were reported from these two studies, or in any of the zoledronic acid studies of patients with “benign” bone disease.

Study 2301: There have been no cases of osteonecrosis of the jaw in either group. There have been two SAEs of aseptic necrosis of the femoral head, one in each treatment group; both patients had a recent history of a hip fracture. Furthermore, there has been one additional case of knee necrosis in treatment group A.

Comment: A large number of MedWatch reports of osteonecrosis of the jaw have been submitted to Agency during the past year. Most of the cases have been in patients being treated for cancer with either pamidronate or zoledronic acid. There are very few cases of osteonecrosis from patients taking alendronate or risedronate for osteoporosis. The Division of Oncology Drug Products is convening their advisory committee on March 4, 2005, to discuss the risk bisphosphonates, primarily those administered intravenously, pose for osteonecrosis of the jaw in patients being treated for cancer.

Gastrointestinal Events

Studies 2304 and 2305: There were a total of 33 (19%) and 28 (16%) upper GI adverse events reported in the zoledronic acid and risedronate groups, respectively. Nausea (9.0% vs. 6.4%); dyspepsia (5.1% vs. 3.5%); abdominal distention (2.3% vs. 1.2%); and vomiting (2.3% vs. 1.7%) occurred more commonly in the zoledronic acid compared with the risedronate groups.

7.1.7.5 Special assessments

Bone Biopsy Data

In study 2304, a small subgroup of patients consented to having bone biopsies at Visit 7 (Day 182). In general, 6 weeks prior to Visit 7, patients received tetracycline capsules and were instructed to take 250 mg four times a day for 3 days, followed by 14 days without tetracycline, and then 3 additional days of the drug. Within 5 to 14 days of the second label ingestion, a transilial bone biopsy was performed according to a standard procedure. Once obtained, the bone specimens were shipped to _____, and subsequently sent to the _____.

There were 7 (5 male) zoledronic acid subjects and 4 (all male) risedronate subjects who took part in the bone biopsy substudy. The mean age of the zoledronic acid subjects was 72 years; whereas it was 64 years for the risedronate-treated subjects. All of these subjects were Caucasian.

Eleven biopsies (7 zoledronic acid and 4 risedronate) were evaluable (contained both cortices with intact trabecular bone and marrow) out of a total of 22 specimens. The 11 non-evaluable specimens consisted of insufficient tissue, containing only one cortex and a few trabecular fragments.

Three additional biopsy specimens were excluded from the per-protocol analyses because they were not obtained from the area of the bone prespecified in the protocol.

Other than finding areas of woven bone, a histological characteristic of Paget's disease, there were no reports of abnormal bone histology (e.g., mineralization defects) in specimens from either treatment group.

The following table provides the histomorphometric variables of interest from the two treatment groups.

Histomorphometric Variables					
Variable	Zoledronic Acid		Risedronate		P-value
	N	Mean	N	Mean	
Osteoid Thickness (Um)	5	4.9	3	5.3	0.4
Wall Thickness (Um)	5	28.6	3	43	0.07
Trabecular Thickness (Um)	5	184	3	171	1.0
Mineral Apposition Rate (um/d)	4	0.57	3	0.52	0.2
Mineralization Lag Time (days)	4	270	3	79	0.6
Activation Frequency (#/year)	4	0.05	3	0.43	0.2

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Studies 2304 and 2305, blood pressure, pulse, temperature, and body weight were measured at Baseline and Day 182.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The following vital sign data are provided for Studies 2304 and 2305 combined. Comparisons are made with risedronate.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The mean changes in sitting systolic blood pressure from baseline to Day 182 were -1.2 mmHg and -2.1 mmHg in the zoledronic acid and risedronate groups, respectively.

The mean changes in sitting diastolic blood pressure from baseline to Day 182 were 1.1 mmHg and 0.7 mmHg in the zoledronic acid and risedronate groups, respectively.

The mean changes in sitting pulse rate from baseline to Day 182 were -0.2 bpm and -0.3 bpm in the zoledronic acid and risedronate groups, respectively.

The mean changes in body weight from baseline to Day 182 were 0.3 kg and 0.4 kg in the zoledronic acid and risedronate groups, respectively.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Blood Pressure and Pulse: The following table provides the number and percentage of patients in each treatment group who at any time during the trials was observed to have an outlier value for systolic or diastolic blood pressure or pulse rate.

Number and Percentage of Subjects with Significant Increase or Decrease from Baseline in Vital Signs at Any Time During Studies 2304 and 2305							
Parameter	Criteria	Zoledronic acid 5 mg			Risedronate		
		N	n	%	N	n	%
Pulse (bpm)	Increase of > 10 units	173	20	11.6	167	18	10.8
	Decrease of > 10 units	173	26	15.0	167	21	12.6
Systolic BP (mmHg)	Increase of > 15 units	175	28	16.0	167	25	15.0

Number and Percentage of Subjects with Significant Increase or Decrease from Baseline in Vital Signs at Any Time During Studies 2304 and 2305

Parameter	Criteria	Zoledronic acid 5 mg			Risedronate		
		N	n	%	N	n	%
Diastolic BP (mmHg)	Decrease of > 15 units	175	35	20.0	167	34	20.4
	Increase of > 10 units	175	19	10.9	167	15	9.0
	Decrease of > 10 units	175	18	10.3	167	12	7.2

Body Weight: Approximately 3.0% of the zoledronic acid subjects and 4.0% of the risedronate subjects had an increase in body weight of > 7% during the two pivotal trials. One point seven percent and 1.2% of the zoledronic acid and risedronate subjects, respectively, had decreases in body weight of > 7% during the two pivotal Paget's trials.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No patient in either of the pivotal Paget's trials discontinued prematurely due to an abnormal vital sign.

7.1.8.4 Additional analyses and explorations

Acute-Phase Reaction

Bisphosphonates, primarily those administered by intravenous injection, have been associated with an acute-phase reaction that generally occurs within days of the infusion and typically includes symptoms such as fever, myalgia, and joint pain

Studies 2304 and 2305: Seventeen (10%) of the zoledronic acid and 7 (4%) of the risedronate subjects reported influenza-like illness within 3 days of the initial dose of study medications. Pyrexia was reported by 13 (7%) and 1 (0.6%) of the zoledronic acid and risedronate groups, respectively.

Study 2301: Six-hundred-forty subjects (17%) in Treatment group A and 71 (2%) in Treatment group B reported pyrexia (there was no standard definition of pyrexia used in the trial); 380 (8%) and 54 (1%) of Treatment group A and B subjects, respectively, reported myalgia; 284 (7%) and 51 (1%) of subjects in groups A and B, respectively, reported influenza-like illness; 239 (6%) of group A subjects reported arthralgia and 54 (1%) of group B did so; bone pain was reported by 160 (4%) of group A patients and by 33 (1%) of group B subjects. Approximately half of these events occurred on Day 1, half on Day 2, and a few on Day 3.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No signals of cardiovascular toxicity in preclinical studies and no clinically significant changes in ECGs were noted in zoledronic acid compared with placebo or active-comparator treated subjects in the pivotal studies that supported approval of the drug for the treatment of hypercalcemia of malignancy and bone metastases. Moreover, oral and intravenous bisphosphonates, as a class have not been implicated in causing cardiac abnormalities. Given the aforementioned, and since ECGs are currently being obtained in a large zoledronic acid osteoporosis fracture trial, no routine ECG monitoring was done in the pivotal Paget's disease studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1

7.1.9.4 Additional analyses and explorations

Not Applicable.

7.1.10 Immunogenicity

As of January 25, 2005, Novartis' Clinical Safety and Epidemiology Group received 25 (21 postmarketing and 4 clinical trial) reports suspicious for anaphylaxis or suspected anaphylaxis with zoledronic acid. The time between zoledronic acid administration and the onset of the first symptoms, was generally during the administration or within 24 hours of receiving study drug.

Brief narratives for these cases are provided in the Appendix.

The currently approved labeling for zoledronic acid contains precautionary language regarding the occurrence of bronchoconstriction in patients with aspirin sensitive asthma following treatment with bisphosphonates. No cases of bronchoconstriction have been reported to date with zoledronic acid.

7.1.11 Human Carcinogenicity

This Reviewer is not aware of any studies that have systematically examined whether zoledronic acid increases or decreases the risk of cancer. Data from preclinical studies do not suggest that

zoledronic acid is genotoxic or oncogenic. In fact, some animal data suggest that bisphosphonates have antiangiogenic properties, which could reduce the metastatic potential of some primary tumors⁴.

7.1.12 Special Safety Studies

Bone biopsies were obtained in a subset of Paget's patients who participated in Study 2304.

See section 7.1.7.5 of this review for additional details.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no data to suggest that bisphosphonates as a class or zoledronic acid in particular are associated with withdrawal phenomena or have any potential for abuse, as use of this term applies to centrally-active compounds such as amphetamines.

7.1.14 Human Reproduction and Pregnancy Data

Not surprisingly given the age of the subjects in the Paget's trials and the predominance of males, no pregnancies were reported. The Division believes that there is a theoretical risk of fetal harm if a pregnant woman were exposed to a bisphosphonate. Class labeling that addresses this theoretical risk has been enacted for all bisphosphonates. The Pregnancy subsection of the Precautions section of the bisphosphonate labels now includes the following language:

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

As of January 25, 2005, Novartis' Clinical Safety and Epidemiology Group has received seven (6 post-marketing and one clinical trial) reports of exposure with zoledronic acid during pregnancy: The short summaries of these reports are provided in the Appendix.

7.1.15 Assessment of Effect on Growth

There is currently an ongoing study comparing the efficacy and safety of zoledronic acid to pamidronate in the treatment of osteogenesis imperfecta in pediatric patients. When completed, this trial will provide some data on the effects of zoledronic acid on linear growth, albeit in a small subset of children with an underlying bone disorder.

7.1.16 Overdose Experience

The following information is provided in the currently approved zoledronic acid labeling:

There is no experience of acute overdose with Zometa® (zoledronic acid) Injection. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In an open-label study of zoledronic acid 4 mg in breast-cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with Non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

7.1.17 Postmarketing and Foreign Experience

At the time of this NDA submission, zoledronic acid is not approved for the treatment of Paget's disease of bone in any country. A marketing application was submitted in April 2004 to the European Agency for Evaluation of Medicinal Products (EMA) in the European Union (EU) for the use of zoledronic acid as a treatment for Paget's disease and is currently under review via the Centralized Procedure. There have been no Health Authority or manufacturer withdrawal actions taken for zoledronic acid for safety or efficacy reasons in any country.

Zoledronic acid is approved and marketed for the following two oncology-related indications outside the United States (89 countries worldwide):

1. Hypercalcemia of malignancy (HCM)
2. Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone.

Two pharmaceutical forms of zoledronic acid exist outside the United States, the originally developed 4 mg powder and solvent for solution for infusion and the 4 mg/5 mL concentrate for solution for infusion. The final solution for infusion (which is administered i.v. to the patient) resulting from either pharmaceutical form is equivalent. Zoledronic acid powder was first registered in Canada on 21 August 2000, for the indication of hypercalcemia of malignancy (HCM). The EU authorization via the Centralized Procedure for this indication was received on 20 March 2001. The second indication was first registered in Malta on 13 August 2001.

European approval was received on 19 July 2002. Zoledronic acid concentrate was first approved in Australia on 24 March 2003, and the EU authorization via the Centralized Procedure was granted on 24 March 2003.

As discussed in section 7.2.2.2 below, osteonecrosis of the jaw (ONJ) has been identified as an adverse event (primarily in patients being treated for cancer) that is very likely related to the use

of zoledronic acid (and intravenous pamidronate). The Division of Oncology Drug Products plans to convene its Advisory Committee in March 2005 to discuss this issue in greater detail.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Paget's Disease Studies: Studies 2304 and 2305 were randomized, double-blind, active-controlled 6-month phase 3 studies involving approximately 350 patients with Paget's disease of the bone. Study 002 was a randomized, double-blind, placebo-controlled 3-month phase 2 study of 176 patients with Paget's disease and study 001 was an open-label 14-day study of 16 patients with Paget's disease. Data from Studies 2304 and 2305 provide the majority of the safety data for the Paget's population.

7.2.1.2 Demographics

The following table provides the baseline demographic characteristics, which were well-matched between groups, for the patients enrolled in the Paget's studies. The population was predominately Caucasian, male, and over the age of 65 years, as would be expected of patients with this disease.

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg N=177	Risedronate N=172	Zoledronic acid < 5 mg (24-400 µg) N=157	Placebo N=35
Sex n (%)				
Male	122 (68.9)	117 (68.0)	93 (59.2)	24 (68.6)
Female	55 (31.1)	55 (32.0)	64 (40.8)	11 (31.4)
Race n(%)				
Caucasian	164 (92.7)	162 (94.2)	140 (89.2)	34 (97.1)
Black	8 (4.5)	4 (2.3)	14 (8.9)	1 (2.9)
Other	5 (2.8)	6 (3.5)	3 (1.9)	0 (0.0)
Age group (years) n(%)				
<65	45 (25.4)	46 (26.7)	37 (23.6)	6 (17.1)
≥65	132 (74.6)	126 (73.3)	120 (76.4)	29 (82.9)
Age (years)				
n	177	172	157	35
mean (SD)	70.8 (9.90)	70.0 (10.79)	70.4 (8.34)	72.0 (10.48)
median	72.0	72.0	71.0	74.0
range	42.0-94.0	34.0-88.0	42.0-88.0	33.0-88.0

As shown below, disease characteristics were balanced between the zoledronic and placebo and risedronate comparator groups. Approximately 50% of the subjects in the phase 3 trials had baseline Alk Phos levels $\geq 3x$ ULN; the majority had calculated CrCl rates of > 50 mL/min; and nearly half had never received drug treatment for their Paget's disease prior to entry into these studies.

Disease characteristics by treatment for Subjects Enrolled in the Paget's Phase 1 - 3 Studies

	Phase III studies		Phase I/II Studies	
	Zoledronic acid 5 mg N=177	Risedronate N=172	Zoledronic acid <5 mg (24-400 ug) N=157	Placebo N=35
Baseline serum alkaline phosphatase (U/L)				
mean (SD)	430.6 (324.86)	426.6 (313.89)	581.9 (376.24)	540.6 (402.83)
median	339.0	305.0	444.0	389.0
range	229.0 - 2822.0	214.0 - 2377.0	213.0 - 2310.0	236.0 - 2362.0
Baseline serum alkaline phosphatase				
<3xULN	5			
$\geq 3x$ ULN	5			2
missing				
Calculated creatinine clearance at baseline (mL/min)				
mean (SD)	85.3 (33.11)	87.0 (33.13)	70.4 (23.90)	70.4 (23.76)
median	80.4	83.1	67.5	68.0
range	30.6 - 217.8	29.4 - 228.0	29.0 - 153.0	33.0 - 145.0
Calculated creatinine clearance at baseline (mL/min)				
<30	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)
30 - <40	5 (2.8)	3 (1.7)	11 (7.0)	2 (5.7)
40-50	18 (10.2)	15 (8.7)	15 (9.6)	4 (11.4)
>50	154 (87.0)	153 (89.0)	107 (68.2)	21 (60.0)
missing	0 (0.0)	0 (0.0)	23 (14.6)	8 (22.9)
Last Paget's disease therapy before randomization				
Bisphosphonates				
oral	5			
iv				
clodronate (iv or oral)				
Others				
None				
Bisphosphonates washout (days)				
<180	5			
180 - <365				
≥ 365				2

7.2.1.3 Extent of exposure (dose/duration)

In the two phase 3 trials, the mean duration of treatment was approximately 60 days, with over 90% of the subjects in each treatment group reporting 90% or greater compliance with study drug administration.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Four studies of patients with osteoporosis provide ancillary safety data. Study 0041 was a randomized, placebo-controlled, double-blind 12-month phase 2 study of 351 women with postmenopausal osteoporosis. Approximately 280 of the 351 subjects enrolled in a 12-month open-label extension study. Study 2310 is an ongoing randomized, double-blind, placebo-controlled 24-month phase 3 study of approximately 1700 men and women who have sustained a hip fracture. Study 2301 is an ongoing, randomized, double-blind, placebo-controlled 36-month, phase 3 study of more than 7000 women with postmenopausal osteoporosis who are receiving annual 5 mg doses of zoledronic acid. This study, which remains partially blinded (treatment groups A and B), provides the largest exposure to zoledronic acid and placebo in a non-oncology population and is referred to frequently in this review.

7.2.2.2 Postmarketing experience

The most significant adverse event reported with use of zoledronic acid post-marketing is osteonecrosis of the jaw (ONJ). Using the AERS database, the Office of Drug Safety has provided the Divisions of Metabolic and Endocrine and Oncology Drugs with consults evaluating reports of osteonecrosis associated with use of zoledronic acid, pamidronate, and the oral bisphosphonates. The vast majority of cases of ONJ have occurred in patients with cancer who often had additional risk factors for the condition such as anemia, radiation treatment, etc. As of this writing, a Change Being Effected labeling supplement is being reviewed by the Division of Metabolic and Endocrine Drugs. The supplement proposes the addition of precautionary language regarding ONJ to the zoledronic acid and pamidronate labels. For more information on this topic, readers are referred to a paper by Ruggiero, et al., entitled Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases, published in the *Oral Maxillofac Surg.* 2004 May;62(5):527-34.

7.2.2.3 Literature

A list of the published papers that were reviewed can be found at the end of this review.

7.2.3 Adequacy of Overall Clinical Experience

The phase 2 data for zoledronic acid in Paget's disease come from 2 studies. In the larger of the two, the effects of 50 ug, 100 ug, 200 ug, and 400 ug of zoledronic acid (administered over 1 hour) on levels of serum alkaline phosphatase were examined in approximately 140 patients. The results indicated all doses of zoledronic acid decreased SAP levels, in a dose-related manner, by a statistically significantly greater amount than did placebo.

Although Novartis argues, based on changes in markers of bone resorption and formation in patients with osteoporosis, that a single 5 mg dose of zoledronic acid is appropriate for the

treatment of Paget's disease, the fact remains that the company does not know if doses lower than 5 mg (say, 3 mg) would prove efficacious in Paget's disease.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

As would be predicted based on its mechanism of action, zoledronic acid produces transient decreases in serum calcium levels, with nadir levels noted one to two weeks post-dose. In the pivotal Paget's studies, the mean changes from baseline to Day 10 in levels of serum calcium were -0.2 mmol/L in the zoledronic acid group and -0.1 mmol/L in the risedronate group. Mean changes of these magnitudes would not be expected to significantly prolong the QTc interval.

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See section 5 of this review and Dr. Suarez's review of this application for details of the pharmacokinetic properties of zoledronic acid.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

By including measurements at Day 10 post-infusion, the company designed the two pivotal Paget's trials to adequately assess the risk for renal injury and hypocalcemia.

7.2.8 Assessment of Quality and Completeness of Data

To the extent that the available information provides for such an evaluation, the data provided in this submission appear to be complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

On 19 January, 2005, Novartis submitted a 120-day safety update for the Paget's NDA. This update extends the period of patient observation from a cutoff date of 1 March 2004 to 1 July 2004.

No new studies in patients with Paget's disease have been initiated since submission of the original NDA. Serious AE information from the extension phases of studies 2304 and 2305 are provided in this safety update.

In addition to the extension phases of studies 2304 and 2305, updated safety information comes primarily from three trials:

1. 0041E2: A now completed phase 2 open-label extension study in postmenopausal women with osteoporosis.

2. 2301: An ongoing, partially blinded phase 3 trial evaluating the fracture efficacy of zoledronic acid in postmenopausal women.
3. 2202: An ongoing, open-label trial of the efficacy and safety of zoledronic acid vs. pamidronate in pediatric patients with osteogenesis imperfecta.

On note, four studies in patients without cancer started prior to 1 July 2004; however, the company reports that no deaths, serious AEs, or other clinically significant adverse events were reported for any of these studies as of the 1 July 2004 cutoff date.

Studies 2304 and 2305: During the extension phases of studies 2304 and 2305 there were two deaths in zoledronic-acid treated subjects and none in the risedronate-treated subjects. One death was attributed to a myocardial infarction in an 86-year-old subject and the other death was coded as due to mitral valve incompetence in an 83-year-old patient. There were three risedronate-treated patients who reported serious AEs (esophageal cancer, fracture of the humerus, and progression of hypertension) and one patient with a serious AE from the zoledronic acid group (pneumonia).

Study 0041E2: There were no deaths reported during this open-label study. As noted in the below table, one patient developed an increase in serum creatinine from baseline > 0.5 mg/dl, although the increased value was not confirmed upon repeat measurement; one developed a creatinine clearance < 30 ml/min; and 5 subjects developed urine protein > 2+ or ≥ 250 mg/dl. From the information provided in the narratives for these subjects, particularly the temporal relationship between the last dose of zoledronic acid and the occurrence of the proteinuria, it is this Reviewer's opinion that the drug was not causally related to the renal events.

Study 0041E2 - Pre-Specified Renal Abnormalities

	2 years of zoledronic acid		3 years of zoledronic acid		5 years of zoledronic acid	
	N	n (%)	N	n (%)	N	n (%)
Total no. of patients with a protocol-defined renal abnormality	19	2 (10.5)	78	2 (2.6)	22	2 (9.1)
Creatinine clearance < 30 mL/min	19	1 (5.3)	78	0	22	0
Increase in serum creatinine from baseline > 44.2 umol/L	19	1 (5.3)	78	0	22	0
Urine protein > 2+ or ≥250 mg/dL	19	1 (5.3)	78	2 (2.6)	22	2 (9.1)

Note: The treatment groups pertain to the total number of years of zoledronic acid treatment across the core, extension 1, and extension 2 studies.

N = number of patients with a relevant post-baseline absolute or change from baseline value.

Three patients were reported to have had renal adverse events coded as renal impairment:

- Patient 3-1554 (in the 5-year treatment group) had a baseline creatinine clearance of 69 mL/min. At month 48, a creatinine clearance of 60 mL/min was reported as an adverse event.

- Patient 3-1555 (in the 3-year treatment group) had a creatinine clearance of 56 mL/min at baseline. At month 48, a creatinine clearance of 54 mL/min was reported as mild renal impairment by the investigator.
- Patient 3-1559 (in the 2-year treatment group) had a baseline creatinine clearance value of 72 mL/min. At month 48, a creatinine clearance of 60 mL/min was reported as an adverse event.

Study 2301: The following table provides an updated summary of deaths, serious AEs, and other clinically important information from the ongoing osteoporosis treatment trial 2301.

Study 2301 - Number (%) of Subjects Who Died, Had Other Serious or Clinically Significant AEs or Discontinued Because of an AE		
	Treatment A n (%)	Treatment B n (%)
Total		
Serious or significant AEs	3031 (78.2)	2626 (67.9)
Death	55 (1.4)	44 (1.1)
SAEs	584 (15.1)	564 (14.6)
Discontinuation due to SAEs	86 (2.2)	65 (1.7)
Discontinuation due to non-serious AEs	31 (0.8)	20 (0.5)
Lab abnormalities leading to premature discontinuation	1 (<0.1)	2 (0.1)
AEs causing concomitant medication taken	2748 (70.9)	2505 (64.8)
AEs due to IV study drug administration	1277 (32.9)	251 (6.5)
Renal AEs leading to deterioration of renal function	57 (1.5)	44 (1.1)
Hypocalcemia (< 8.0 mg/dl)	7 (0.2)	0 (0.0)

Adverse events classified in this group are any occurrences of pyrexia, myalgia, arthralgia, bone pain, and influenza-like illness occurring within 3 days of study drug infusion

Study 2202: There have been no deaths in this study. There were 6 cases of hypocalcemia reported as serious AEs in the safety update; all subjects received zoledronic acid.

Comment: Compared to the data provided in the original NDA submission, the data provided in the 120-day safety update do not raise any new concerns. In study 2301, which provides the largest patient exposure to zoledronic acid, as expected, there remains a slight imbalance between treatment groups in the incidence of renal adverse events leading to deterioration of renal function. Regarding hypocalcemia, in the original submission there were 4 reports of hypocalcemia in treatment group A and none in treatment group B; the numbers are now 7 vs. 0.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Hypocalcemia and Hypophosphatemia: Paget's disease is characterized by excessive bone turnover, a process that requires an ample supply of calcium and phosphorus, since these are core components of mineralized bone. One of the known effects of bisphosphonate treatment in

patients with Paget's disease is a transient lowering of serum calcium and phosphorus concentrations. This is the result of decreased bone resorption coupled with a continued increase in bone formation (at least in the short-term).

The body responds to the mismatch between supply and demand of calcium and phosphorus in the following ways. Decreased levels of serum calcium increase the release of PTH, which in turn triggers 3 mechanisms: 1) increased synthesis of serum 1, 25 vitamin D which increases the absorption of calcium and phosphorus from the small intestine; 2) increased release of calcium and phosphorus from bone directly by PTH, and 3) increased reabsorption of calcium and increased excretion of phosphorus by the kidney.

In the two pivotal trials reviewed herein, 21% of subjects treated with zoledronic acid vs. 3.0% of patients treated with risedronate developed hypocalcemia by Day 10. Eighteen percent vs. 1.3% of zoledronic acid and risedronate-treated patients, respectively, developed hypophosphatemia by Day 10.

In the active-controlled trial used to support approval of risedronate for the treatment of Paget's disease, in which patients received 30 mg of risedronate daily for 2 months, transient decreases in serum calcium and phosphorus concentrations were noted, with nadirs occurring between days 30 to 60. It thus makes sense to examine the changes in serum calcium and phosphorus that occurred at the Day 63 time point in the zoledronic acid trials.

Of the subjects who had normal serum calcium levels at baseline, 2.4% of the zoledronic acid subjects and 4.8% of the risedronate subjects had low serum calcium levels at Day 63. Of the subjects who had normal serum phosphorus levels at baseline, 0.6% of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

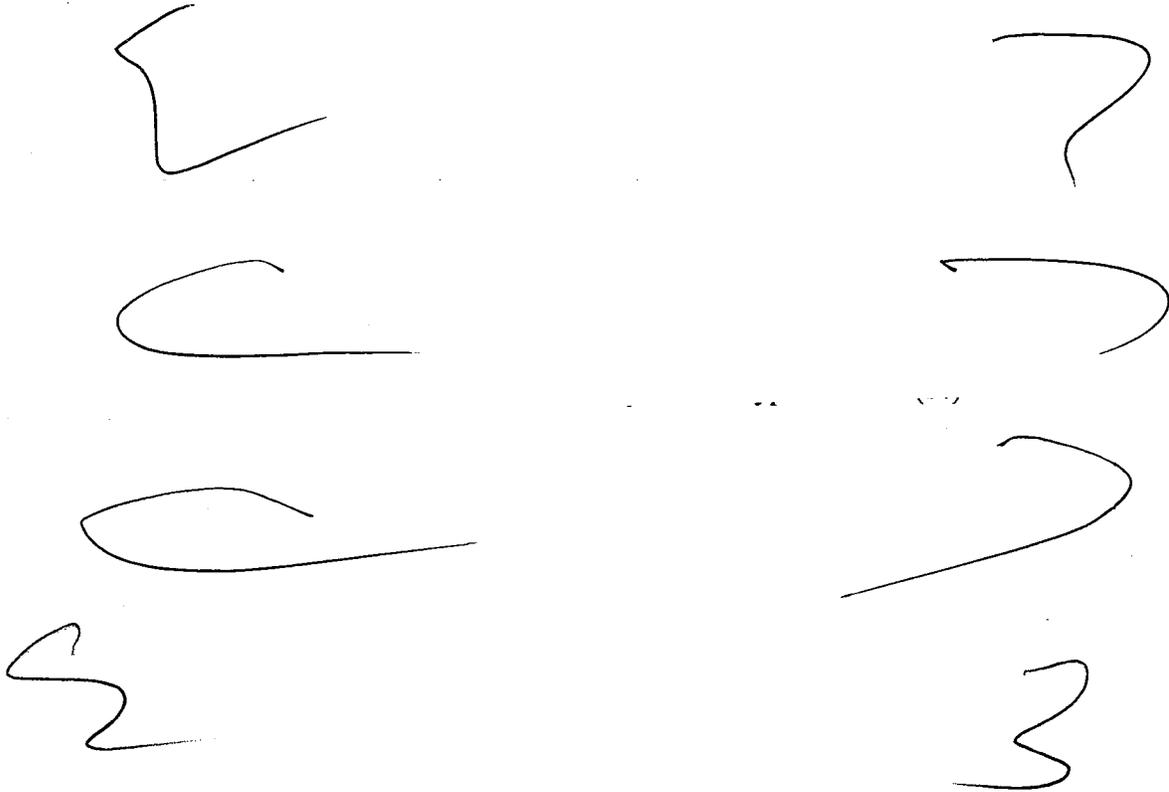
In the pivotal Paget's studies for alendronate, in which 40 mg was administered daily for 6 months, serum calcium and phosphorus were measured at Months 1, 3 and 6. The nadirs for these two minerals appeared to have occurred at Month 1. The mean reductions in serum calcium and phosphorus at Month 1 were -0.45 mg/dl and -0.47 mg/dl, respectively. In the zoledronic acid trials, the mean reductions in serum calcium and phosphorus at Day 10 were -0.8 mg/dl and -1.7 mg/dl, respectively. Further, approximately 19% of the alendronate-treated subjects developed serum calcium levels below 8.5 mg/dl, compared with approximately 32% of the zoledronic acid subjects. One (1.5%) of the alendronate patients developed a serum calcium level below 8.0 mg/dl vs. 12 (8%) of the zoledronic acid-treated participants.

Notwithstanding the difficulties of comparing data from different trials, taken together, the available evidence indicates that the risk for developing mild-to-severe hypocalcemia and hypophosphatemia is greater with zoledronic acid than with risedronate and probably alendronate. Moreover, since patients treated with zoledronic acid appear to develop hypocalcemia much more rapidly than those treated with oral bisphosphonates, this *may* put them at even greater risk for symptomatic hypocalcemia and hypophosphatemia.

Although none of the patients with low levels of serum calcium or phosphorus developed severe clinical sequelae such as seizure, cardiac arrhythmia, hemolysis, or rhabdomyolysis, a number of patients did develop markedly low calcium and phosphorus levels. It stands to reason, then, that if the drug were used in a broader range of Paget's patients, many of whom will have additional risk factors for hypocalcemia such as vitamin D deficiency and concomitant use of medications such as furosemide, an unacceptably high number of patients may suffer ill clinical consequences from a single 5 mg infusion of zoledronic acid. This brings to the fore the importance of characterizing the effects that supplemental calcium and vitamin D have on the occurrence of hypocalcemia and hypophosphatemia.

While it is reasonable to assume that the risk for developing low serum levels of calcium and phosphorus would be reduced by supplementing patients with calcium and vitamin D a few days prior to and a couple of weeks following dosing with zoledronic acid, this has yet to be empirically tested. Patients in the zoledronic acid trials were *instructed* to take 500 mg BID of supplemental calcium and 400 to 1000 IU per day of vitamin D during the studies, but the sponsor did not collect data to verify if, when, or how much of the supplements were actually taken.

In response to the Division's concern about the calcium and phosphorus data, Novartis proposed to handle the problem through labeling, as detailed below.

The image contains several large, handwritten scribbles and lines, likely representing a signature or initials. There are four distinct marks: a large 'L' shape on the left, a large '3' shape on the right, a large 'C' shape in the middle-left, and a large 'S' shape in the middle-right. These marks are scattered across the lower half of the page.

Given the increased risks for developing hypocalcemia and hypophosphatemia with zoledronic acid compared with risedronate and most likely alendronate – two approved and effective therapies for Paget's – I believe Novartis should provide empiric evidence that supplementation with calcium and vitamin D significantly reduces the risk for developing hypocalcemia and hypophosphatemia following treatment with zoledronic acid before the drug is approved.

Until Novartis provides such evidence, this Reviewer does not believe that the data in the NDA support a favorable balance of benefits to risks for the 5 mg dose of zoledronic acid when used to treat Paget's disease of bone.

Acute-Phase Reaction: A constellation of adverse events which resemble those that occur during an acute-phase reaction have been reported in patients when treated with bisphosphonates, primarily by injection. As described in section 7.1.8.4 of this review, the symptom complex includes but is not limited to influenza-like illness, pyrexia, rigors, myalgia, fatigue, arthralgia, lethargy, and headache. The majority of these symptoms occurred within 72 hours of receiving the zoledronic acid infusion. The occurrence of an acute-phase reaction following drug administration is not a serious safety concern, although it may increase the odds that the patient refuses a second dose. Novartis is currently conducting a study to examine the efficacy of pre-treatment with ibuprofen or Tylenol to reduce the incidence of the symptoms of the acute-phase reaction following intravenous administration of zoledronic acid.

Renal Injury: Increases in serum creatinine, which in some cases progressed to frank renal failure, have occurred in patients treated with zoledronic acid, principally in those with an underlying malignancy who received q 3-4 week dosing. The risk of renal injury (i.e., increased serum creatinine) appears to be most strongly related to the dose and rate of infusion of zoledronic acid and to baseline renal function, with decreased creatinine clearance conferring greater risk. The currently approved zoledronic acid labeling includes precautionary language regarding renal toxicity and also includes recommendations to enhance renal safety, such as reducing the dose for patients with impaired baseline renal function. There was no evidence of an increased risk for renal injury following a single 5 mg dose of zoledronic acid in the patients with Paget's trials reviewed herein, albeit the sample size is relatively small.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

For the Paget's disease indication, pooling of data from the two pivotal studies, 2304 and 2305, provide the most accurate estimate of zoledronic acid's efficacy and safety relative to treatment with risedronate. Partially-blinded safety data from the ongoing osteoporosis treatment trial, 2301, provide useful information due to the size of the database. As of the date of filing of this NDA, over 7000 postmenopausal women had received one infusion of 5 mg zoledronic acid or

placebo, and approximately half of these subjects have also received a second, annual dose of drug or placebo.

7.4.1.2 Combining data

In the following section, results of exploratory analyses of pooled data from the Paget's studies 2304 and 2305 are provided.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable, as a single dose was used in the pivotal Paget's trials.

7.4.2.2 Explorations for time dependency for adverse findings

In an analysis of adverse events that occurred within 3 days of drug administration, the following events, many of which could be considered part of an acute phase reaction, were reported by a greater percentage of patients in the zoledronic acid vs. the risedronate group: Influenza-like illness, myalgia, pyrexia, fatigue, headache, rigors, bone pain, arthralgia, nausea, back pain, and dizziness.

In an analysis of adverse events that occurred after 3 days of drug administration, the following events were reported more frequently by the risedronate vs. the zoledronic acid groups: influenza-like illness, headache, nausea, arthralgia, and back pain.

7.4.2.3 Explorations for drug-demographic interactions

When analyzed by age above and below 72 years, hypocalcemia was reported in 6 (6.5%) of the zoledronic acid and none of the risedronate subjects at or above 72 years of age. In the subjects less than 72 years, 1 (1.2%) risedronate subject and none of the zoledronic acid subjects developed hypocalcemia. Other adverse events occurred with a different frequency between zoledronic acid vs. risedronate treated groups in those subjects > 72 vs. < 72 years, however it is difficult to determine if these differences are clinically significant.

When analyzed by gender, there were a number of adverse events that occurred with a different frequency between zoledronic acid vs. risedronate treated groups in males vs. females, and vice versa. It is difficult to determine if these differences between genders are clinically meaningful, however.

Analyses by race are not feasible given that the majority of patients in the trials were Caucasian.