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*APPLICATION NUMBER:*

**22-080**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	22-080; N-000BL; N-000-BS; N-000 -BM
<b>Submission Dates</b>	October 16, 2006; June 20, 2007; June 27, 2007; July 3, 2007
<b>Brand Name</b>	RECLAST®
<b>Generic Name</b>	Zoledronic acid
<b>Reviewer</b>	S.W. Johnny Lau, R.Ph., Ph.D.
<b>Team Leader (Acting)</b>	Sally Y. Choe, Ph.D.
<b>Pharmacometric Reviewers</b>	Christine Garnett, Pharm.D.; Joo-Yeon Lee, Ph.D.
<b>Pharmacometric Team Leader</b>	Jogaroo Gobburu, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology 2 (HFD-870)
<b>ORM Division</b>	Metabolism and Endocrinology Products (HFD-510)
<b>Sponsor</b>	Novartis Pharmaceutical Corporation
<b>Formulation; Strength</b>	IV solution; 5 mg/100 mL
<b>Relevant IND</b>	43,240
<b>Indication</b>	To treat postmenopausal osteoporosis in women

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### 1 Executive Summary

The sponsor seeks approval for the 5 mg zoledronic acid (RECLAST®) to be infused no less than 15 minutes once yearly to treat postmenopausal osteoporosis (PMO) in women via NDA 22-080. Zoledronic acid (5 mg infused no less than 15 minutes; RECLAST®) is approved to treat Paget's disease of the bone (NDA 21-817). Zoledronic acid (4 mg infused no less than 15 minutes; ZOMETA®) is approved to treat hypercalcemia of malignancy (NDA 21-223) and is also approved to

treat multiple myeloma and bone metastases of solid tumors (NDA 21-386). Zoledronic acid is a 3<sup>rd</sup> generation bisphosphonate that inhibits osteoclast activity and reduce bone turnover.

For NDA 22-080, the sponsor did not conduct new in vivo clinical pharmacology study but conducted a pivotal Phase 3 clinical efficacy and safety study in PMO women. This review focuses on zoledronic acid's in vitro plasma protein binding data and the pivotal clinical study's renal safety data. Zoledronic acid use has been associated with renal failure in cancer patients and dose adjustment per baseline renal function is recommended for the treatment of multiple myeloma and bone metastases of solid tumors (see ZOMETA<sup>®</sup> label). Due to the potential that zoledronic acid may cause renal impairment in the PMO patients, the Pharmacometrics group was consulted to analyze the pivotal Phase 3 clinical study's renal safety data. Based on the pivotal Phase 3 study in PMO patients, there was no trend for more patients to experience renal deterioration with once yearly repeated dosing of zoledronic acid as compared to placebo dosed patients.

### **1.1 Recommendations**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) reviewed NDA 22-080's Clinical Pharmacology and Biopharmaceutics information and finds it acceptable with the following recommendations:

- No zoledronic acid dose adjustment based on the baseline renal function is necessary to treat postmenopausal osteoporosis in women.
- The sponsor should agree to the recommended labeling changes.

### **1.2 Phase IV Commitments**

None.

### **1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings**

#### **Pharmacokinetics**

In vitro mean zoledronic acid protein binding in human plasma ranged from 27.7% at 200 ng/mL to 52.8% at 50 ng/mL.

#### **Dose Selection**

Since the sponsor studied only 1 dose (5 mg zoledronic acid/year vs. placebo) in the pivotal Phase 3 study, the efficacy and safety of lower doses such as 1, 2 or 4 mg zoledronic acid/year have not been evaluated for the treatment of PMO in women.

#### **Safety**

Generally in Study ZOL446H2301, 1.8% of PMO patients receiving zoledronic acid experienced renal deterioration within 9 – 11 days postdose as compare to 0.8% of PMO patients receiving placebo. Renal deterioration was transient and serum creatinine concentrations return to predose baseline values. There is no trend for more PMO patients to experience deterioration with once yearly repeated dosing of zoledronic acid.

#### **Biopharmaceutics**

The to-be-marketed IV 5 mg zoledronic acid solution contains 4950 mg mannitol \_\_\_\_\_ whereas the clinically-tested IV 5 mg zoledronic acid solution contains 37.5 mg NaCl and 4750 mg glucose \_\_\_\_\_. It is very unlikely that mannitol in the to-be-marketed formulation would affect the exposure of zoledronic acid.

S.W. Johnny Lau, R.Ph., Ph.D.  
OCP/DCP2

FT signed by Sally Choe, Ph.D., Acting Team Leader \_\_\_\_\_ 7/ /07

An Optional Intra-Division Level Clinical Pharmacology Briefing for NDA 22-080 was conducted on July 27, 2007; participants included J. Wyeth, D. Fishbain, A. Noory, T. Ong, J. Gobburu, R. Ramchandani, B. Booth, M. Khurana, W. Lubas, C. Garnett, J-y. Lee, E. Fadiran, V. Bhattaram, C. Sahajwalla, S. Dóddapaneni, S. Choe, and J. Lau.

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## 2 Question-Based Review

### 2.1 General Attributes

#### 2.1.1 What is the formulation for the to-be-marketed IV 5 mg zoledronic acid solution?

Table 1. Composition of the to-be-marketed (commercial) IV mg/100 mL solution.

Ingredients	Theoretical amount <sup>1</sup>	Function	Reference Standards
zoledronic acid monohydrate	5.330 <sup>2</sup>	Drug substance	_____
Mannitol	4950.0	_____	USP
Sodium citrate	30.0	_____	USP
Water for injection	_____	_____	USP

<sup>1</sup> the \_\_\_\_\_ overall, which allows the withdrawal of the labeled amount of zoledronic acid from the vial, is not included.

<sup>2</sup> corresponds to 5.0 mg zoledronic acid anhydrous

#### 2.1.2 What is NDA 22-080's proposed indications and dosage regimen?

To treat postmenopausal osteoporosis (PMO) in women. Patients should be intravenously infused 5 mg zoledronic acid for no less than 15 minutes once yearly.

### 2.2 General Clinical Pharmacology

Zoledronic acid clinical pharmacology information is available in:

- Skerjanec et al. The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 43:154-62 (2003)
- Chen et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 42:1228-36 (2002)
- Chang et al. Renal failure with the use of zoledronic acid. *N Engl J Med* 349:1676-9 (2003)
- Markowitz et al. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Intl* 64:281-9 (2003)

NDA 21-817, 21-223, and 21-386's Clinical Pharmacology reviews also contain zoledronic acid clinical pharmacology information

#### 2.2.1 What are the zoledronic acid clinical pharmacokinetic (PK) characteristics?

Zoledronic acid clinical PK information for the 5 mg IV infusion over 15 minutes was reviewed by Dr. Sandra Suarez-Sharp for NDA 21-817 (treatment of Paget's disease indication). NDA 22-080 does not contain any new in vivo clinical pharmacology information. This review focuses on the new in vitro zoledronic acid human plasma protein binding data.

Study PCS(EU) R0400374 examined the in vitro 50, 500, and 5000 ng/mL <sup>14</sup>C-zoledronic acid human plasma protein binding (n = 5).

Table 2. In vitro <sup>14</sup>C-zoledronic acid human plasma protein binding results for Study PCS(EU) R0400374.

Nominal concentration [ng/mL]	Human pool		Bound fraction [%]	Unbound fraction	
	Actual concentration			Mean	± SD
	Plasma [ng/mL]	Ultrafiltrate [ng/mL]			
5000	4752	3540	25.5	74.5	± 0.5
500	476	271	42.9	57.1	± 5.9
50	48	23	52.8	47.2	± 2.2

Study DMPK R0500513 examined the in vitro 2, 20, 200, and 2000 ng/mL <sup>14</sup>C-zoledronic acid human plasma protein binding (n = 3).

Table 3. In vitro <sup>14</sup>C-zoledronic acid human plasma protein binding results for Study DMPK R0500513.

Nominal concentration [ng/mL]	Human, plasma pool		Bound fraction [%]	Unbound fraction	
	Actual concentration			Mean	± SD
	Plasma [ng/mL]	Ultrafiltrate [ng/mL]			
2000	1972	1548	21.5	78.5	± 0.5
200	194	140	27.7	72.3	± 0.4
20	19.0	12.7	33.2	66.8	± 1.3
2	2.1	1.18	44.1	55.9	± 1.5

Study DMPK R0500513's zoledronic acid protein binding results are lower than those for Study PCS(EU) R0400374. The conduct of Study DMPK R0500513 was almost identical to that of Study PCS(EU) R0400374. The sponsor is unclear about this inter-study variability.

Hence, this reviewer recommends the label to contain both studies' results as "In vitro mean zoledronic acid protein binding in human plasma ranged from \_\_\_\_\_ at 50 ng/mL."

### 2.2.2 How is the proposed yearly zoledronic acid dose determined?

The sponsor conducted a randomized Phase 2 dose-finding study (CZOL4460041) in 351 postmenopausal women with osteopenia or osteoporosis [lumbar spine bone mineral density (BMD) T-score = -2] with 5 IV zoledronic acid treatment groups versus placebo over 1 year. Table 4 below details the lumbar spine (L1-L4) BMD % change from baseline.

	ZOL446 4x0.25 mg	ZOL446 4x0.5 mg	ZOL446 4x1 mg	ZOL446 2x2 mg	ZOL446 1x4 mg	Placebo
<b>% Change Month 6</b>						
N	50	48	48	53	54	56
Mean (%)	4.4	4.0	3.5	3.9	4.5	0.7
SD	2.7	3.1	3.2	3.6	3.0	2.8
<b>% Change Month 12</b>						
N	49	48	49	53	52	54
Mean (%)	5.7	5.4	4.8	4.9	5.0	0.4
SD	2.8	3.2	2.6	3.3	3.3	3.3

All dosing regimens showed similar and statistically indistinguishable increases in BMD over 1 year. The 1 mg dose administered every 3 months (4 x 1 mg group) resulted in slightly smaller numerical gains in BMD than the other regimens (not statistically significant). No particular dose regimen was shown to be the most effective.

Reductions in bone turnover markers (serum CTx and urine NTx) were also similar for all dosing regimens. However, higher total doses were associated with a longer duration of effect on bone markers. The sponsor's goal is to develop a treatment that lasts for 1 year to overcome the burdensome dosing and compliance issues associated with current oral bisphosphonates.

Bauer et al [*J Bone Miner Res* 19:1250-1258 (2004)] showed that reduction in bone-specific alkaline phosphatase (BSAP) by at least 30% over the 1<sup>st</sup> year of alendronate therapy is associated with a statistically significantly lower risk of both non-spine and hip fractures. In Study CZOL4460041, for the once yearly 4 mg dose of zoledronic acid, 16/45 (35.6%) of the patients did not achieve the 30% reduction in BSAP threshold (slight difference in N; 52 for lumbar spine BMD as in Table 4 and 45 for SBAP).

Surrogate markers such as BMD are not sufficiently robust to predict fracture outcome. Hence, fracture outcome studies are required with bisphosphonates for registration. At the time of the dose selection for the Phase 3 study, IV ibandronate dosage form did not show anti-fracture efficacy despite notable increases in BMD, which may be in part due to inadequate suppression of biochemical markers of bone turnover over the entire dosing interval [Stakkestad et al. *Ann Rheum Dis* 62:969-975 (2003)].

Garnero et al [*J Bone Miner Res* 15:1526-1536 (2000)] showed bone turnover is an independent predictor of fracture risk. Consistent and sustained suppression of biochemical markers of bone turnover over the entire dosing interval is an important goal for management of osteoporosis. Hence, the sponsor chose 5 mg zoledronic acid as the annual dose to treat PMO in the Phase 3 study to ensure that adequate suppression of bone markers was maintained during the entire dosing interval.

### 2.2.3 What is zoledronic acid's efficacy to treat PMO in women?

See Dr. William Lubas' medical efficacy review for zoledronic acid. Study ZOL446H2301 is the pivotal study to support NDA 22-080. Table 5 below details the study design:

Study No.	Study objective/ Population	No. of patients <sup>1</sup>	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
2301	Phase III, double-blind, randomized, placebo-controlled efficacy/safety study in postmenopausal women with osteoporosis	7765	36 months	3 x 5 mg Zol/12 months (15-minute IV infusions)  Placebo	(a) Proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I patients <sup>2</sup>  (b) Time to first hip fracture in Strata I and II patients

<sup>1</sup> Randomized

<sup>2</sup> Stratum I: patients taking calcium and vitamin D only and no additional concomitant osteoporosis medications. Stratum II: patients taking calcium and vitamin D and additional concomitant osteoporosis medications (but not bisphosphonates).

Key: IV = intravenous, Zol = zoledronic acid (ZOL446)

New morphometric vertebral fractures, the 1<sup>st</sup> part of the coprimary endpoint, occurred in 87/2260 = 3.8% of zoledronic acid-treated patients compared to 300/2352 = 12.8% of placebo-treated patients over 36 months (mITT, Stratum I data). This corresponds to a statistically significant absolute risk reduction of 8.9% and a relative risk reduction of 70% (95% CI: 62% to 76%, p < 0.0001). The 3-year event rates of hip fractures based on Kaplan-Meier estimates, the 2<sup>nd</sup> part of the coprimary endpoint, were 1.45% (n = 52) for the zoledronic acid-treated patients and 2.50% (n = 87) of placebo-

treated patients over 36 months (ITT, combined Strata I and II data). The hazard ratio of 0.60 (95% CI: 0.43 to 0.85) for the zoledronic acid group versus the placebo group represents a 40% reduction in the risk of hip fractures ( $p = 0.0032$ ).

## 2.2.4 What are zoledronic acid's major safety issues to treat PMO in women?

### Renal Safety

Renal impairment has been observed upon the administration of zoledronic acid in patients with pre-existing renal compromise or additional risk factors (oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration), majority of whom received a 4 mg dose every 3 - 4 weeks, it has been observed in patients even after a single administration [Chang et al. *N Engl J Med* 349:1676-9 (2003)].

Dr. Christine Garnett performed the pharmacometric review for Study ZOL446H2301's renal safety data and determined the necessity of dose adjustment per renal function in PMO patients (see this review's Appendix 4.3 for details).

Overall, small numbers (42 or 1.8%) of patients experienced renal deterioration within 9 to 11 days of 5 mg zoledronic acid infusion compared to that of placebo (19 or 0.8%). Table 6 below shows the % of patients with renal deterioration by baseline renal function.

Table 6. Increase from Baseline in SCr within 9 to 11 days Post-Infusion

	Baseline CL <sub>Cr</sub> , ml/min	Zoledronic Acid n/N (%)	Placebo n/N (%)
Overall Increase in Scr >0.5 mg/dL from baseline	30- <40	7/131 (5.3%)	4/160 (2.5%)
	≥40 - ≤50	7/372 (1.9%)	4/358 (1.1%)
	50 - < 60	7/550 (1.3%)	2/513 (0.4%)
	≥ 60	21/1267 (1.7%)	19/2338 (0.8%)
	All Patients	42/2320 (1.8%)	19/2338 (0.8%)

Renal deterioration was transient, in spite of some acute deterioration. By the end of the 1<sup>st</sup> year, SCr concentrations were within 0.5 mg/dL of baseline values prior to subsequent dosing.

Based on the data from 2320 PMO patients, there was no trend for more patients to experience renal deterioration with once yearly repeated dosing of zoledronic acid as compared to placebo dosed patients.

Potential reasons for the lower incidence of renal deterioration in PMO patients compared to those of cancer patients are: 1) less frequent dosing of zoledronic acid and 2) less frequent monitoring for SCr changes in the clinical study.

From the approved labeling, the pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance = 50-80 mL/min, N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance = 30-50 mL/min, N=11) showed an average increase in plasma AUC of 43%.

Dose adjustment is recommended for multiple myeloma and bone metastases patients with renal impairment. However in PMO patients, Clinical Pharmacology does not recommend any dose adjustment for renal impairment with the following reasons:

- Zoledronic acid is not recommended in women with severe renal impairment
- Overall, small numbers of patients experienced renal deterioration within 9 – 11 days of 5 mg zoledronic acid infusion compared to placebo.
- Renal deterioration is transient.
- No trend exists for more patients to experience renal deterioration.

### **Atrial Fibrillation**

See Dr. William Lubas' medical safety review for zoledronic acid, especially the serious atrial fibrillation issue with bisphosphonate use Black et al. *NEJM* 356:1809-1822 (2007) and Cummings et al. *NEJM* 356:1895-1896 (2007). Briefly, serious atrial fibrillation occurred more frequently in the zoledronic acid group than the placebo group (50 vs. 20 patients,  $p < 0.001$ ) for the PMO women. These events may not be zoledronic acid exposure related since majority of these events happened more than 30 days after drug infusion.

See Dr. Jo Wyeth's (Office of Surveillance and Epidemiology) review on the spontaneous reports analysis that the effects of zoledronic acid on the risk of atrial fibrillation is inconclusive.

### **2.2.5 What would be the recommended optimal IV zoledronic acid dose to treat PMO in women?**

Since the sponsor studied only 1 yearly dose (IV 5 mg zoledronic acid vs. placebo) on the anti-fracture efficacy of zoledronic acid in the pivotal Phase 3 study, there is no anti-fracture efficacy data for the lower doses. The IV 1, 2 or 4 mg zoledronic acid administered yearly may still be efficacious and safe for the treatment of PMO in women.

## **2.3 General Biopharmaceutics**

### **2.3.1 Does difference exist between the to-be-marketed formulation and the clinically-tested formulation?**

Yes. The to-be-marketed formulation contains 4950 mg mannitol \_\_\_\_\_ (see Question 2.1.1). Some of Study ZOL446H2301's patients also received the to-be-marketed formulation. The original clinically-tested formulation for Study ZOL446H2301 only differs from the to-be-marketed formulation of 37.5 mg NaCl and 4750 mg glucose \_\_\_\_\_. Since these formulations were intravenously administered, there is no bioavailability issue between them. Mannitol is an osmotic diuretic (50 - 200 g per day intravenously administered over 3 – 5 minutes as 20% hypertonic solution [Goodman & Gilman The Pharmacological basis of Therapeutics, 7<sup>th</sup> ed]). However, the less than 5 g mannitol in the zoledronic acid solution is \_\_\_\_\_ and is infused over 15 minutes. It is very unlikely that mannitol in the to-be-marketed formulation would cause osmotic diuresis and affect the elimination of zoledronic acid. The formulation change seems acceptable. See NDA 21-817's Clinical Pharmacology review for this issue.

## **2.4 Bioanalytical**

### **2.4.1 Is the bioanalytical method properly validated for zoledronic acid measurement?**

NDA 22-080 does not contain any new in vivo clinical pharmacology or biopharmaceutics information. No bioanalytical analysis was performed for NDA 22-080.

## **3 Labeling Comments**

Strikethrough text means recommended deletion. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

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       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

## 1 Study design

<i>Objectives</i>	The objective of this study was to assess the <i>in vitro</i> plasma protein binding of [ <sup>14</sup> C]ZOL446 in human plasma over a range of concentrations. Since previous studies indicated an impact of the calcium or iron concentration on protein binding of [ <sup>14</sup> C]ZOL446, the plasma concentrations of the two metals as well as the concentration of magnesium were determined. In addition the protein binding was determined in plasma supplemented with calcium chloride or the chelator EDTA.
<i>Test compound</i>	[ <sup>14</sup> C]ZOL446
<i>Concentrations</i>	50, 500 and 5000 ng/mL [ <sup>14</sup> C]ZOL446
<i>Test system</i>	Species: human Sex: male Material: defrosted plasma containing heparin. One pool (n = 3) and five individual plasma samples. The pooled plasma was supplemented with 0, 0.5 or 2 mM calcium chloride and 1 or 3 mM EDTA.
<i>Methods</i>	<i>In vitro</i> plasma protein binding: Incubation at 37°C for 30 min after spiking, separation of the unbound fraction by ultrafiltration. Detection technique: Liquid scintillation counting (LSC).

## 2 Key findings

- [<sup>14</sup>C]ZOL446 (50 – 5000 ng/mL) was weakly bound to proteins in human plasma with a clear concentration dependency of the binding. The variation between individuals was small. All determined unbound fractions were in the range of 40 – 47% at 50 ng/mL, 49 – 60% at 500 ng/mL and 72 – 80% at 5000 ng/mL, the corresponding means were 45, 57 and 75%, respectively.
- Addition of calcium chloride (0.5 and 2 mM) to the plasma led to a small increase in protein binding. However, only after addition of 2 mM calcium chloride the unbound fractions at 50 and 5000 ng/mL [<sup>14</sup>C]ZOL446 were below the ranges found in not-calcium-supplemented plasma. At 0.5 mM calcium chloride the unbound fractions were 40, 58 and 74%, at 2 mM calcium chloride they were 35, 53, and 64%, for 50, 500 and 5000 ng/mL [<sup>14</sup>C]ZOL446, respectively.
- Addition of the chelator EDTA (1 and 3 mM) to the plasma lead to a clear decrease in protein binding at the lower [<sup>14</sup>C]ZOL446 concentrations. At 1 mM EDTA the unbound fractions were 63, 68 and 79%, at 3 mM EDTA they were 74, 76, and 78%, for 50, 500 and 5000 ng/mL [<sup>14</sup>C]ZOL446, respectively.

- Measured calcium, magnesium and iron concentrations in the used plasma samples were in the ranges of 1.9 – 2.2 mM, 0.76 – 0.94 mM and 11.6 – 18.8  $\mu$ M, respectively, being all close to normally found plasma concentrations for these three metals. Over these small ranges of concentrations no correlation to protein binding was evident.

### Conclusion

Plasma protein binding of [ $^{14}$ C]ZOL446 in human was weak and concentration dependent as reported earlier [DMPK(CH) R01-899]. An increase of protein binding by addition of calcium and a decrease by addition of chelators, which has been earlier observed in animal plasma [DMPK(CH) R01-899], was confirmed for human plasma. However, the data indicate that in human plasma only major changes in the calcium concentration result in changes in plasma protein binding.

Reviewer's comment: This study is acceptable.

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## 1 Summary

### Study design

<i>Test compounds</i>	[ <sup>14</sup> C]ZOL446 and [ <sup>14</sup> C]ibandronate
<i>Concentrations</i>	2, 20, 200 and 2000 ng/mL
<i>Test system</i>	Species: rat (Hanover Wistar), dog (beagle) and human. Sex: male Material: defrosted plasma containing heparin; plasma pools with n = 3; for human in addition three individual plasma samples; the pooled human plasma was supplemented with 0, 2 and 4 mM calcium chloride and 2 and 4 mM EDTA, the pooled animal plasma with 0 and 2 mM calcium chloride and 2 mM EDTA.

### Methods

#### In vitro plasma protein binding:

Incubation at 37°C for 30 min after spiking, unbound fraction ( $f_u$ ) investigation by ultrafiltration.

Detection technique: Liquid scintillation counting (LSC).

### Key results

The unbound fractions of both compounds increased with the plasma concentration in dog and human plasma. This concentration dependency was not clearly evident for rat plasma. For both compounds the same species ranking was observed: plasma protein binding was highest for rat, medium for dog and lowest for human. In all species plasma protein binding was increased in plasma supplemented with calcium chloride and decreased in plasma supplemented with the chelator EDTA.

In rat plasma protein binding of [<sup>14</sup>C]ZOL446 was clearly higher as compared to protein binding of [<sup>14</sup>C]ibandronate. Also in dog plasma protein binding of [<sup>14</sup>C]ZOL446 was higher as compared to protein binding of [<sup>14</sup>C]ibandronate, however, the difference was less pronounced as compared to rat. For both compounds the lowest degree of plasma protein binding was observed in human plasma. The variability between plasma samples from different human individuals was low. Protein binding of [<sup>14</sup>C]ZOL446 was marginally higher as compared to protein binding of [<sup>14</sup>C]ibandronate.

Species	Concentration range [ng/mL]	Unbound fraction [ <sup>14</sup> C]ZOL446 [%]	Unbound fraction [ <sup>14</sup> C]ibandronate [%]
rat	2 – 2000	12 – 20	24 – 49
dog	2 – 2000	51 (2 ng/mL) – 64 (2000 ng/mL)	59 (2 ng/mL) – 75 (2000 ng/mL)
human	2 – 2000	56 – 61 (2 ng/mL) and 76 – 79 (2000 ng/mL)	60 – 66 (2 ng/mL) and 78 – 82 (2000 ng/mL)

**Conclusions**

The reported data indicate that when measured side by side under identical experimental conditions the protein binding of ibandronate in human plasma is similar or slightly lower as compared to binding of ZOL446. In rat and dog plasma the protein binding of ibandronate is lower as compared to ZOL446. The reported data allow for a comparison of exposure to unbound ZOL446 and ibandronate across the covered species, e.g. in the context of safety assessments.

Reviewer's comment: This study is acceptable.

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## Study report synopsis

**Name of finished product:** Reclast®/Aclasta® **Name of active ingredient:** zoledronic acid

**Title of study:** A multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D

**Investigators:** \_\_\_\_\_

**Study center(s):** A total of 240 centers in 27 countries are participating in the CZOL446H2301 trial.

**Publication(s):** None

**Study period:** First patient enrolled: 22-Jan-2002 Last patient completed: 01-Jun-2006 however data cut for this report was 31-Mar-2006

**Development phase:** III

**Objectives:** The primary efficacy objectives were to assess:

- The proportion of patients with at least one new vertebral fracture over 3 years in Stratum I (mITT)
- The time to first hip fracture in all patients (Stratum I+II).

Key secondary efficacy objectives were to assess:

- The proportion of patients in Stratum I with at least (a) one new vertebral fracture, and (b) one new and/or worsening vertebral fracture overall and by severity
- The reduction in new vertebral fractures over 36 months in patients without baseline vertebral fractures, with one baseline vertebral fracture, with at least two baseline vertebral fractures, and in those patients who are 75 years of age or older
- The time to first clinical fracture, clinical vertebral fracture, and non-vertebral clinical fracture
- The percent change in BMD over 36 months relative to baseline for the total hip, femoral neck, and lumbar spine
- The relative change in the biochemical markers of bone formation over 36 months (P1NP and BSAP)
- The relative change in the biochemical marker of bone resorption (b-CTx) over 36 months
- The change in stadiometer height over 36 months relative to baseline
- The number of days of disability during the study due to a fracture or back pain that cause limited activities and bed rest

Safety objectives were to evaluate:

- the overall AE profile
- changes in laboratory parameters from baseline
- changes in vital signs from baseline
- changes in renal function 9-11 days following each study drug infusion and over the course of the entire study
- changes in ECG parameters after the third study drug infusion
- bone quality through histomorphometry measurements taken from bone biopsies at 36 months

The original protocol was dated 22-Oct-2001. There were 6 amendments to the protocol: Amendment 1 (25-Mar-2002), Amendment 2 (26-Nov-2002), Amendment 3 (25-Nov-2003),

Amendment 4 (18-Dec-2003), Amendment 5 (17-Jun-2005), and Amendment 6 (28-Feb-2006). Complete details are provided in Appendix 1.1.

Since the study is ongoing, this report is based on an analysis of all data with a cut-off date of 31-Mar-2006.

**Methodology:** This is an international, multi-center, randomized, double-blind, placebo-controlled trial in postmenopausal women with osteoporosis. Participants were classified and placed into one of two strata for treatment based on their "usual care" concomitant osteoporosis medication use at or prior to randomization. "Usual care" was comprised of various medications that included hormone replacement therapy, selective estrogen receptor modulators (raloxifene), calcitonin, tibolone, tamoxifen, dehydroepiandrosterone(s), ipriflavone, or medroxyprogesterone. Those in Stratum I received calcium and vitamin D only in addition to their assigned study drug, but no additional concomitant osteoporosis medications were allowed. The "usual care" for women in Stratum II involved taking calcium and vitamin D, plus any one of the additional osteoporosis medications listed above.

**Number of patients:**

**Planned:** Approximately 7400 patients were to be enrolled in this study. Participants were placed into one of two strata for treatment based on their "usual care" concomitant osteoporosis medication use at or prior to randomization. A minimum of 3114 patients were to be enrolled into Stratum I and a maximum of 4286 patients were to be enrolled into Stratum II. Within each stratum, patients were randomized to receive either zoledronic acid or placebo.

**Actual:** Enrollment was complete at the time of the data cut-off for this interim analysis (31-Mar-2006). A total of 7736 patients are included in the intent-to-treat population: 6084 (78.65%) from Stratum I and 1652 (21.35%) from Stratum II. Patients were randomized to zoledronic acid (3875 patients) or placebo (3861 patients). Of those randomized, 5115 (66.12%) patients have completed the study, 1135 (14.67%) patients were discontinued, and 1486 (19.21%) patients were still ongoing.

**Indication and main criteria for inclusion:** Postmenopausal women aged 65 through 89 years of age (at randomization) with osteoporosis documented by either (1) radiological evidence of at least two mild or one moderate existing vertebral fracture(s) and a femoral neck BMD T-score  $\leq -1.5$ , or (2) a femoral neck BMD T-score  $\leq -2.5$  with or without evidence of an existing vertebral fracture(s). Patients were required to have washed out of their prior bisphosphonate therapy in both strata and all osteoporosis medications in Stratum I prior to being eligible for study entry.

**Investigational and reference therapy:** The investigational therapy was supplied as a solution (5 mg zoledronic acid in 5 mL of sterile water for infusion) and the matching placebo was supplied as a placebo solution (5 mL of sterile water for infusion) both were further diluted with 100 mL of normal saline. In addition, a new dosage form consisting of a 5 mg/100 mL zoledronic acid or placebo in a ready-to-infuse plastic bottle was made available. Zoledronic acid or matching placebo was given as a single, slow, 15-minute intravenous infusion. Batch and formulation numbers are provided below.

Formulation	Formulation number	Batch number
Zoledronic acid 5 mg / 5 mL sterile water (vial)	3761400.00.001	Y 0200201, Y 1061101, Y 0630702
Matching placebo (5 mL sterile water) (vial)	3758000.00.002	Y 0190201, Y 1001101
	3758000.00.004	Y 0350702
Zoledronic acid 5 mg/100 mL normal saline (ready-to-infuse bottle)	3769387.001	Y 0210103
Matching placebo (100 mL normal saline) (ready-to-infuse bottle)	7004299.001	Y 0360203

**Duration of treatment:** Patients received a single 15-minute intravenous administration of zoledronic acid 5 mg or placebo once per year at 0 (Day 0), 12, and 24 months and were then monitored over a 3-year period.

**Criteria for evaluation:**

**Efficacy:** Efficacy assessments consisted of the following evaluations:

- Morphometric vertebral fractures – all incident vertebral fractures were primarily based on morphometric and defined by at least a 20% decrease in any vertebral height (at least 4 mm) with a back-up confirmation by semi-quantitative reading.
- Clinical fractures – all the clinical fractures were adjudicated by the endpoint committee, primarily based on an initial report from the investigator and required confirmation either from an x-ray report or report of a surgical procedure.
- Bone mineral density (BMD) – BMD was measured by dual x-ray absorptiometry (DXA).
- Bone marker measurements (CTx, BSAP, P1NP) – Serum samples were collected and analyzed at a central laboratory in batch mode for a given patient. Fasting was required for CTx tests.
- Height measurements – Height was measured using a stadiometer.
- Disability measurements – The number of days with limited activities or bed-rest after a fracture or after a back pain was captured through a series of questionnaires in the case report form (CRF).

**Safety:** Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry, and urine values, regular measurement of vital signs, and the performance of physical examinations. Special safety evaluations include the assessment of renal abnormalities at pre- and post-annual dose administration, electrocardiogram pre- and post- the third dose of study drug, and bone biopsies after 3 years of study treatment.

**Pharmacology:** No pharmacokinetic evaluations were done.

**Statistical methods:**

**Sample size and power considerations**

With approximately 3700 patients per treatment group, a two-sided log-rank test for equality of survival curves had approximately 90% power at a significance level of 5% to detect a 50% reduction in the incidence of hip fractures. This assumed a placebo fracture rate of 1.8% over 3 years under an exponential model and an annual exponential drop out rate of 0.054.

A 2-group continuity corrected chi-square test with a 5%, 2-sided significance level had approximately 90% power to detect a 50% reduction in the proportion of patients with a new morphometric vertebral fracture over 3 years with 1126 patients per treatment group. This assumed a placebo fracture rate of 1.9% per year.

A 2-group continuity corrected chi-square test with a 5%, 2-sided significance level had approximately an 80% power to detect a difference in the proportion of patients with a new and/or worsening vertebral fracture at 1 year when the sample size in each group is 1479 patients. This assumes an incidence of new and/or worsening vertebral fracture of 2.25% over the first year of the study in the placebo group and a 60% reduction in the zoledronic acid group.

**Efficacy**

Mean, median, standard deviation, minimum and maximum values are presented for continuous variables by treatment group and overall, as appropriate. The number and percentage of patients in each category are presented for categorical variables by treatment group and overall.

**Primary efficacy variables**

The analyses of primary efficacy variables were performed on the ITT (time to first hip fracture), mITT (proportion of new morphometric vertebral fractures), and per-protocol populations for the primary endpoints, respectively. A closed testing procedure was performed to maintain the overall significance level at 5%. The proportion of patients with new morphometric vertebral fractures at Month 36 from Stratum I was to be analyzed first at a 4.96% level of significance. If a statistically significant result was obtained, a confirmatory analysis of time to first hip fracture was to be performed at the 4.06% level. The significance levels were adjusted to these values to account for a previously conducted interim efficacy analysis using data up to a cut-off date of 06 August 2006.

Between-treatment differences to the time to first hip fracture were evaluated using a log-rank test stratified by stratum to compare the survival functions between the two treatment groups. The hazard ratio for time to first hip fracture and its corresponding 95% confidence interval and p-value were computed using a stratified Cox proportional hazards regression model with treatment as a factor and stratified by stratum.

The analysis of the proportion of patients with at least one new morphometric vertebral fracture was performed using a logistic regression model with treatment and baseline vertebral fracture status (i.e. number of vertebrae with prevalent fracture) as explanatory variables. All p-values reported are based on likelihood-ratio tests.

#### Key secondary efficacy variables

The analysis of key secondary variables and other variables were performed on the mITT population for morphometric vertebral fracture variables and on the ITT population for all other variables. To control the Type I at an overall 5% level, a closed testing procedure was constructed a priori to define the order for which secondary efficacy variables would be evaluated.

1. Analyses of bone mineral density (BMD): Percentage change from baseline at each analysis visit was analyzed for all BMD efficacy variables. Between-treatment differences were evaluated using a three-way ANOVA model with treatment, stratum, and region (or center) as explanatory variables. The treatment differences in least square means are presented along with their 95% confidence interval.
2. Biochemical markers of bone turnover: The biochemical markers, serum b-CTx, BSAP, P1NP were analyzed based on the  $\log_e$  ratio of the post-baseline value relative to baseline. Between-treatment differences were evaluated using an analysis of covariance (ANCOVA) model with treatment, stratum, center, and  $\log_e$  transformation of the baseline measurement as explanatory variables. The relative treatment effect defined as the exponentiation of the least square mean difference of the  $\log_e$  ratio between the two groups was presented along with its 95% confidence interval.
3. Stadiometer Height: Between-treatment differences were evaluated using a three-way ANCOVA model with treatment, stratum, region, and baseline height as explanatory variables.
4. Disability: The days of disability due to clinical fractures and back pain were the last 2 steps in the closed testing procedure. Between-treatment differences for each variable relative to days of reduced activities and days of bed rest were assessed using a Wilcoxon rank-sum test.

#### **Safety**

The number and percentage of patients who report AEs were summarized according to primary system organ class and preferred term by treatment in descending order of frequency within each primary system organ class with respect to the zoledronic acid treatment group. Where applicable, adverse events were also presented by treatment and stratum.

A summary of clinical laboratory evaluations are presented with respect to hematology, serum chemistry, and urinalysis. Vital signs and body weight include systolic/diastolic blood pressure, pulse rate, and body weight. Descriptive statistics (mean, median, standard error, minimum and maximum) for the baseline, each study visit, the last visit, and change from baseline to each visit are presented. These descriptive summaries are presented by laboratory test group and treatment group. In addition,

shift tables are provided to compare a patient's baseline laboratory evaluation relative to each study visit and the last visit.

Several additional special efficacy and safety populations were analyzed and the statistical methods used for those analyses are presented in detail in Section 6 (Statistical Methods).

## Results:

### Efficacy

This 3-year study demonstrates that a single annual infusion of 5 mg zoledronic acid is highly efficacious in reducing vertebral and hip fractures as compared to placebo. This is the first osteoporosis study to show reductions for both vertebral and hip fractures within one single study; detailed results are indicated below:

- Treatment with zoledronic acid reduced the risk of new morphometric vertebral fractures by 70% ( $p < 0.0001$ ) over 36 months.
- Zoledronic acid reduced the likelihood of having a hip fracture over time by 40% (hazard ratio of 0.60, ( $p = 0.0032$ )).
- In patients who were treatment-naïve to bisphosphonate therapy, zoledronic acid significantly reduced the risk of hip fractures by 51% (hazard ratio of 0.49,  $p < 0.001$ ).
- Patients who received zoledronic acid had the risk of morphometric vertebral fractures reduced by 60% over 1 year, 71% over 2 years, and 70% over 3 years compared to patients receiving placebo. New/worsening fractures and moderate/severe fractures were reduced by approximately 60%-70% over 1, 2, and 3 years. All results were significant (all  $p < 0.001$ ).
- Consistent statistically significant reductions in the risk of morphometric vertebral fractures over 3 years were demonstrated across all pre-defined categories, including age, geographical region, BMI, baseline femoral neck BMD T-score, prior use of bisphosphonates, number of baseline vertebral fractures, and baseline renal function.
- Zoledronic acid significantly reduced the risk of clinical fractures by 33%, clinical vertebral fractures by 75%, and clinical non-vertebral fractures by 25% (all  $p < 0.001$ ).
- Zoledronic acid was superior to placebo in increasing or preserving BMD in patients over 36 months at the total hip, femoral neck, trochanter, lumbar spine, and distal radius. Significant increases relative to placebo were observed as early as 6 months at all sites except the distal radius where significant differences were observed beginning at 12 months.
- Markers for bone formation and resorption were reduced following study drug administration with zoledronic acid and were maintained within pre-menopausal levels at the end of every 12-month period. The effect on reduction of bone markers was sustained over 36 months and no further reduction of those markers was observed with repeat dosing.
- Zoledronic acid significantly reduced the magnitude of height loss at Month 24 and Month 36 (both  $p < 0.0001$ ).
- Zoledronic acid significantly reduced the number of days of "limited activity" time and bed rest due to fracture and back pain when compared to placebo (all  $p < 0.01$ ).

### Safety

- The overall incidence of AEs and SAEs was comparable between treatment groups.
- The 5 most frequently occurring AEs were associated with transient, early onset (within 3 days) post dose symptoms including: pyrexia, myalgia, influenza like illness, headache, and arthralgia.
- Consistent with other bisphosphonates, there was a slight imbalance between zoledronic acid and placebo for reported hypocalcemia events [11 events (0.28%) vs. 5 (0.13%), respectively]. These events were transient and asymptomatic.
- There was no difference in long-term renal function parameters between zoledronic acid and placebo. Transient, short-term changes in renal function as demonstrated by increases in serum creatinine  $> 0.5$  mg/dl from pre-dose to post-dose (9-11 days) occurred more

commonly after dosing with zoledronic acid (42 (1.81%) vs. 19 (0.81%) for zoledronic acid and placebo, respectively).

- There was an increased rate of atrial fibrillation SAEs relative to placebo that was not consistent with the rate of non-serious atrial fibrillation AEs nor consistent with the ECG data (approximately equal in both groups); therefore, this is most likely not a drug related effect.
- Bone biopsies demonstrated reductions in bone turnover with normal bone quality. All patients with bone biopsy samples had evidence of labeling in either the trabecular or the cortical bone, indicating persistence of bone turnover.

**Conclusions:**

- Zoledronic acid was superior to placebo in reducing the proportion of patients with at least one new morphometric vertebral fracture over 36 months (relative risk reduction of 70%,  $p < 0.0001$ )
- Zoledronic acid significantly reduced the risk of having a hip fracture over time (hazard ratio of 0.60,  $p = 0.0032$ )
- Zoledronic acid significantly reduced the risk of hip fractures by 51% (hazard ratio of 0.49,  $p < 0.001$ ) for patients who were not previously treated with bisphosphonates ( $p < 0.001$ ).
- All other key secondary morphometric and clinical fracture endpoints show a significant reduction in the risk of fractures at all time points evaluated
- Zoledronic acid significantly increased gain in bone density at 6 months at the spine, hip, and femoral neck and continued to show sustained improvement in BMD at 36 months (all  $p < 0.0001$ ).
- The effect on reduction of bone markers was sustained over 36 months with no further reduction of bone formation or resorption markers with repeat dosing.
- Zoledronic acid significantly lessened the loss of height over 36 months ( $p < 0.0001$ ).
- Zoledronic acid demonstrated a significant reduction in the days of disability and days of bed rest compared to placebo.
- Zoledronic acid was generally safe and well tolerated.
- There was no evidence of a long-term effect on renal function following the administration of zoledronic acid in this patient population, however transient short-term effects were observed.
- There was a similar number of adverse events and serious adverse events in both groups.

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