CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-386
21-223/S-003

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-386

Drug :	**ZOMETA**
Generic name:	Zoledronic acid; zoledronate
Formulation:	——— lyophililized powder for reconstitution and intravenous infusion.
Indications:	Bone metastases due to malignancy and bone lesions due to multiple myeloma
Applicant:	Novartis Pharmaceuticals Corp. 59 Route 10 Hanover NJ 07936-7661
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	8/21/01; 9/21/01; 9/24/01; 9/28/01; 12/05/01; 12/06/01; 12/21/01

Primary/Pharmacomteric Reviewer: Brian Booth, Ph.D.

Pharmacometric Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	N.A.M. Atiqur Rahman, Ph.D.
Type of Submission:	NDA-Original (category 6P)

I. Executive Summary

The applicant submitted NDA 21-386, ZOMETA for marketing approval as a treatment for osteolytic bone metastases secondary to prostate cancer and other solid tumors such as breast, lung and colon, and secondary to multiple myeloma. The proposed dosing regimen of Zometa is a 4 mg intravenous infusion over **no less than 15 minutes**.

A. Overall Recommendations

The clinical pharmacology and biopharmaceutics information submitted in the NDA for Zometa is acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics. The key clinical pharmacology issue is the nephrotoxicity of Zometa. Limited data are available for patients with severe renal impairment, but the PK/PD modeling suggest that the risk of renal deterioration increases with AUC. This information and a warning about the use of Zometa in patients with renal impairment have been suggested for the labeling. The sponsor also repsorted that renal impairment occurred in several patients who were treated with both thalidomide and Zometa, which suggest that there may be some mechanistic basis for a drug-drug interaction. The sponsor should incorporate the labeling changes made by FDA, address the comments noted, and conduct the proposed phase 4 studies.

B. Phase 4 Commitments

1. Limited information is available to guide dosing of Zometa in patients with bone metastases and severe renal impairment. You should conduct a phase 4 pharmacokinetic, saftey and efficacy study in patients with renal dysfunction ≥ 3 mg/dl. The dose of Zometa to be administered should be adjusted to match the $AUC_{0\text{-}24h}$ in patients with normal renal function, and safety, efficacy and biomarker suppression should be assessed. A suitable patient population may be patients with multiple myeloma. Please submit the protocol to FDA for review.

2. Renal toxicity has been observed in patients treated with both thalidomide and Zometa. You should conduct a drug-drug interaction study to evaluate the effect of thalidomide on the pharmacokinetics and safety of Zometa in patients with multiple myeloma. Please submit the protocol to the FDA for review.

C. Comments

1. The WARNING section of the label should specifically caution against use of Zometa in patients with severe renal impairment to avoid further deterioration in renal function.

2. The applicant updated the extent of Zometa protein binding in the clinical pharmacology section of the labeling. Originally, the applicant indicated that Zometa protein binding was 22%, which was determined from in vitro studies using the plasma of three male volunteers. This value has been edited to 56%. These latter studies were conducted, in triplicate, using the plasma derived from a single male volunteer. The methodologies used in both studies appear quite similar, and it is unclear why the applicant considered the latter study more accurate. However, because the original study contained more subjects than the newer study, the protein binding extent should remain as 22%. Regardless of the exact figure, the extent of protein binding is too low to be of any clinical significance.

3. The applicant used ——— to measure radiolabeled Zometa. This assay was not properly validated. The data generated was deemed acceptable because it was in agreement with data generated by a validated assay. However, for future use, the — assay should be validated according to the FDA Guidance for Industry entitled "Bioanalytical Method Validation".

Briefing Date: 12/21/01

Reviewer: Brian Booth, Ph.D.

Team Leader: NAM Atiqur Rahman, Ph.D.

CC: NDA 21-386
HFD-150/Division File
HFD-150/VauseD, IbrahimA, ScherN, WilliamsG
HFD-860/MehtaM, RahmanNAM, BoothB
CDR/Biopharm

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II. Table of Contents

IIb. List of Abbreviations

Ae: Amount of drug excreted in the urine
$Ae_{0\text{-}24h}$: Amount of drug excreted in the urine up to 24 hours.
AUC: Area under the concentration vs. time curve
$AUC_{0\text{-}24h}$: Area under the concentration vs. time curve up to 24 hours
AUC_{inf} or AUC_{∞}: Area under the concentration vs. time curve from time "0" to infinity.
$AUC_{0\text{-}last}$: Areas under the concentration vs. time curve from "0" to the last observation.
BAP: bone alkaline phosphatase; bone-specific alkaline phosphatase
BWT: Body weight in kilograms
CAL: calcium
C_{end}: Peak plasma concentration of the drug at the end of the infusion
C_{max}: Peak plasma concentration of the drug
CL: Clearance
CL_{total}: Total systemic clearance of the drug
CL_r: Renal clearance of the drug
CL_{cr}: Creatinine clearance of the drug
CRTC: Creatinine clearance of the drug
CTX: C-telopeptide
CYP450: Cytochrome P-450
DEO: Deoxypyridinoline
E_{ave}: Average pharmacodynamic response
Hr, hrs: hours
HYD: hydroxyproline
L: Liter
LOD: lower limit of detection
LOQ: lower limit of quantification
Min: minutes
ml, mL: milliliter
N: Normal
NDA: New Drug Application
Ng/ml: nanograms per milliliter
NTX: N-telopeptide
Kg, kg: kilograms
PD: pharmacodynamics
PK: pharmacokinetics
PYR: pyridinoline
Q_2, Q_3: Intercompartmental clearance of peripheral compartments two and three, respectively
RIA: Radioimmunoassay
$T_{1/2}$, $t_{1/2}$: Half-life
USP: United States Pharmacopeia
V, V_1: Volume of distribution
V_2, V_3: volume of peripheral compartments two and three, respectively
µg/L: micrograms per liter

III. Summary of Clinical Pharmacology Findings

Zometa is a third generation bisphosphonate that possesses an in vitro potency that is three to four orders of magnitude greater than the previous bisphosphonates, in terms of osteoclast inhibition. Zometa has been approved for the treatment of Hypercalcemia of Malignancy, and currently the applicant is seeking marketing approval of Zometa for the treatment of osteolytic bone metastases secondary to solid tumors (prostate, breast, lung, colon) or multiple myeloma.

The applicant demonstrated that Zometa does not inhibit cytochrome P-450 isozymes in vitro, and consequently, did not study P-450 based in vivo drug-drug interactions. Protein binding was originally reported as 22%, but then amended to 56%. The latter figure was derived from a single male volunteer and the original estimate of protein binding is likely more accurate. ^{14}C-labeled studies of Zometa in vivo resulted in the recovery of a single radioactive species, which indicated that Zometa itself was not metabolized in vivo. This result suggested that hepatic metabolism of Zometa does not occur in vivo, and therefore, the effect of hepatic impairment on Zometa pharmacokinetics or pharmacodynamics was not studied.

Studies of radio-labeled and unlabeled Zometa (64 patients; 503/503E, J001, 506/506E) indicated that renal excretion was the main route of elimination. Within 24 hours of dosing 39 ± 16% of Zometa was recovered in the urine. However, it should be noted that fecal recovery of Zometa was not reported.

Zometa is characterized by a three-compartment pharmacokinetic model. Zometa possesses a "distributive" phase that is characterized by a half-life (α-$t_{1/2}$) of 0.24 hrs, a β-$t_{1/2}$ of 1.87 hours and γ-$t_{1/2}$ of 146 hours. The terminal elimination phase is characterized by prolonged period in which Zometa concentrations are slightly higher than the limit of quantification of the assay. It is believed that Zometa is slowly released back into the circulation following initial rapid sequestration in the bone. The β-$t_{1/2}$ serves as the effective half-life for the drug, and exposure is described in terms of a twenty-four hour period ($AUC_{0\text{-}24h}$) instead of $AUC_{0\text{-}\infty}$ because of the inaccuracy in determining the terminal elimination phase of the drug.

The clearance of Zometa, determined by a population pharmacokinetic analysis, was reportedly dependent upon creatinine clearance, age, sex, weight. The FDA re-analysis indicates that CL is dependent upon creatinine clearance alone. Age, race, were not significant cofactors. Weight improved the assessment of volume of distribution. Clearance was approximately 7 L/hr.

The applicant conducted a renal impairment study of Zometa in patients with normal, mild or moderate impairment (Study 506). The results indicated that the $AUC_{0\text{-}24h}$ of Zometa increased by 20-40% with mild impairment and 40-50% with moderate impairment. These data also suggested that an increase of 50-60% $AUC_{0\text{-}24h}$ in severe renal impairment could be expected. In the only patient with severe renal impairment studied, the $AUC_{0\text{-}24h}$ increased by 60% when creatinine clearance decreased from 46 to 9.1 ml/min. The FDA PK/PD analysis indicated that drug efficacy was independent of dose, but Zometa did reduce the likelihood of a skeletal related event. Furthermore, the risk of a renal event was correlated with creatinine clearance and Zometa AUC. Therefore, a dosing adjustment in patients with moderate to severely impaired renal function appears warranted.

IV. Question Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

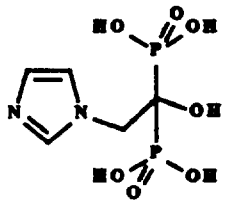


Figure 1. The chemical structure of Zometa

Zometa (zoledronic acid; zoledronate; 2-(imidazol-1-yl)-1-hydroxy ethane-1, 1-bisphosphonic acid monohydrate) is a third generation bisphosphonate. Zometa has the molecular formula $C_5H_{10}N_2O_7P_2H_2O_2$ and a molecular weight of Wt 290.1. Zometa is highly soluble in 0.1N sodium hhydroxide, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of 0.7% solution of Zometa in water is approximately 2. Zometa is shipped in sterile, single-use vials as a white crystalline powder which contains 4.264 mg of Zometa, 220 mg of mannitol, USP and 24 mg of sodium citrate, USP. Zometa is reconstituted either in 100 mL of 0.9% saline, USP or 5% dextrose, USP and infused over **no less than** 15 minutes.

What is the proposed mechanism of action and the therapeutic indication?

The mechanism of action of Zometa and bisphosphonates in general, is not entirely clear. Bisphosphonates have a high affinity for divalent calcium, and bind avidly to hydroxyapatite in bone. Bisphosphonates bind to areas of bone with high rates of turnover, and inhibit bone resorption by osteoclasts. Bisphosphonates may also induce osteoclast apoptosis.

The C-P-C bond of bisphosphonates is resistant to hydrolysis by phosphatases. The three generations of bisphosphonates differ from one another in side chain substitution. The heterocyclic imidazole ring side chain makes it 100 to a 1000 times more potent than pamidronate (second generation), which itself is 10 to 100 times more potent than the first generation drugs (e.g. etidronate).

Zometa is approved for the treatment of Hypercalcemia of Malignancy. In the current submission, approval is being sought for the use of Zometa to treat several indciations, namely ostelytic, osteoblastic and mixed bone metastases of solid tumor, and osteoblastic lesions of multiple myeloma.

What is the proposed dosage and route of administration?

Treatment with Zometa is recommended as a 4 mg intravenous infusion over no **less than 15 min**. Additional cycles of therapy are recommended if the patient demonstrates clinical benefit.

What efficacy and safety information contributes to the assessment of clinical pharmacology data?

Safety and efficacy were studied in three pivotal trials. Study 010 was an active-control (Aredia) trial of Zometa in 1648 breast cancer and multiple myeloma patients. Study 011 was a placebo controlled study of Zometa in 766 patients with solid tumors other than breast or prostate cancer, and study 039 was a placebo controlled trial of Zometa in 640 prostate cancer patients.

The efficacy endpoint for Zometa was skeletal related events (SREs), which included bone fractures, spinal compressions, bone irradiation or surgery, and/or hypercalcemia of malignancy. Safety consisted primarily of nephrotoxicity, and to a lesser extent nausea, vomiting, myalgia, pyrexia and anthaglia.

Was the relationship between drug effect or adverse events with Zometa plasma concentrations established?

The efficacy and safety markers were not related to Zometa dose or plasma concentration by the applicant. However, in the clinical pharmacology studies, the applicant attempted to correlate plasma concentrations to biomarkers of bone remodeling. The biomarkers were not correlated to efficacy or safety endpoints in the clinical safety or efficacy studies.

B. General Pharmacology

1. Distribution

The pharmacokinetics of Zometa are characterized by a three-compartment model. The $t_{1/2\alpha}$ derived from the population pharmacokinetic modeling was 0.24 hr which indicates rapid distribution of the drug. The volume of distribution based on the population pharmacokinetic modeling was reported as 6.48 L; this value is slightly lower than the estimate determined by FDA modeling (7.97 L). Zometa like other bisphosphonates, appears to rapidly and extensively bind to bone. The drug is then slowly released back into the circulation and excreted. This process is believed to take years, as indicated by the prolonged $t_{1/2\gamma}$ (146 hrs). However, study limitations have prevented an accurate assessment of the elimination for Zometa or other bisphosphonates.

Protein Binding.

The extent of Zometa-protein binding is unclear. The applicant's original study was conducted in whole blood and plasma obtained from three male volunteers. The mean binding was 22 % over 50 to 5000 ng/ml). However, in more recent studies, the

applicant reported protein binding of 55%, but only in one male volunteer. This latter study also indicated that binding was affected by the choice of coagulant. Protein binding was greater in heparinized plasma (which was used in the original study). Regardless of this uncertainty, the protein binding is too low to be of clinical concern in renally or hepatically impaired patients. Because the original study used plasma from three volunteers, it is likely more accurate and the labeling should state protein binding is 22%.

2. Metabolism: Is there any clinically significant metabolism of Zometa?

Typically, bisphosphonates are not metabolized in humans. The P-C-P bond is resistant to hydrolysis. The applicant did not report any in vitro P-450 (CYP 450) studies to determine the ability of any isozymes to metabolize Zometa. However, the sponsor did investigate the ability of Zometa to inhibit CYP 450 isozymes. The figure below indicates that no significant inhibition occurred following 15-minute incubations of Zometa with any CYP 450 isozyme. Studies also indicated that Zometa did not induce any irreversible CYP450 inhibition.

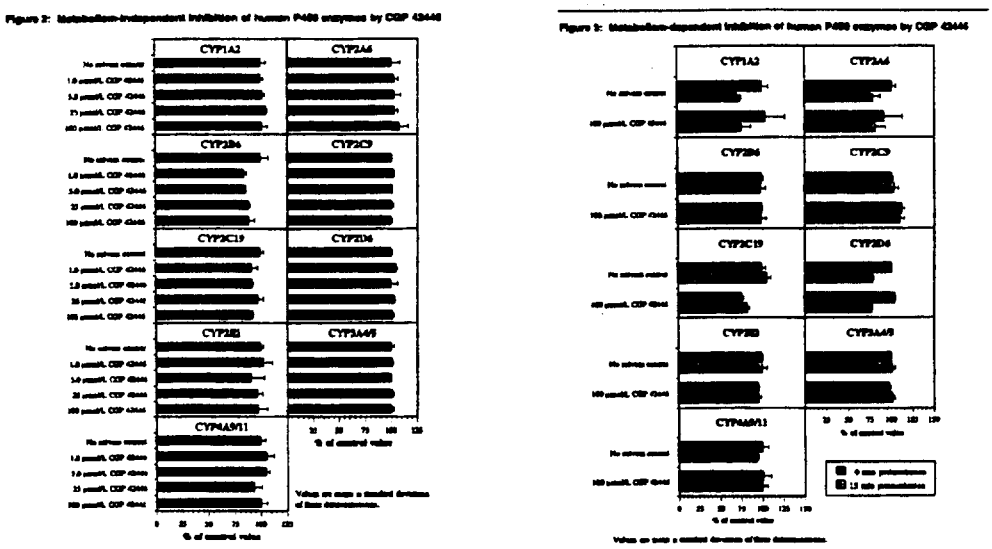


Figure 2. Results of Applicant's in vitro CYP450 Inhibition Studies

The lack of CYP 450 inhibition was the basis for applicant's decision not to study in vivo drug-drug interaction studies. Further evidence that Zometa itself is not metabolized in vivo was derived from the study of ^{14}C-Zometa in Study 506/506E. The plasma and urine samples indicated that only a single ^{14}C-containing peak was obtained, suggesting that no other metabolites are formed. These studies were the basis for the applicant's decision not to study the effect of hepatic impairment in vivo on Zometa disposition.

3. Excretion: What is the route of drug excretion?

Zometa is excreted primarily in the urine as the parent molecule. Urinary excretion was measured in three studies using both labeled and unlabeled compound. Approximately

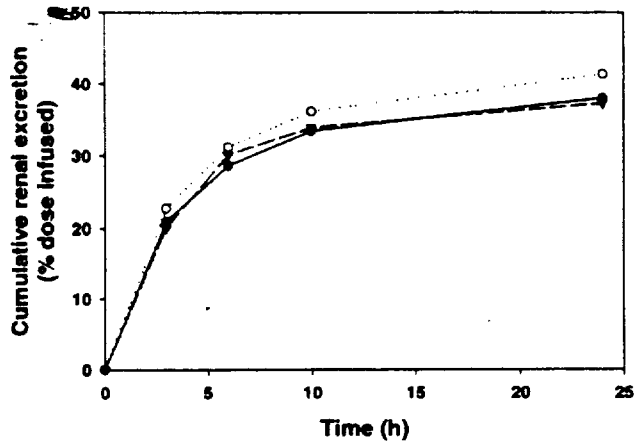
40% of the dose is recovered in the urine within 24 hours of administration. Fecal excretion was not measured.

Table 1. Urinary Excretion of Zometa

Study	Dose/Renal Impairment	Urinary Excretion, 24 hrs (% Dose Administered)
Study 503/503E	4 mg/normal (n=12)	38 ± 13
	8 mg/normal (n=12)	41.3 ± 14.3
	16 mg/normal (n=12)	37.2 ± 16.5
Study J001	2 mg/normal (n=3)	48.2 ± 12.2*
	4 mg/normal (n=3)	67.2 ± 43.8*
	8 mg/normal (n=3)	60.9 ± 19.6*
Study 506/506E	4 mg/normal (n=9)	36.2 ± 15.1
	4 mg/mild (n=7)	40.4 ± 18.8
	4 mg/moderate (n=3)	27.9 ± 10.2

* calculated to infinity.

Excretion of Zometa approaches an asymptote within 24 hrs (see figure). Complete urinary excretion of Zometa was estimated to reach 48 to 67% in Study J001, which underscores the avid binding of Zometa to bone. The extent of urinary excretion of Zometa is similar to other bisphosphonates.



Symbols: ● (4 mg), O(8 mg), and ▼ (16 mg)

Figure 3. Urinary accumulation of Zometa (Applicant Study)

4. Pharmacokinetics

Have the pharmacokinetics of Zometa been adequately characterized in the target populations at the indicated 4 mg dose?

The pharmacokinetics of Zometa have been studied at doses ranging from 2 to 16 mg in three studies. Study 503/503E was conducted in the USA in 36 patients with bone metastases. Study J001 was conducted in Japan in nine patients with bone metastases and Study 506/506E was conducted in Canada in 19 cancer patients with renal impairment. The 64 patients studied were characterized mostly by breast, prostate, colon, lung and multiple myeloma primary cancers. However, the dosing regimen in the Clinical pharmacology studies was Zometa once every 28 days, which differed from the clinical studies in which Zometa was administered once every 21 days. However given the relatively short β-half-life of Zometa (~2 hrs), this difference in dosing frequency is unlikely to be significant despite the prolonged γ-half-life of Zometa (~ 146 hrs) which is due to Zometa concentrations that are barely detectable.

The disposition of Zometa is characterized by a three-compartment model. The α "absorptive" phase is rapid (14 minutes), which is followed by the β phase, in which Zometa is excreted into the urine. The $t_{1/2}$ represents the effective half-life of the drug is estimated as 1.87 hrs. A prolonged γ phase follows, in which Zometa which is apparently adsorbed to bone, is released back into the circulation and excreted into the urine. This γ phase is poorly characterized, due to practical sampling limitations, and the $t_{1/2}$ of this phase is estimated to be 146 hours. This γ elimination $t_{1/2}$ is likely longer than this estimate. Due to the inaccuracy of the terminal elimination phase, the applicant

determined the pharmacokinetics based on the β-phase of Zometa (the 24-hr period post dosing). The figure below from Study 506/506E shows the typical plasma concentration vs. time curve the 4 mg dose over three cycles of treatment. This data indicates that no significant drug accumulation occurs with repeated infusions of Zometa.

Figure 7-2. **Mean (±SD) zoledronic acid plasma concentration-time profiles following intravenous infusion of 4 mg over 15 min over three 28-day cycles in patients with normal renal function (logarithmic scale).**

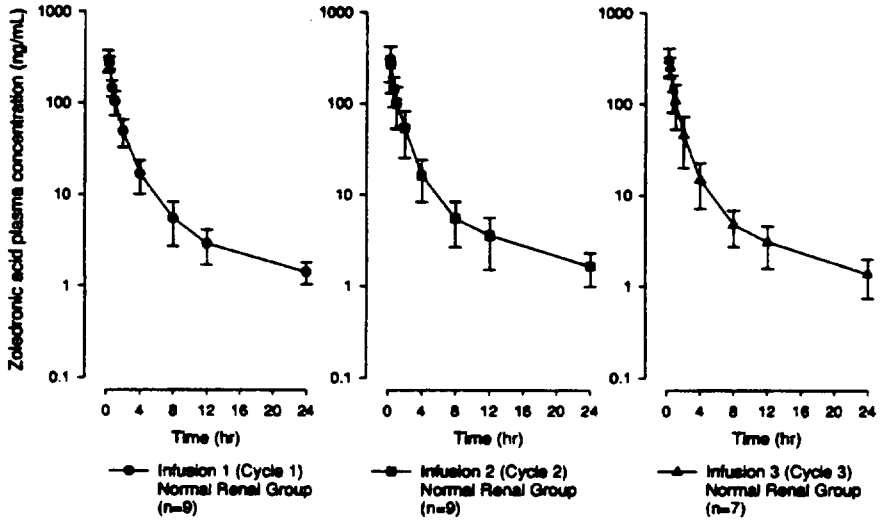
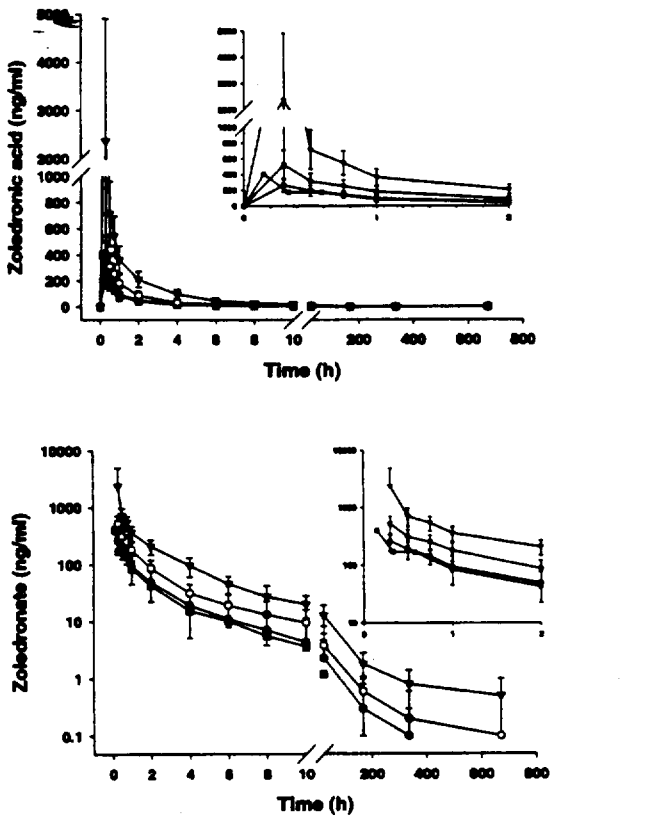


Figure 4. Plasma concentration vs. time plots of 15-min infusions of 4 mg doses of Zometa (from Applicant Study 506/506E). Infusions were repeated at 28- day intervals.

The disposition of 4, 8 and 16 mg doses of Zometa are shown in the following figure obtained from Study 503/503E. The disposition of the doses are nearly identical.

Figure 5.2-1 Mean zoledronic acid concentration-time profiles in 36 patients



Symbols: ■ (4 mg/5 min), ● (4 mg/15 min), ○ (8 mg/15 min), and ▼ (16 mg/15 min)
Upper panel: linear-linear scale; lower panel: log-linear scale

Figure 5. The plasma concentration vs. time curves for 4, 8 and 16 mg doses of Zometa from Applicant Study 503/503E.

The basic pharmacokinetic parameters of Zometa following the first cycle of therapy in the three studies are compared in the two tables below. At 4 mg, the C_{max} appeared significantly greater in the Japanese study. However, the $AUC_{0\text{-}24h}$ following 4 mg of Zometa is approximately the same across all three studies (~ 400ng*h/ml).

Table 2. C_{max} (ng/ml) of Zometa After the First Cycle of Treatment

Zometa Dose mg	Study 503/503E	Study J001	Study 506/506E
2	ND	453 ± 162 (n=3)	ND
4	264 ± 86 (n=7)	668 ± 251 (n=3)	308.8 ± 70.7 (n=9)
8	523 ± 186 (n=12)	1142 ± 190 (n=3)	ND
16	2252 ± 2636 (n=12)	ND	ND

ND: not done

Table 3. $AUC_{0\text{-}24h}$ (ng*h/ml)of Zometa After the First Cycle of Treatment

Zometa Dose mg	Study 503/503E	Study J001	Study 506/506E
2	ND	344 ± 98 (n=3)	ND
4	420 ± 218 (n=7)	540 ± 232 (n=3)	408.2 ± 98.9 (n=9)
8	769 ± 256 (n=12)	1133 ± 386 (n=3)	ND
16	2004 ± 559 (n=12)	ND	ND

ND: not done

Multiple Dosing

Generally, Zometa is administered as a single dose. However, additional doses may be administered once every 28 days, if needed. The long elimination $t_{1/2}$ of Zometa (146 hours) poses the possibility that Zometa may accumulate upon repeated dosing, and lead to unwanted toxicity. The plasma concentration time curves for Zometa following the firs, second and third cycles of treatment are shown in the Figure 6.

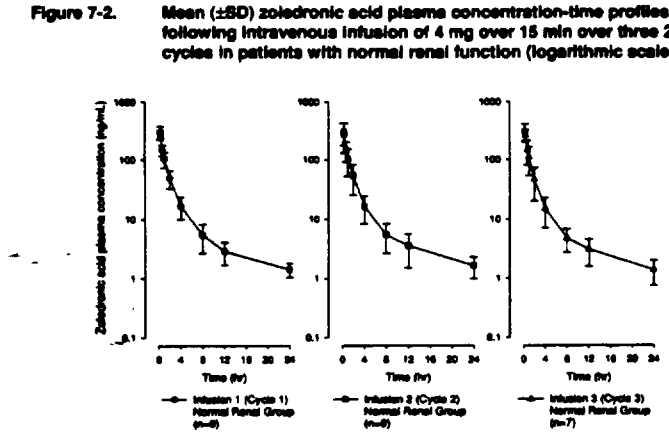


Figure 6. Plasma concentration vs. time curves for three cycles of 4 mg infusions of Zometa. (Applicant Study 506/506E)

Figure 5.2-3 A representative plasma concentration-time profile for Patient 501-119

A: linear-linear scale; B: log-linear scale.

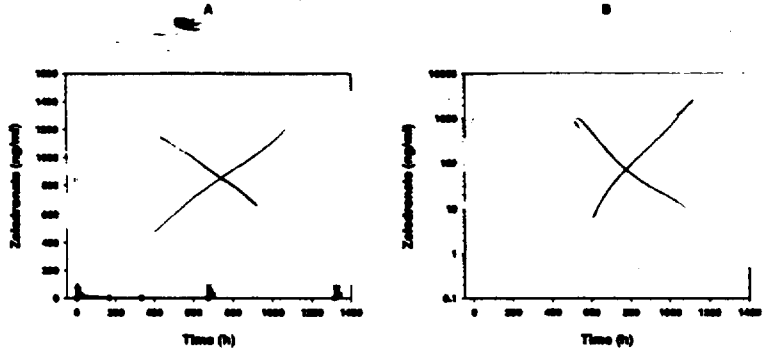
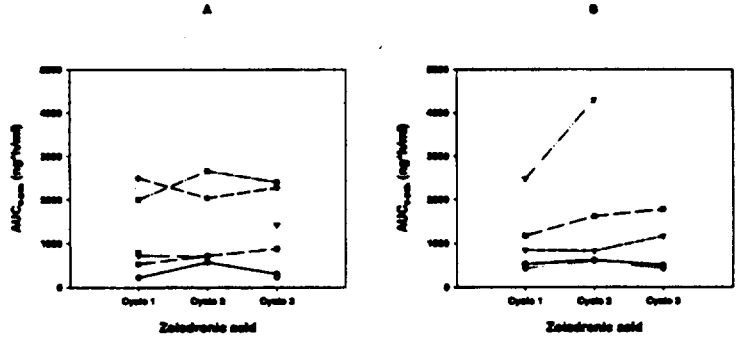


Figure 5.2-4 AUC_{0-24h} by treatment cycle



A: Patients with a 28-day dosing schedule. Symbols are: ● (501-116, 4 mg), O(501-124, 4 mg), ▼ (501-120, 8 mg), ∇ (501-122, 8 mg), ■ (501-127, 8 mg), □ (501-119, 16 mg), and ◆ (501-121, 16 mg).

B: Patients with various dosing intervals between Cycle 1 and Cycle 2, and a 28-day dosing interval between Cycle 2 and Cycle 3. Symbols are: ● (501-103, 4 mg), O(501-115, 4 mg), ▼ (501-107, 8 mg), ∇ (501-102, 16 mg), ■ (501-110, 16 mg).

Figure 7. Plasma concentration vs. time curves for repeated cycles of Zometa treatment from Applicant Study 503/503E

These data are typical of the data obtain from all three Zometa pharmacokinetic studies and they indicate that no significant quantities of the drug accumulate with repeated dosing. Therefore, concern for toxicity upon repeated dosing are unwarranted.

Dose Proportionality

In order to establish that the pharmacokinetics of Zometa are first order over the range of dosing studied, the AUC and Cmax were plotted against dose. In study 503/503E, the $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}last}$ were plotted from 4 to 16 mg.

Figure 5.2-6 AUC vs. zoledronic acid dose

A: AUC_{0-24h} vs. dose B: AUC_{0-last} vs. dose

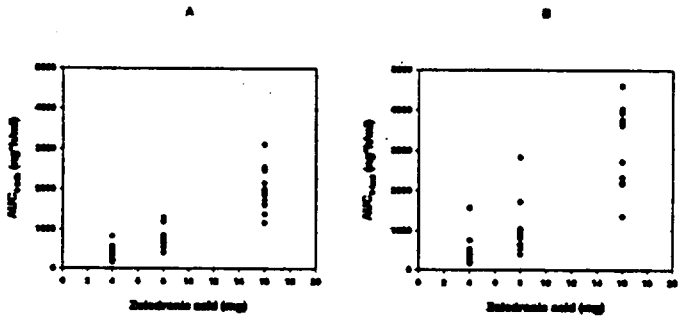


Figure 8. AUC vs. Dose from Applicant Study 503/503E

A power analysis indicated that doubling the dose lead to a 2.32 fold increase in AUC_{0-24h}, suggesting dose proportionality. The same analysis with the AUC_{0-last} indicated a 2.76 fold change in the exposure with a doubling of the dose, but this result may be confounded by unbalanced sampling among the three doses.

In study J001, the dose proportionality was also assessed for Cmax and AUC from 2 to 8 mg of Zometa.

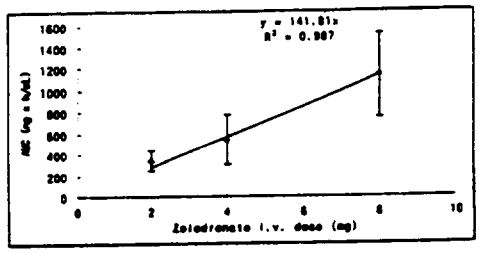


Figure 11.4.4.1g Relationship of CGP42446 dose to drug blood concentration-time area under the curve (AUC0-24) (mean ± SD).

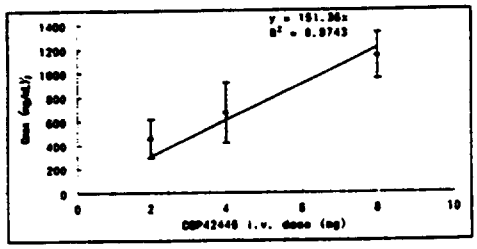


Figure 11.4.4.1h Relationship of CGP42446 dose to drug blood concentration immediately after administration (Cmax) (mean ± SD).

Figure 9. Dose proportionality of C_{max} and AUC from Applicant Study J001.

The data were linearly regressed, and the correlation coefficients were 0.99 and 0.87 for AUC and Cmax respectively. These data also support the conclusion that the Zometa pharmacokinetics are linear, apparently over the range of 2 to 16 mg.

Pharmacodynamics

The applicant sought to address two pharmacodynamic issues with the clinical pharmacology studies. The first issue was to address the possibility that Zometa induced renal damage, and secondly, the applicant attempted to correlation Zometa with changes in biomarkers for bone remodeling.

Renal function

In regard to the effect of Zometa on renal function, the sponsor monitored creatinine clearance of the patients over the three cycles of treatment studied in 503/503E.

Figure 5.3-5 Individual creatinine clearance in 36 patients by treatment cycle

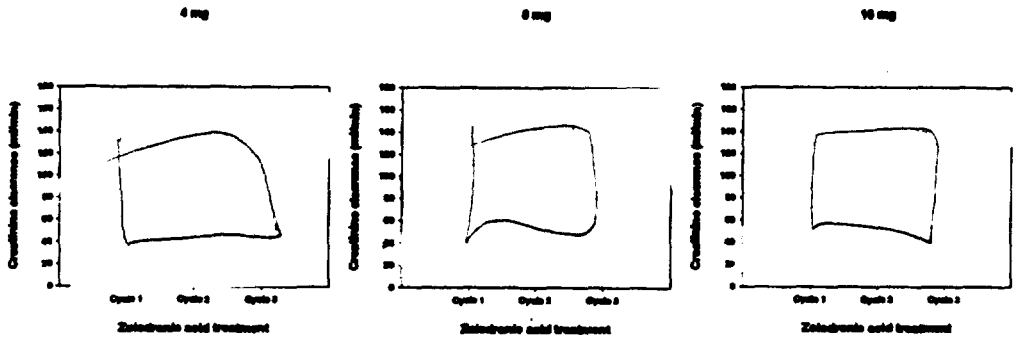


Figure 10. Effect of Zometa on renal function from Applicant Study 503/503E.

The creatinine clearances at the 4 and 8 mg doses of Zometa appear unaffected by the cycle of treatment, which suggests that renal function was not altered by Zometa. At 16 mg, one patient developed renal impairment related to disease, but creatinine clearance also appears to generally decline. However, a statistical analysis performed by the applicant (ANOVA) indicated that there were no statistically significant changes in creatinine clearance regardless of dose. Furthermore, a comparison of the amount of Zometa excreted in urine by patients treated with 16 mg for more than one cycle indicates that there is no apparent decrease in Zometa excretion, which would be expected if kidney function became impaired.

Table 4. Zometa Urinary Excretion After 16 mg Doses for Multiple Cycles.

Patient	Amount Excreted$_{0\text{-}24h}$ (% of dose)-Cycle 1	Amount Excreted$_{0\text{-}24h}$ (% of dose)-Cycle 2	Amount Excreted$_{0\text{-}24h}$ (% of dose)-Cycle 2
102*	33.9	10.11	NA
110	54.8	49.9	47.7

119	22.3	21.3	20.4
121	34.3	40.2	41.0

NA: not available. * Patient 102 developed renal impairment related to disease.

Effect of Zometa on Bone Remodeling.

In study 503/503E, the applicant determined the effect of Zometa on markers of bone remodeling, and attempted to correlate these with the pharmacokinetics of the drug. The following biomarkers were measured

Serum: bone alkaline phosphatase (BAP) which is a marker of bone formation, C-telopetide (CTX)

Urine: N-telopeptide (NTX), hydroxyproline(HYD), pyridinoline (PYR), deoxypyridinoline (DEO), calcium (CAL). The urinary markers were normalized to creatinine excretion.

The PD is reported as the average assessment of visits 3-t (E_{ave}). As shown in the figure below, the urinary markers of bone resorption were decreased following treatment with Zometa, regardless of dose during the first cycle of therapy. CTX decreased by 55 to 75% on the second day following Zometa administration, and remained inhibited during the entire cycle of treatment. BAP, increased during Zometa treatment.

Figure 5.3.3.1. Distribution of bone marker values at baseline and after ZOL administration

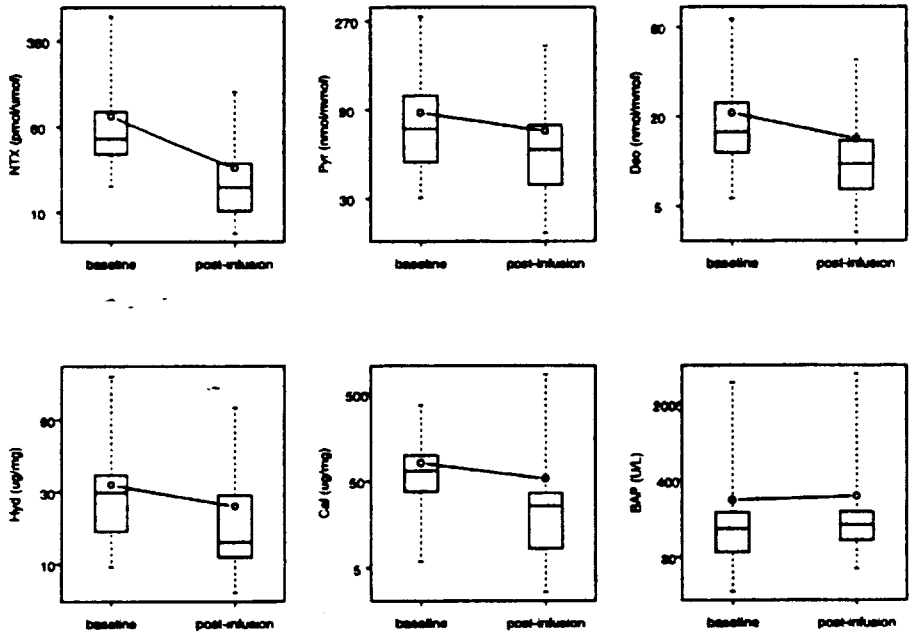


Figure 11. Effect of Zometa on bone remodeling biomarkers from Applicant Study 503

All of the PD markers except calcium and BAP were determined to be statistically significant changes.

Table 5. Summary statistics of the difference between E_{ave} and baseline measurement from Applicant Study 503/503E

PD bone marker	N	Mean	Std. Err	p-value
NTX	33	-51.90	14.37	0.001
Hydroxyproline	35	-9.64	2.40	< 0.001
Pyridinoline	33	-16.29	4.77	0.002
Deoxypyridinoline	33	-7.01	1.66	< 0.001
Calcium	35	-26.87	26.13	0.311
Bone alkaline phosphatase	33	32.85	21.51	0.137

Correlation of the PD markers to an estimate of the amount of drug remaining in the body (Dose-Amount excreted in urine ($Ae_{0\text{-}24\ h}$) was made with the model

$$Ln(E_{ave}) = ln(baseline[sic.PD\ marker]) + ln(Dose- Ae_{0\text{-}24\ h})$$

An ANCOVA of these results indicated that only urinary calcium and serum BAP were correlated to dose.

Table 6. Estimated ANCOVA coefficient and standard error on ln(Dose-$Ae_{0\text{-}24}$) and p-value for testing coefficient equal to zero from Applicant Study 503/503E

Bone Marker	Coefficient	SE	p-value
NTX	0.040	0.151	0.792
CTX	0.179	0.192	0.357
Hydroxyproline	0.198	0.109	0.079
Pyridinoline	0.087	0.086	0.322
Deoxypyridinoline	0.043	0.114	0.710
Calcium	-0.595	0.288	0.047*
Calcium**	-0.420	0.222	0.067**
Bone Alkaline Phosphatase	0.211	0.077	0.01*

*: significant at 0.05 level

**: estimated after removing an outlier, marginally significant

Therefore, the sponsor concluded that Zometa induced significant changes in markers of bone resorption, which were apparent from day 8 to 29, but only urinary calcium and serum BAP were correlated with dose.

In study 506/506E, the effect of Zometa on number of the same PD markers was evaluated. In these studies, the investigator observed similar effects on CTX and NTX as in study 503/503E, namely protracted decreases in NTX and CTX that were apparently unrelated to dose, although no statistical treatment appears to have been attempted.

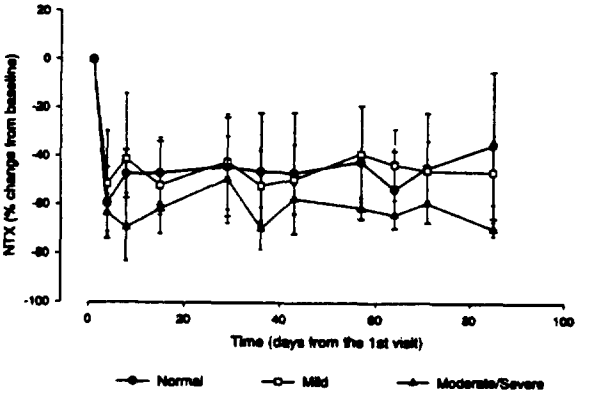


Figure 11. Time course of mean (±SD) NTX from Applicant Study 503.

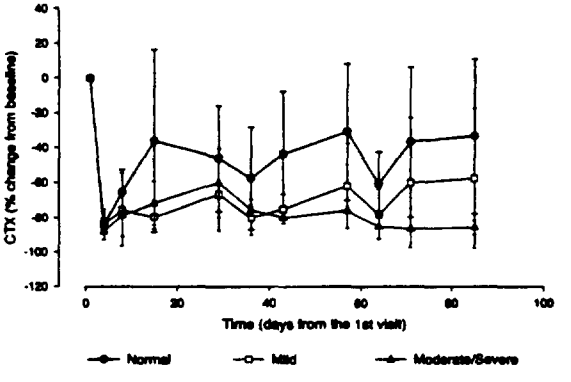


Figure 12. Time course of mean (±SD) CTX from Applicant Study 503

In contrast study 503/503E, Zometa had no apparent effect on serum BAP.

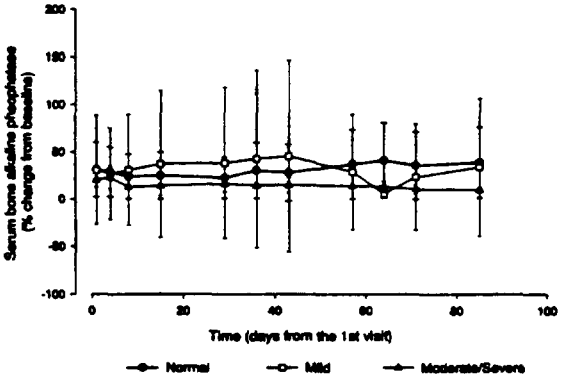


Figure 13. Time course of mean (±SD) serum BAP from Applicant Study 503

The reduction of the urinary biomarkers of bone resorption were also observed In the Japanese study J001. Over the same period (8 to 29 days), NTX, PYR,DEO, CLA, and HYD were decreased, also irrespective of dose. However, serum BAP was decreased in the 4 and 8 mg Zometa groups (-36 to -94%) in contrast to study 503/503E (refer to the study synopsis in the Appendix for tables of data). In conclusion, all three studies provide evidence that Zometa inhibits bone resorption, but no reliable correlation between dose and effect was established.

5. Intrinsic Factors

Does Age, Race or Gender influence the pharmacokinetics of Zometa?

The effect of specific patient demographic characteristics on the pharmacokinetics of Zometa were not well addressed by the applicant. There were 64 patients studied among the three studies (503/503E, J001, 506/506E). One patient was excluded due to progressive disease. There were 26 females and 37 males; 39 patients were white, 15 black and 9 were Asian (Japanese). Age ranged from 38 to 80 years. The sponsor calculated the CL and V for the three races, these are presented in the table below.

Table 7. CL and V Derived from the Population Pharmacokinetic Model of Zometa

Parameter	White (n=39)	Blacks (n=15)	Asians (n=9)
CL (L/hr)	5.22 ± 1.77	5.45 ± 2.37	4.18 ± 1.88
V (L)	9.16 ± 2.46	8.68 ± 3.2	5.85 ± 1.54
CLcr (ml/min)	85.0 ± 28.6	79.7 ± 27.8	89.3 ± 34.9

Although the Asian group appears have different Zometa pharmacokinetics, a population pharmackinetic analysis of the complete data base indicated that race and age clearly had no effect of Zometa disposition. Plots of the CL estimates relative to age, race and gender from the population pharmacokinetic modeling are presented below.

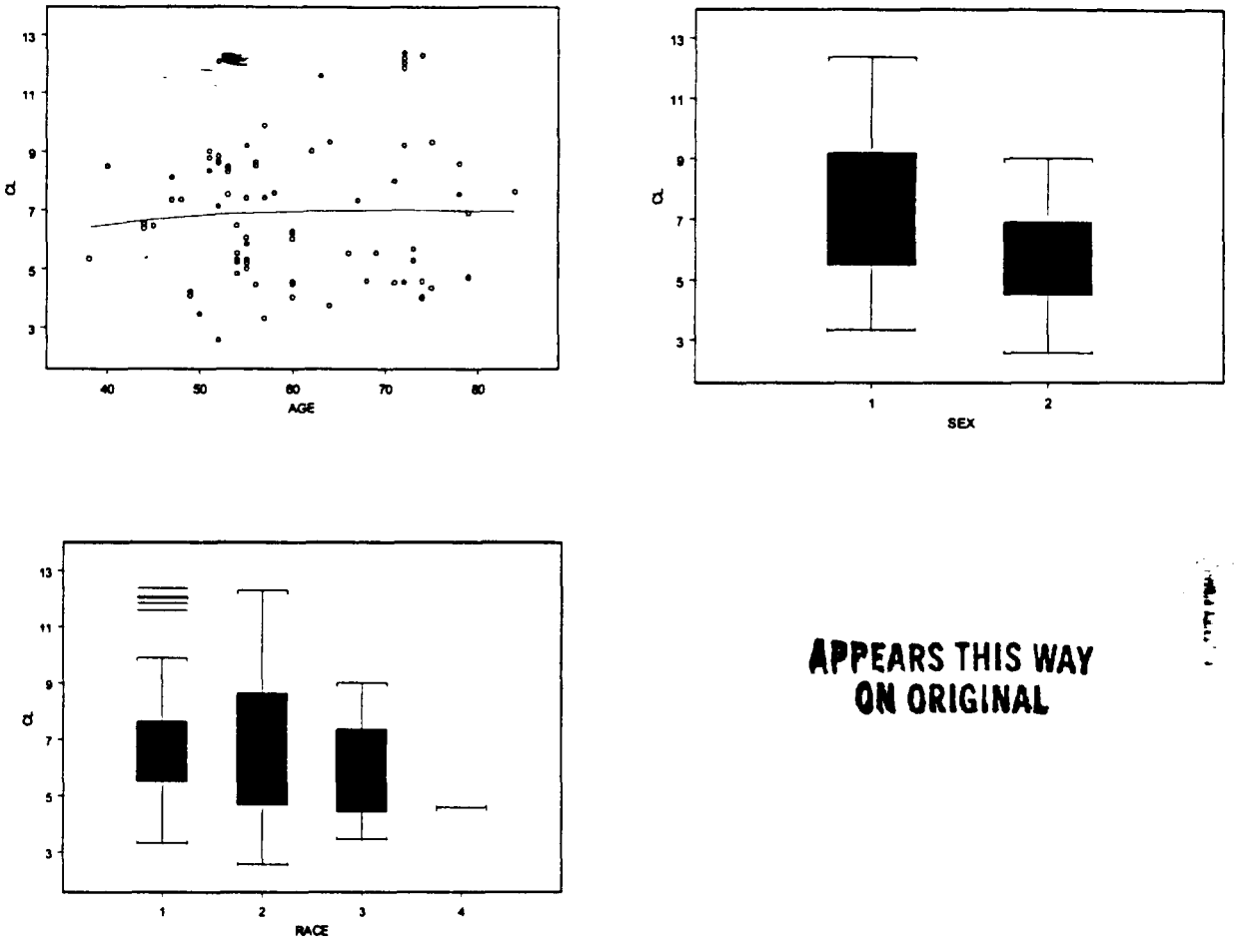


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Figure 14. Effect of age, sex and race on Zometa CL from FDA analysis.

Zometa clearance is clearly unaffected by age. In terms or race, the Asian group (group 3) do appear to have a lower clearance of Zometa, but the variability in data, the small difference and the low number of subjects preclude the conclusion that there is a clinically significant difference. The sexes also appear to have different clearances. However, the difference is small and the variability overlaps. The final population model for Zometa was best fit by a model that incorporated sex. However, the difference may be attributed to the characteristic differences in body weight between the subjects, as the population model chosen relies only on weight and provide CL estimates that were indistinguishable from the model that incorporated sex. Therefore, it is concluded that age, gender and race have no significant effect on Zometa pharmacokinetics.

Does Hepatic Impairment Affect Zometa disposition?

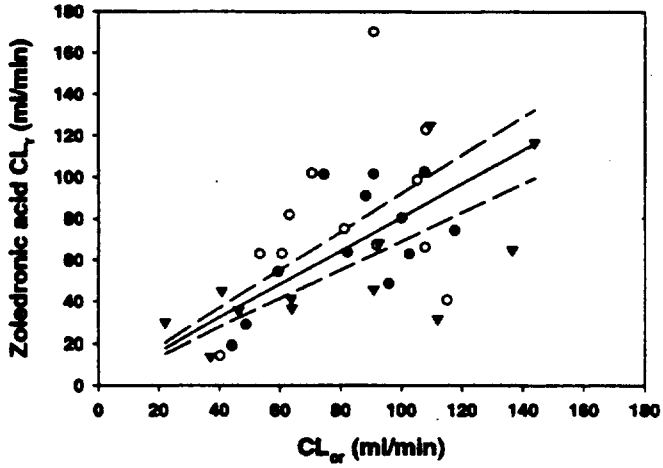
Zometa, like other bisphosphonates, is apparently not metabolized in vivo. In vivo study of ^{14}C-labeled Zometa indicated the presence of only one species in blood and urinary

samples. Therefore, it is unlikely that hepatic impairment will affect Zometa disposition. No in vivo hepatic impairment studies were conducted.

Does Renal Impairment Affect Zometa disposition?

Studies 503/503E and 506/506E both established that Zometa clearance was correlated with renal clearance.

From Study 503/503E, the applicant correlated Zometa CL_r (calculated instead of total



Symbols and lines: ● (4 mg), O(8 mg), and ▼ (16 mg), — (regression line, y=0.81x, p<0.0001), --- (95% confidence interval).

Figure 15. Creatinine clearance vs. renal clearance in from Applicant Study 503/503E

clearance) linearly with creatinine clearance (r=0.54; Cockcroft-Gault formula). A similar determination was made in study 506/506E. In this case, the Zometa CL_r creatinine clearance correlation was 0.69 (urine creatinine concentrations).

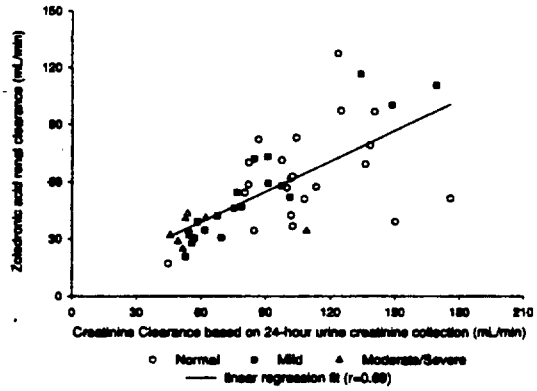


Figure 16. Urinary creatinine clearance vs. Zometa renal clearance from Applicant Study 503/503E

The dependence of Zometa clearance on renal excretion suggests that renal impairment would be an important consideration for Zometa dosing. The applicant reported in Study 506/506E that Zometa AUC_{0-24h} tends to increase with increasing renal impairment (see the table below).

Table 8. AUC0-24 in normal and mild and moderate renal impairment from Applicant Study 506/506E

Parameter	Renal function group	Infusion	N	Least square estimates	Ratio (relative to normal)	p-value
AUC(ng/ml*h)	Normal	1	9	397.35		
	Mild		7	511.37	1.29	0.0832
	Moderate/Severe		3	560.54	1.41	0.0749
	Normal	2	9	391.51		
	Mild		7	532.67	1.36	0.0975
	Moderate/Severe		3	495.53	1.27	0.3244
	Normal	3	7	409.19		
	Mild		7	517.23	1.26	0.2908
	Moderate/Severe		2	578.09	1.41	0.2986

In this study, after the first cycle of treatment, the mean Zometa AUC_{0-24h} was increased by 29 and 41% in mild and moderately impaired patients, respectively. This increase remains relatively constant in later cycles of treatment.

The applicant plotted the Zometa AUC_{0-24h} vs. creatinine clearance for all cycles of treatment. And derived a linear relationship they did not describe well in the report. Nevertheless, this relationship allows for a prediction of the increase in Zometa AUC_{0-24h}.

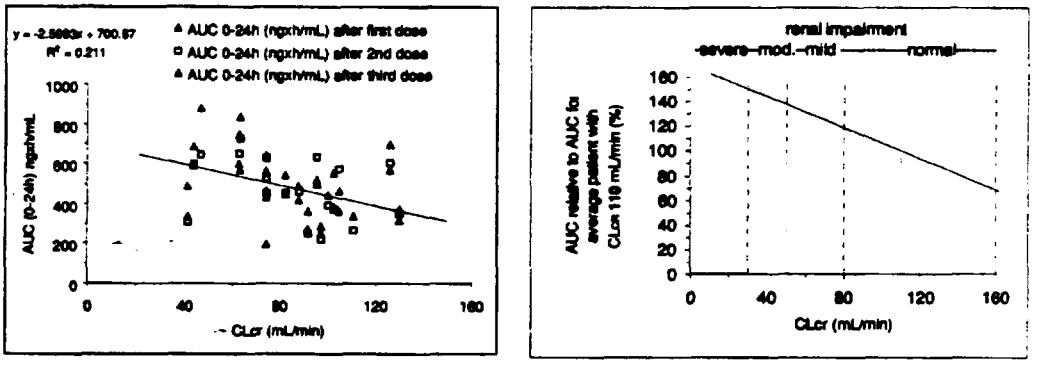


Figure 17. The relationship between AUC and creatinine clearance from Applicant Study 506/506E

This relationship predicts the following increase on Zometa exposure

Table 9. Effect of renal Impairment on Zometa Exposure

Renal Impairment	% increase in Zometa AUC_{0-24h}
Mild	20-40
Moderate	40-50
Severe	50-60

Therefore, one could expect Zometa exposures in severe renal impairment to approximate those of the 8 mg dose. Patients treated with 8 mg of Zometa are at risk for renal deterioration and renal failure. In the database submitted, one patient developed severe renal impairment (CL_{cr} decreased from 46.6 to 9.08 ml/min, cycle 1 to cycle 2, respectively). In this individual, AUC_{0-24h} increased from 2758 ng*h/ml to 4435 ng*h/ml, a 60% increase.

From the FDA population pharmacokinetic modeling and PK/PD correlations, it was shown that the risk of a renal deterioration doubled for a patient with the upper limit of moderate renal impairment (Clcr = 30 ml/min) compared to a patient with normal creatinine clearance (average 100 ml/min) when 4 mg of Zometa was administered. This risk tripled at a creatinine clearance of 10 ml/min.
Therefore, dose reductions in patients with mild to severe renal impairment should be made, contrary to the applicants conclusion that no action is required because these patients have not actually been studied.

Is dosing adjustment necessary for pediatric patients?

The applicant requested and was granted a pediatric waiver to determine the safety and effectiveness in pediatric patients because the incidence on non-hematological malignancies is low, and those studies are practically difficult to complete.

6. Extrinsic factors

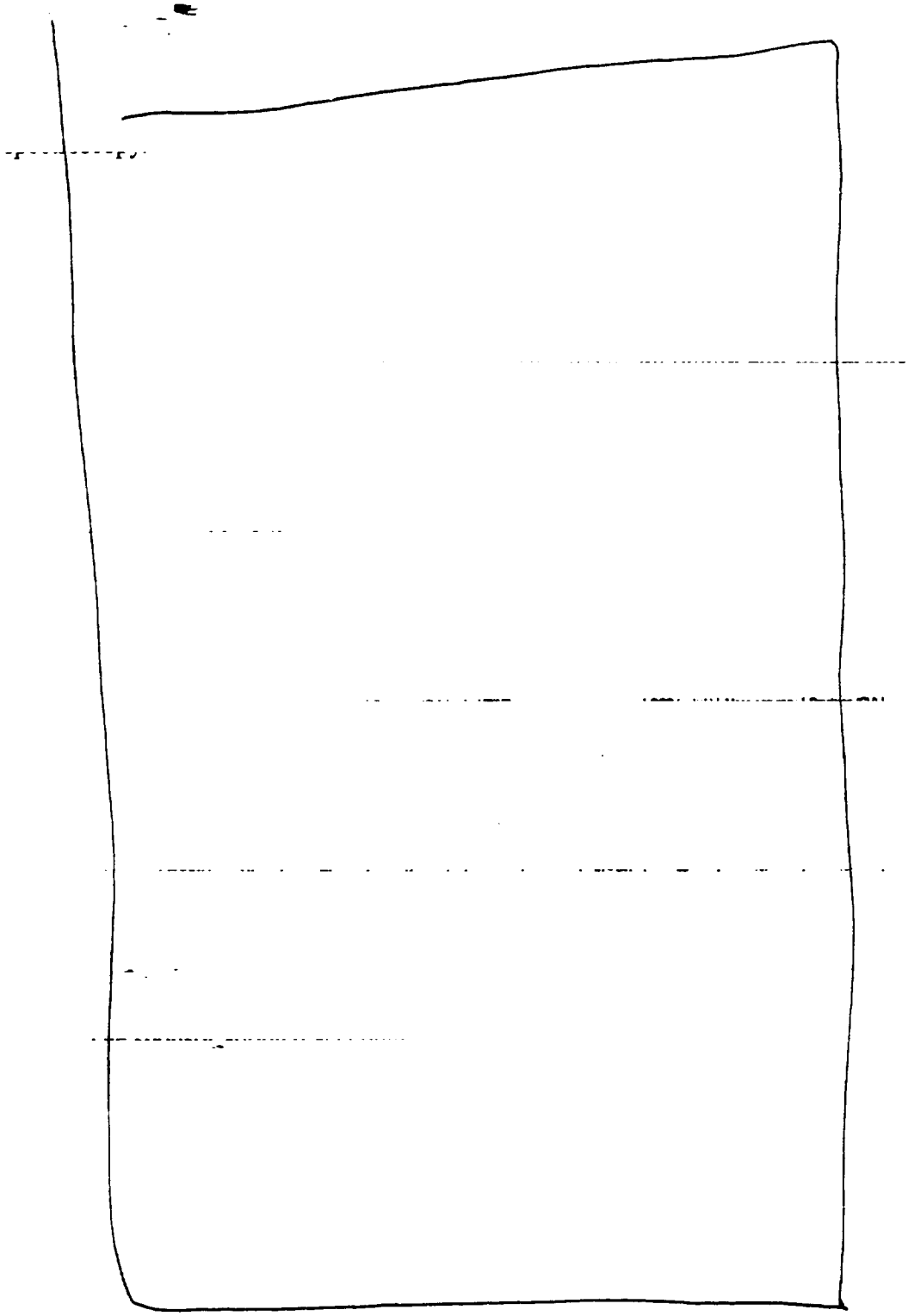
Is there any in vitro evidence to suggest in vivo drug-drug interactions?

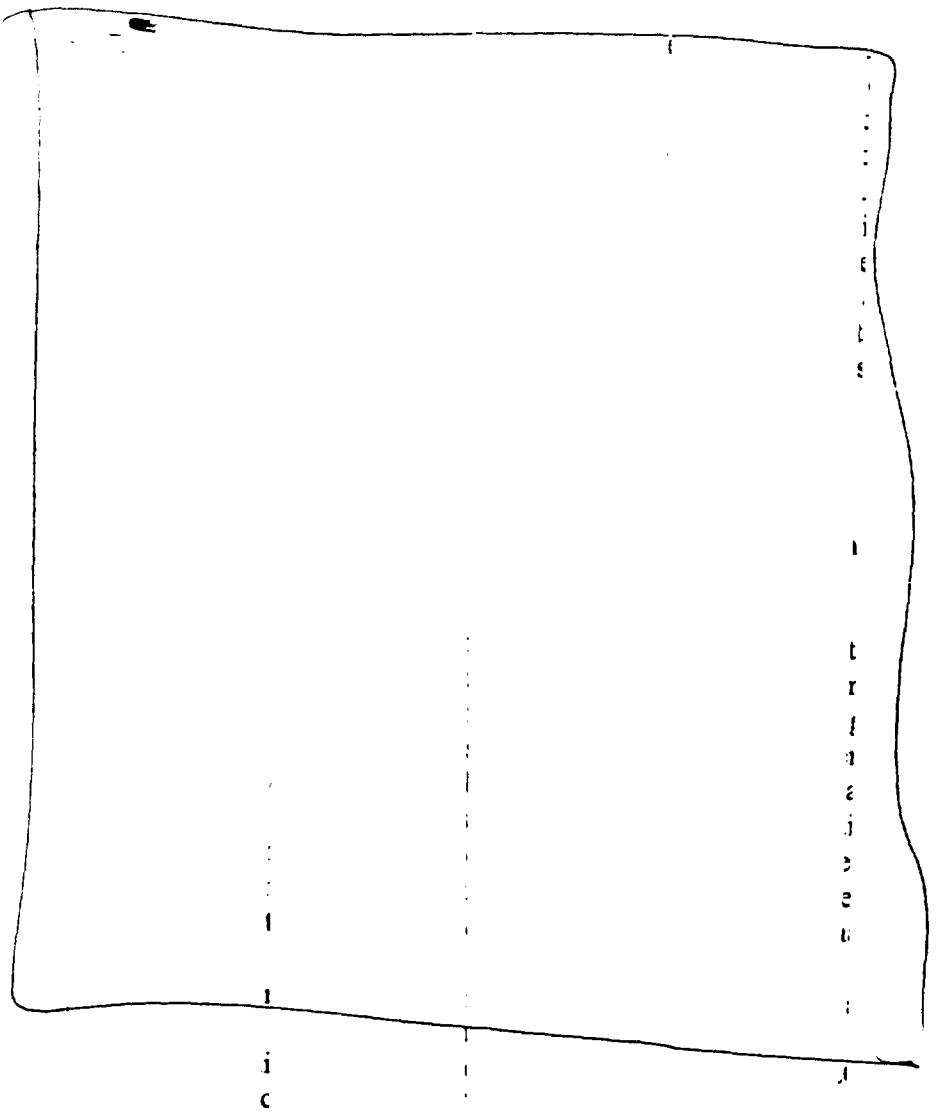
Zometa is not metabolized in vivo and therefore will not be affected by competitive substrates or enzyme inhibition. Furthermore, in vitro P-450 studies demonstrated that Zometa does not inhibit any CYP 450 isozyme, and therefore, is not likely to inhibit any other co-administered drug that is a substrate for this enzyme system. No drug-drug interaction studies have been performed in vivo.

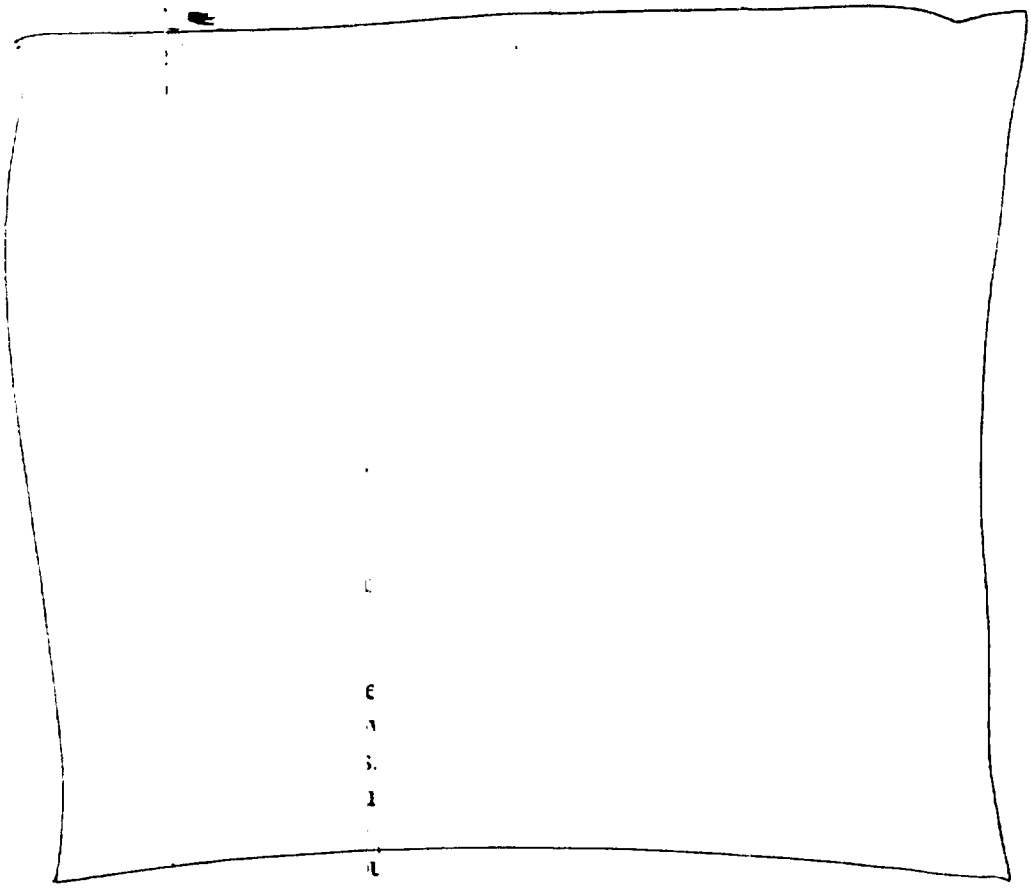
Does the label specify co-administration of other drugs, and have the interaction potential between these drugs been evaluated?

Co-administration of Zometa with other anticancer drugs is not specified in the label, but concomitant administration with other anticancer drugs such as tamoxifen, cyclophosphamide, doxorubicin, paclitaxel, anastrozole and others are reported without interaction.

7. Analytical Methodologies







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Appendix 2: Pharmacometric Report

Clinical Pharmacology and Biopharmaceutics

Pharmacometrics Review

NDA: **21-386**
Volumes: **9-15, item 6**
Compound: **Zometa; zoledronic acid; zoledronate**
Submission Date: **08/21/01**
Sponsor: **Novartis**

Pharmacometrics Reviewer: *Brian Booth*
Pharmacometrics Team Leader: **Joga Gobburu**

Title

Population Pharmacokinetic Analysis and PK/PD Correlations

Objective

1. To establish a pharmacokinetic model for deriving the basic pharmacokinetic parameters, together with covariate effects, for use in the drug labeling, if necessary.

Data

Data were obtained from 64 patients in three trials (Studies 503/503E, J001 and 506/506E) who were treated with either a 5 or 15 minute infusion of Zometa once every four weeks for up to three cycles. Eleven samples were taken over the course of the first day of dosing, and once on days 8, 15 and 29 in the first cycle of therapy. In subsequent cycles of dosing, samples were only taken for the first 24 hours. Doses of Zometa ranged from 2 to 16 mg. The demographic characteristics of the patients are listed in Table 1.

Table 1. Demographic Characteristics of Patients in Studies 503/503E, J001, and 506/506E

Characteristic	Mean	Range
Gender	38 males, 26 females	
Age	60.4 ± 11 yrs	38 to 84 yrs
Race	39 whites, 15 blacks, 9 Asians, 1 "other"	
Body Weight	75.7 ± 15.9 kg	15.9 to 75.7 kg*
Creatinine Clearance (CL_{cr})	84.0 ± 28.9 ml/min	

* Baseline determinations

Methods

The plasma concentration-time course of Zometa was described by a three-compartment model with zero order input and first order elimination from the central compartment, as shown in Figure 1. The modeling in the current submission was updated from the original model, which was submitted and reviewed as NDA 21-223. The original modeling was based on the patients in studies 503 and J001. The patients from the renal impairment study (506/506E) have been included in the current submission. The effects of age, weight, sex, dose and creatinine clearance on total clearance were investigated. The applicant assumed that the random effects were log-normally distributed. Residual error was described by a proportional model, unless the concentration was less than the limit of quantification (LOQ) when it was set as an additive model. The final model chosen by the applicant was based on an examination of residual plots, correlation plots (e.g. predicted concentration vs. observed concentration) and effect on minimum objective function (MOF). Data from all doses were fit simultaneously with NONMEM (ver5.0).

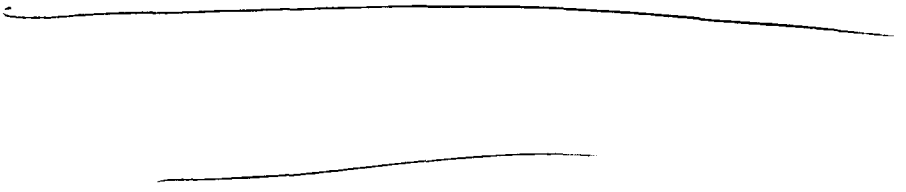


Figure 1. Applicant's Three Compartment Model.

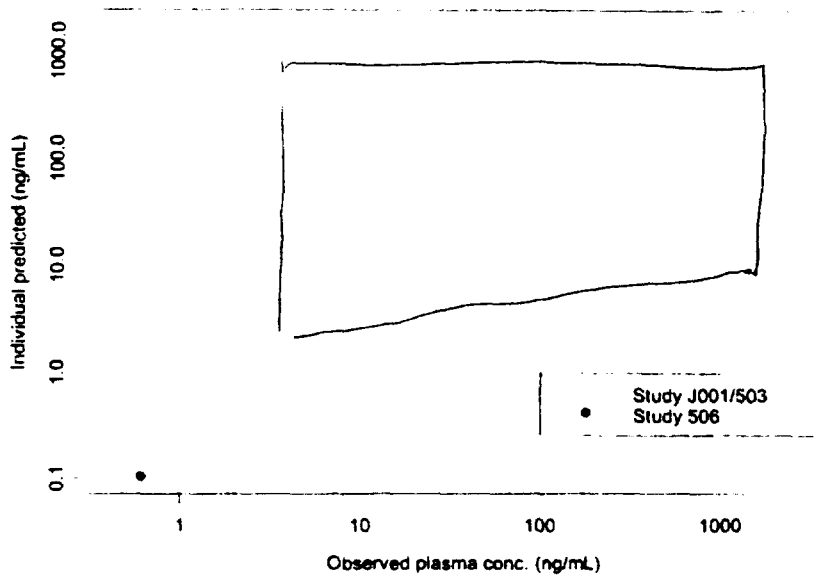
Table 2. Objective Function Values of Various Covariate Models

Number of Covariates	Covariate included CLcr	Gender	Age	Dose	Wt	MOF
0						
1	X					
		X				
			X			
				X		
					X	
2	X	X				
	X		X			
	X			X		
	X				X	
3	X	X	X			
	X	X		X		
	X	X			X	
4	X	X	X	X		
	X	X	X		X	
5	X	X	X	X	X	
4		X	X	X	X	
	X		X	X	X	
	X	X		X	X	
	X	X	X		X	
	X	X	X	X		3.7

* Applicant's final model

In addition, the sponsor plotted the individually-predicted drug concentrations vs the observed concentrations, as well as the weighted residuals (WRES) vs the population predicted concentrations of the final model (see the figure on the next page). The predicted vs observed concentrations appear tightly clustered around the line of identity suggesting that the model satisfactorily fits the data. A similar conclusion is derived from the WRES vs population predicted curve, in which the data appear equally scattered on either side of the line of identity.

Figure 2. Observed vs. Individually Predicted Concentrations based on the Applicant's Final Model. Axes are logarithmic.



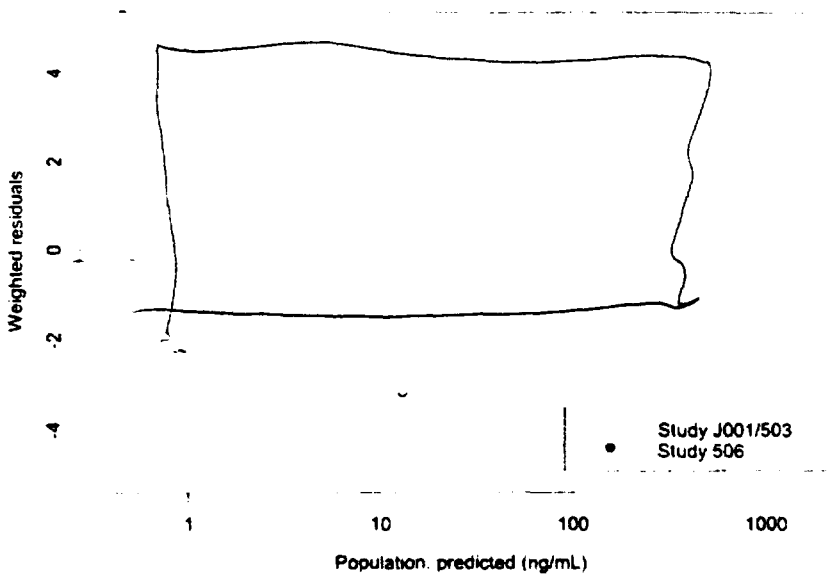


Figure 3. Weighted residuals vs. population predicted concentrations for the applicant's

final model. The x-axis is logarithmic

This final model yielded the following parameter estimates of zometa

Table 2. Final model: MOF value, parameter estimates and their standard errors

MOF Parameter	7223 Estimate	SE	Parameter	Estimate	SE
θ_1 (L/h)	5.04	0.477	θ_2 (Cl_{cr})	0.71	0.125
V_1 (L)	6.48	1.49	θ_3 (Bwt)	-0.121	0.323
Q_2 (L/h)	5.27	0.393	θ_4 (Age)	0.577	0.312
V_2 (L)	480	42.9	θ_5 FEM	0.75	0.0919
Q_3 (L/h)	9.24	2.03	θ_6 Dose	-0.113	0.0836
V_3 (L)	10.3	0.883			
Inter-patient Variability		**%CV**	**Intra-patient Variability**		**%CV**
Var(η_1) CL	0.133	3.1	Var(ε_1)	0.119	1.65
Var(η_2) V_1	0.361	35.8	Var(ε_2)	0.04	
Var(η_3) Q_2	0.0435	1.49			
Cov($\eta_1\eta_2$)	0.0693	2.77			

The applicant made the following conclusions regarding Zometa

- The α-,β-, and γ-half-lives were 0.24, 1.87 and 146 hours.
- Creatinine clearance would affect total Zometa clearance.
- For 40 or 120 kg patients, clearance would be 108% and 94% of a 75 kg patient.
- For 40 or 90 year old patients, clearance would be 79 and 126% of a 60 year old patient
- Plasma clearance of a female is 75% of a male.
- For patients administered 2, 8 or 16 mg, plasma clearance would be 108, 92 or 86%, respectively, of patients administered a 4 mg dose.
- The inter- and intra-subject variability for clearance is 36 and 34%, respectively.

Reviewer Comments on Applicant 's Modeling

The applicant did not provide any reasoning to support these conclusions, other than the model fitting results. Based mechanistic expectations, we disagree with the applicant's conclusions that

- Zometa clearance decreases as the patient's weight increases. Typically, as weight increases, so does clearance, and it is not clear why that paradigm would not be true for Zometa as well.
- Zometa clearance increases as the patient ages. Generally we expect renal clearance of drugs to decrease with age.

- Zometa clearance decreases with increasing dose. The applicant supplied figures in the report to study 503/503E as well as J001 that indicated graphically that Zometa clearance and Cmax were proportional to dose.
- The applicant did not explore relationships between any of the pharmacokinetic parameters, other than systemic clearance, with any covariates. Biology dictates that volume of distribution is dependent upon body size. Therefore, the omission of this relationship from the model requires a strong defense, which the applicant did not make.
- The applicant's error model was designed to switch from a proportional error model to an additive error model if the plasma concentration fell below the limit of quantification (LOQ). An examination of the database indicated that none of the concentrations were below the LOQ. The applicant did not provide any justification for this unconventional residual error model.
- The results reported by the applicant could not be reproduced with the control stream and dataset supplied. This appears to result from differences in the Fortran compiler used by the applicant and the FDA. The FDA uses a Digital Fortran Compiler, version 6.1. The Agency is looking into a means of procuring bench-mark datasets for qualifying the installation and usage of NONMEM. The applicant is encouraged to do the same, as this is mutually beneficial.
- The applicant used first order estimation method in NONMEM (FO). However, the database consisted of full pharmacokinetic profiles (dense data), and conventional wisdom indicates the use of first order conditional estimation (FOCE) with interaction because a proportional residual error model was employed. The applicant did not provide any explanation for using FO instead.

Therefore, although the model supplied by the applicant may be "best" fit by NONMEM, it appears not to be physiologically "best".

Reviewer's Model

The methodology employed by FDA is essentially the same as that of the applicant. The following differences should be noted:

- Zometa is excreted renally. Taking the patient characteristics (Table 1) into consideration, Cl_{cr} should be expected to be an important covariate to describe variability in CL. The other pharmacokinetic parameters (V_1, V_2, V_3, Q_2 and Q_3) were described using allometric principles.
- The applicant's error model was designed to switch from a proportional error model to an additive error model if the plasma concentration fell below the limit of quantification (LOQ An examination of the data base indicated that none of the concentrations were below the LOQ, and the error model was simplified to a combination error model (Y = F*EXP(ERR(1)) + ERR(2)).
- The applicant did not estimate the inter-individual variability (η; IIV) on the V_2, Q_3 and V_3. These were added to the model. In all of the models attempted, IIV on Q_3

resulted in a failure of NONMEM to minimize successfully, and this IIV was not estimated in the final model.

- Database quality was verified by examining the data of several patients in the file, and plotting the data and demographics against the patients' identifiers.
    - The 15-minute sample for subject 2109 (10050 ng/ml) was 3 to 4 times greater than other samples at corresponding timepoints in patients treated with the same dose. This datum was removed from the analysis because it appeared to be either a typographical error or data outlier.
    - The several concentrations of Zometa in patient 1102 were over 100 ng/ml 10 to 24 hours after drug administration. In other patients treated at the same dose (16 mg), these plasma concentrations were less than 1 ng/ml. These data may have been outliers or typographical errors, and they were excluded from the analysis. These data are

Time (hrs)	Concentration (μg/L)
2051.3	198
2053.3	176
2055.3	123
2069.3	59.6

- Clearance was plotted against demographic factors to graphically determine whether any relationship was apparent (See Appendix).

In the final model. Clearance was described as

This model was chosen based on MOF, parameter estimates, diagnostic plots (e.g. predicted vs observed concentration) and physiological soundness. Table 3 indicates the minimum objective functions observed from the various models built to model the Zometa data.

Table 3. MOFs for Zometa Plasma Concentration Models

Model	Minimum Objective Function
Base	
Weight $^{0.75}$-on all CL parameters	
Weight $^{0.75}$-on all CL parameters + AGE	
Weight $^{0.75}$-on all CL parameters + CRTC	
Weight$^{0.75}$-on all CL parameters + RACE	
Weight$^{0.75}$-on all CL parameters + SEX	
Weight $^{0.75}$-on all CL parameters + Dose	
Weight $^{0.75}$- on CL, V_1 only	
Weight $^{0.75}$- on CL only	
Weight –on all parameters	
Weight-on CL, V_1 only	
CRTC on CL only	
CRTC, Weight $^{0.75}$-both on CL only	
CRTC on CL, BWT on V_1, Q_2, V_2, Q_3, V_3	

CRTC on CL, $BWT^{0.75}$ on CL, V_1 Q_2, V_2, Q_3, V_3	
CRTC + Age on CL, BWT on V_1 Q_2, V_2, Q_3, V_3	
CRTC + Race on CL, BWT on V_1 Q_2, V_2, Q_3, V_3	
CRTC + Dose on CL, BWT on V_1 Q_2, V_2, Q_3, V_3	
CRTC + Sex on CL, BWT on V_1 Q_2, V_2, Q_3, V_3	

The final model (FDA Model) describes CL and V as

This model is essentially the same model that was submitted for Zometa in the original NDA (NDA 21-223), and deemed acceptable. The diagnostic plots of predicted concentration vs. observed concentration, and weighted residuals (WRES) vs. time are shown below.

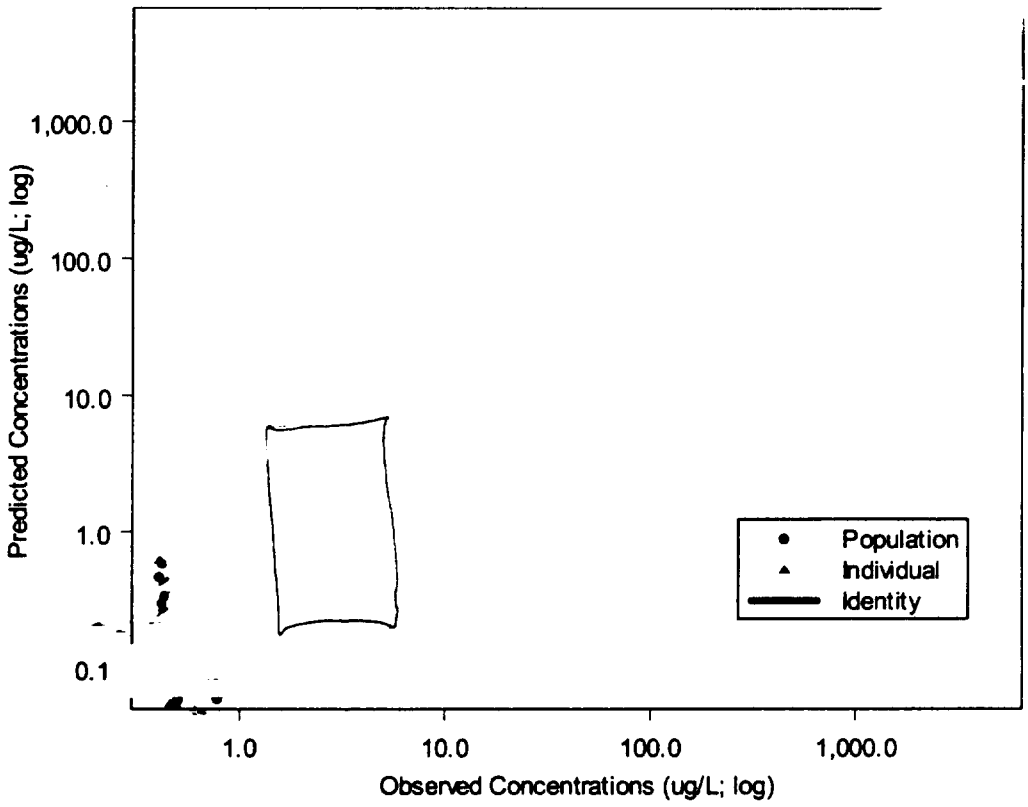


Figure 4: Predicted vs. Observed concentrations with the FDA final model (Model: CRTC (on CL), WT (on V_1), (MOF

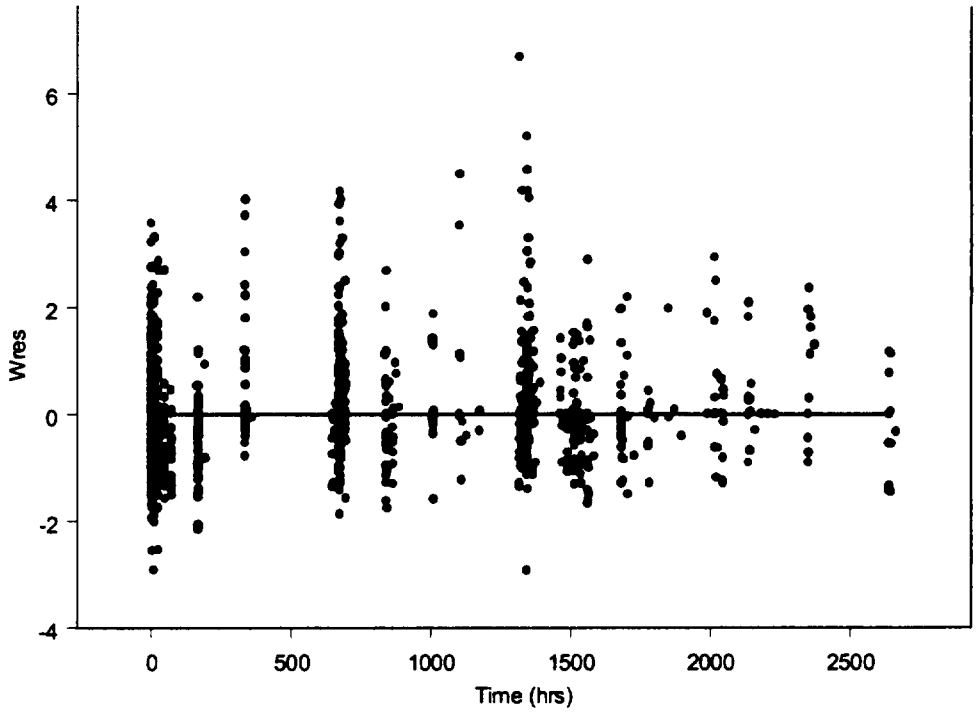


Figure 5: The Weighted residuals (WRES) vs. time for the final FDA model.

Both the individually predicted and population predicted concentrations of Zometa appear to be well described by the model (see Figure 4). The WRES plot indicates a small bias which is not likely important (see Figure 5). At the low concentrations, the model underpredicts the concentrations (see Figure 6). This also observed from the applicant's model. These specific data corresponded predominantly to late observations in cycles 2 or 3 of therapy, and may represent release of drug from bone back into the circulation.

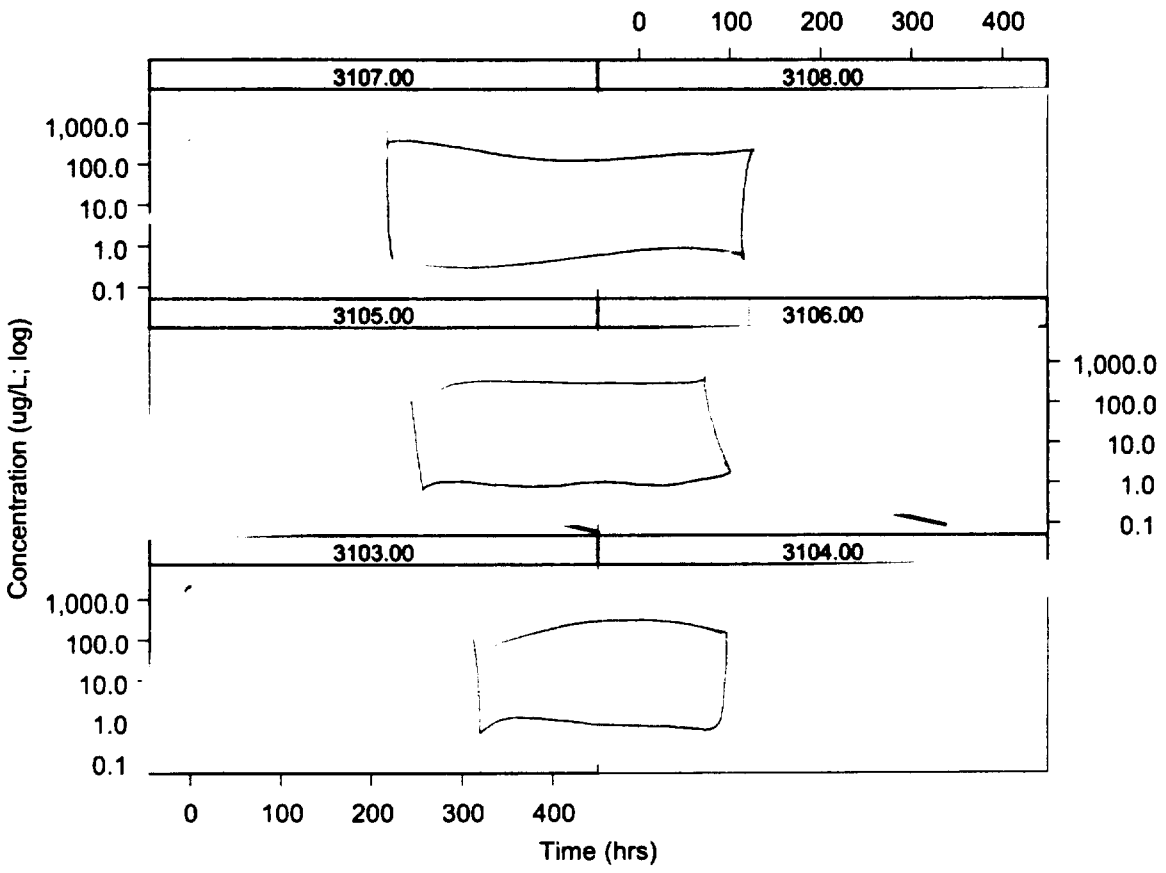


Figure 6. Observed (•), individually predicted (dashed) and population predicted (solid) concentrations based on the FDA final model.

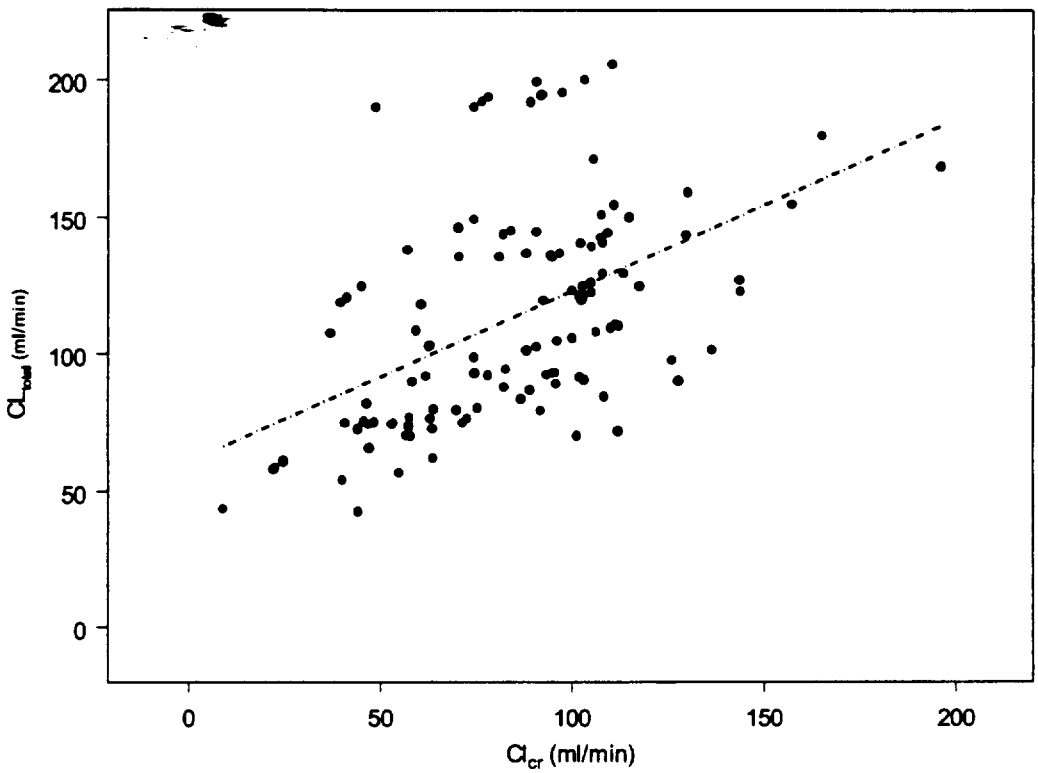


Figure 7. Total Zometa clearance vs. creatinine clearance based on the FDA model

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A comparison of the pharmacokinetic parameter estimates among the FDA amodels and the applicant's model is made in Table 4.

Table 4. Zometa Population Pharmacokinetic Parameter Estimates by FDA and Applicant Models

Parameter	FDA Base Model	FDA Final Model	Applicant's Model
MOF	—	—	—
CL	6.11 (L/hr/70 Kg)	6.53 (L/hr/70 Kg/90 ml/min)	5.04 (L/hr/90ml/min/75 Kg/60 yrs/mg/4)
V (V_1)	8.18 (L/70 kg)	7.86 (L/70 kg)	6.48 (L)
Q_2	3.61 (L/hr/70 Kg)	3.43 (L/hr/70 Kg/90 ml/min)	5.27 (L/hr/90ml/min/75 Kg/60 yrs/mg/4)
V_2	170 (L/70 kg)	173 (L/70 kg)	480 (L)
Q_3	8.64 (L/hr/70 Kg)	7.86 (L/hr/70 Kg/90 ml/min)	9.24 (L/hr/90ml/min/75 Kg/60 yrs/mg/4)
V_3	9.21 (L/70 kg)	8.43 (L/70 kg)	10.3 (L)
CRTC (CL_{cr})	ND	0.387	NR
(CL)-%CV	38	31	13
(V_1)-%CV	35	26	36
(Q_2)-%CV	28	24	4.0
(V_2)-%CV	9.0	17	ND
(V_3)-%CV	19	17	ND
ERR-%CV	29	29	119
ERR (μg/L)	0.34	0.32	0.04

ND; not done. NR not reported.

The final FDA model shows that CL is dependent upon CL_{cr} alone, which is consistent with the known route of drug elimination. This relationship is depicted in Figure 7. Volume of distribution is dependent on weight, which is consistent with conventional physiological knowledge. Although the "best" NONMEM FDA model also included a gender term on CL estimation, realistically this is probably not well-founded because gender is already incorporated into the creatinine clearance calculation (Cockroft-Gault formula).

The estimates of the α-$t_{1/2}$, β-$t_{1/2}$ and γ-$t_{1/2}$ of Zometa have not been calculated by FDA. However, the similarity in the parameter estimates of Zometa between the applicant and the FDA models suggest that the differences would be acceptably small (approximately 15%), and the applicant's estimates in the labeling are acceptable.

Model Qualification

In order to ascertain the ability of the PK model to predict zometa concentrations reasonably, simplified posterior predictive check (sPPC) was applied. According to this

Exposure - Response

Methods

Zometa (Zoledronic acid) is a bisphosphonate and is a potent inhibitor of bone resorption. Bisphosphonates bind to bone surfaces in the areas of high bone turnover and inhibit bone resorption by osteoclasts. Although the precise mechanism is not fully understood, bisphosphonates also inhibit bone resorption at the cellular level, predominantly by inhibiting osteoclast function. Several pharmacodynamic (effectiveness and safety) measures of pharmacological and clinical end points of zometa were considered. Attempts were made to correlate Zometa exposure on the bone resorption biomarkers (PYD, DEO, CAL, BAP, HYD, NTX and CTX). In addition, correlations between Zometa exposure and skeletal related events (SREs) the efficacy endpoint, and renal events. The toxicity endpoints were attempted.

Data

Pivotal efficacy data in the treatment of bone metastases are provided by 3 large double-blinded studies (039, 010 and 011), two of which (039 and 011) were placebo-controlled and the other active controlled (010). In the original pivotal study protocols, patients were to be randomized to either 4 or 8 mg of Zometa, administered as 5-minute iv infusions. Following a protocol amendment, due to safety concerns, the infusion time was increased to 15 minutes and the volume increased from 50 to 100 mL. A second amendment led to a dose reduction from 8 mg to 4 mg.

Study 039 included 643 prostrate cancer patients with metastatic bone lesions. In this trial, 214 patients received 4 mg of Zometa, 221 received 8/4 mg of Zometa and 208 patients received placebo.

Study 011 included 773 cancer (any type) patients with metastases other than breast cancer, multiple myeloma or prostrate cancer. In this trial, 257 patients received 4 mg of Zometa, 266 received 8/4 mg of Zometa and 250 patients received placebo.

Study 010 included 1648 patients with metastatic breast cancer or multiple myeloma. In this trial, 564 patients received 4 mg of Zometa, 526 received 8/4 mg of Zometa and 558 received Aredia (pamidronate), the active control.

Exposure

The pivotal trials did not include any Zometa plasma concentration measurements. However, the population pharmacokinetic (pop PK) model from the preceding section, based on data collected in studies J001, 503 and 506 predicts the plasma concentration very well. Hence, the pop PK model and its parameters were used to predict the typical AUC values given the dosing regimen in the clinical studies. The AUC represents the average overall exposure in these patients.

Biomarkers

In conditions of high bone turnover, such as in cancer patients with metastatic bone disease, increased serum levels and urinary excretion of the bone resorption markers pyridinoline and deoxypyridinoline, and their associated N-telopeptides are observed. These may serve as significant predictors of the presence of bone metastases, although these biomarkers have not been validated as disease prognostic factors or as surrogates for Zometa action.

Effectiveness Endpoint

The clinical expectation is that the drug delays or avoids the occurrence of any skeletal related events like fractures in patients with bone metastasis. The primary clinical endpoint was the proportion of patients having at least one skeletal related event (SRE). SREs included:

- Radiation therapy to bone
- Surgery to bone
- Pathologic bone fractures
- Spinal cord compression
- Change in antineoplastic therapy
- Tumor-induced hypercalcemia of malignancy (TIH)

TIH was specifically excluded as an endpoint by FDA because it reflects a different disease. Each SRE item had equal weight. Of the SREs, the time to the occurrence of the first SRE was of interest and was described using Cox proportional hazards models.

Safety Endpoint

The safety endpoint of primary concern was that of the renal function deterioration, which was defined as an increase of 0.5 mg/dL of creatinine from baseline, where the upper level of a normal creatinine baseline was defined as 1.4 mg/dL. The time to start of the renal function deterioration was considered for the analysis, which was described using Cox proportional hazards models.

All analyses were conducted using SAS (6.12).

Results and Discussion

Summary statistics of some relevant prognostic variables is presented in Table 5 below.

Table 5. Summary statistics of AUC and baseline creatinine clearance, by treatment group.

Variable	Mean	Std Dev	Minimum	Maximum
Control Group				
AUC, mg.h/L	0	0	0	0
CLcr, mL/min	75.22	26.33	19.58	242.46
4 mg Group				
AUC, mg.h/L	0.68	0.09	0.44	1.31
CLcr, mL/min	73.39	24.65	12.63	209.49
8 mg Group				
AUC, mg.h/L	1.36	0.20	0.86	2.27
CLcr, mL/min	75.12	27.61	18.36	224.40

Biomarkers

Initially, biomarker data from studies J001, 503 and 506 were considered for modeling. Based on the mechanism of action of the drug, attempts were made to describe the time course of effect of Zometa on the biomarkers using indirect response models. The first biomarker observation collected during these trials was at 24 h after the dosing. Maximal change in the biomarker occurred by 24 h. Further, no samples after the last dose were collected. Therefore, it was not possible to model these data. Nevertheless, a visual inspection of the time courses of biomarker levels indicated a decrease from baseline that was similar in extent at 4 mg and 8 mg doses of Zometa for each of the biomarkers. A typical example of this drug effect is shown for deoxypyridinoline (Figure 9).

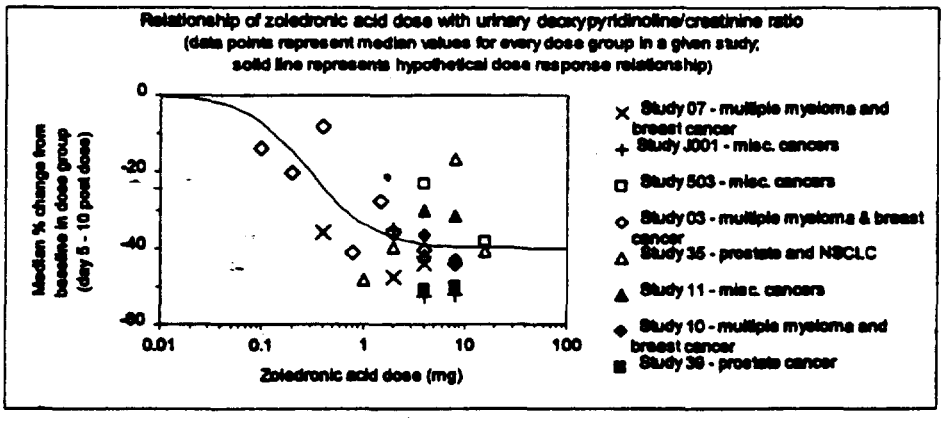


Figure 9. Dose effect of Zometa on DEO levels from Applicant NDA Summary

Analysis of the biomarker data from the pivotal trials yielded similar results. Treatment (i.e., placebo versus drug) and not Zometa dose *per se*, was found to be correlated with

the changes in biomarkers, when data from all the 3 trials were combined. As might be expected, for study 010, where the control group received another bisphosphonate, no significant difference was found between the treatment and control group (p=0.88). A separate analysis of studies 011 (p=0.08) and 039 (p<0.001) indicated Zometa treatment was correlated with biomarker suppression.

Effectiveness

Analysis of the pivotal trial data was performed both separately (by trial) as well as combined. Earlier discussions with clinical and statistical reviewers indicated a preference towards separate analyses and these results will be presented in this review. Various prognostic factors such as previous episodes of SREs (yes or no), age, body weight, sex, treatment (control or Zometa) and AUC were explored. Figure 10 and TABLE 6 shows the effect of previous SRE and Zometa treatment (regardless of dose) on hazard ratio for an SRE.

Table 6. Parameter estimates of the proportional hazard model for the time to first SRE event data, with respect to exposure.

Study	Total Observations	Parameter	Estimate	P-value	Hazard Ratio
039	**641**	**Treatment**	**-0.24 ± 0.13**	**0.0700**	**0.79**
		Previous SREs	**0.39 ± 0.13**	**0.0025**	**1.48**
011	**768**	**Treatment**	**-0.30 ± 0.12**	**0.0110**	**0.74**
		Previous SREs	**0.31 ± 0.13**	**0.0170**	**1.37**
010	**1643**	**Treatment**	**-0.04 ± 0.08**	**0.6000**	**0.96**
		Previous SREs	**0.82 ± 0.09**	**<0.0001**	**2.27**

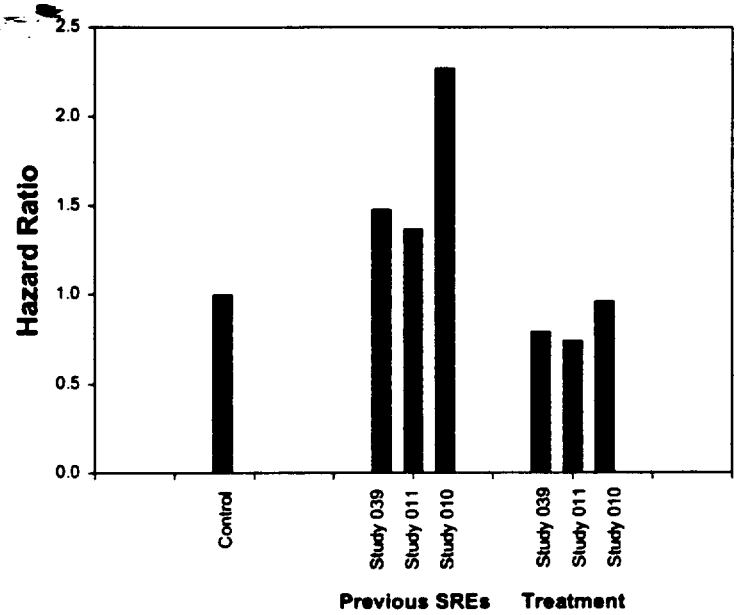


Figure 10. Effect of Previous SRE or Zometa treatment on Hazard ratio.

In TABLE 6 and figure 9 above, patients with a previous SRE had a greater likelihood of a subsequent SRE than patients who had not experienced a prior SRE. Furthermore, treatment with Zometa decreased the hazard ratio, except for study 010, which suggested that treatment is an important covariate (see Figure 11).

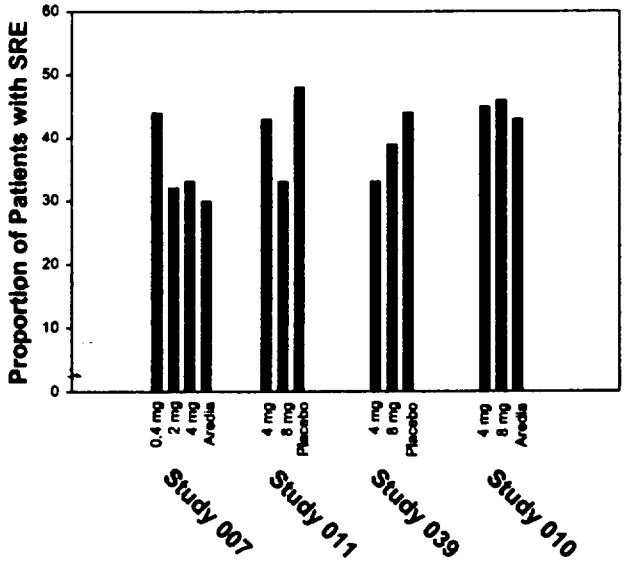
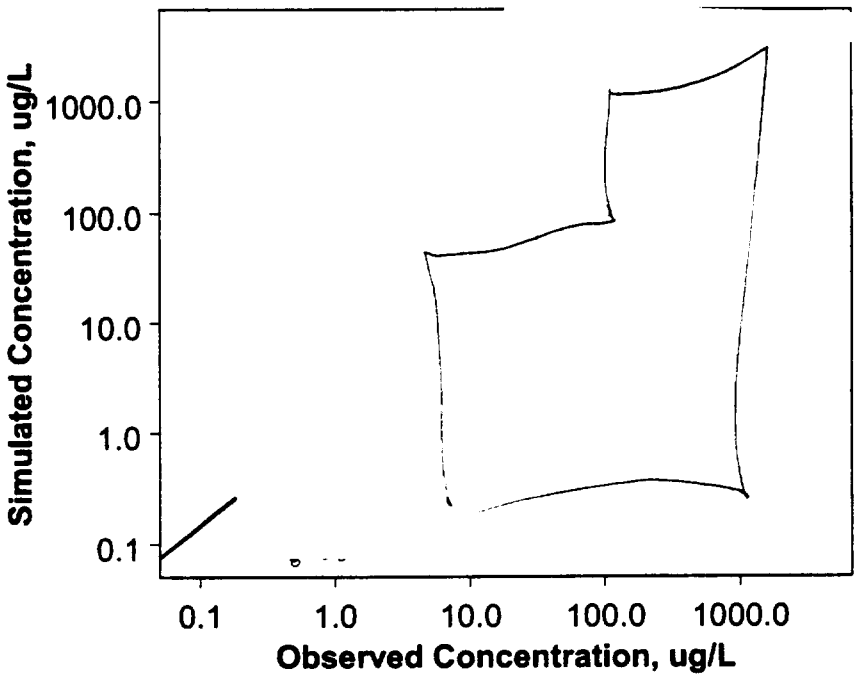


Figure 11. The Effect of Zometa dose on SREs

method the final **population** parameter estimates were employed to simulate several replications of the concentration profiles of zometa according to the trial designs of J001, 503 and 506. Simulated versus observed concentrations graphs were congruent based on visual inspection. Results from one such replication are presented below in Figure XX. Thus it can be said that the final PK model qualified to predict zometa concentrations reliably.

Figure 8. Observed and simulated (based on population PK estimates) Zometa concentrations using the final PK model.



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In all studies neither Zometa dose nor AUC influenced the SREs (see Figure 10). It may beargued that the plasma AUC, which was used in this analysis, is the incorrect covariate for correlations because the mechanism of action is due to drug activity at the bone. However, it should be noted that the linear, 3-compartment PK model ensures that the AUC of Zometa in plasma and bone are in a constant proportion. Therefore, the plasma AUC is a reasonable surrogate for bone AUC. The lack of effect of dose or AUC suggests that the drug effect might be saturated at 4 mg. Regardless, Zometa was effective as the hazard ratio for the treatment is estimated to be about 0.75, which suggests that the risk of an SRE is 25% less if treated with Zometa than if left untreated.

Unequivocally in all the studies previous history of SREs is strong prognostic factor. Patients who have had a previous SRE event have about 50% higher risk of having an SRE, for studies 039 and 011. In study 010, this risk seems to be about 130%. The reason why the risk probabilities are different, for same prognostic factor, between 010 and 039, 011 is not obvious. Study 011 and 039 included predominantly males (70%, 100%) and study 010 included predominantly females (83%) whose mean age is about 60 years. It is well known that post-menopausal women, owing to hormonal deficiency, are more prone to SREs.

Further analyses were conducted to explore if any of the biomarkers could be important prognostic factors instead of exposure. It is reasonably well-known that bisphosphonates inhibit bone resorption. Bone resorption leads to elevated levels of pyridinoline in the systemic circulation and it is expected that a reduction of the resorption suppresses these circulating levels. As shown in Table 7, pyridinoline change appears to be correlated with the SRE hazard rate. But the results seem to be inconsistent across the studies. In study 011, both previous SREs and pyridinoline did not affect SREs. In the previous analysis where treatment was used as a prognostic variable, previous SREs were found to be a significant covariate. The reason for such a discrepancy could be due to the number of observations in these analyses, because pyridinoline levels were reported for every patient (768 vs. 431). If results from study 011 were ignored, then both studies 010 and 039 indicate that pyridinoline change is indeed a prognostic factor for SREs. Hence the higher the pyridinoline levels the higher the SREs hazard. The parameter estimate for this effect is in the expected direction. The hazard ratio for the pyridinoline is about 1.003, implying that unit change in pyridinoline level leads to 0.3% increase in the probability of an SRE. The range of pyridinoline change is between –95% to 1300%. The 75th and 25th quantiles are 29% and –33%. A patient at the 75th has about 18% more probability of an SRE when compared to a patient at the 25th quantile.

Table #7. Parameter estimates of the proportional hazard model for the time to first SRE event data, with respect to biomarkers.

Study	Total Observations	Parameter	Estimate (± SE)	P-value	Hazard Ratio
039	**490**	**Pyridinoline**	**0.003 ± 0.0006**	**<0.0001**	**1.003**
		Previous SREs	**0.33 ± 0.14**	**0.016**	**1.40**
011	**431**	**Pyridinoline**	**0.0009 ± 0.001**	**0.39**	**1.001**
		Previous	**0.14 ± 0.17**	**0.39**	**1.15**

		SREs			
010	**985**	**Pyridinoline**	**0.002 ± 0.0005**	**0.0001**	**1.002**
		Previous SREs	**0.77 ± 0.11**	**<0.0001**	**2.16**

Safety

Time to onset of renal function deterioration was found to be correlated with each of the exposure measures – Cmax, AUC, Zometa dose and treatment. Based on the –2 log-likelihood estimate, the proportional hazard model which had AUC (5344) offered better fit over Cmax (5361), dose (5466) and treatment (5484). All of the aforementioned models contain identical number of parameters. A change of 10.83 for one degree of freedom corresponds to a p-value of 0.001. Therefore, it is hypothesized that cumulative exposure, rather than acute increases in concentration of circulating Zometa might result in a gradual deterioration of the kidney function. A separate analysis of the 3 studies consistently indicated that AUC and baseline creatinine clearance (Base CLcr) are important predictors of renal deterioration, which is not surprising given the relationship between CLcr and Zometa CL_{total} (see Figure 12).

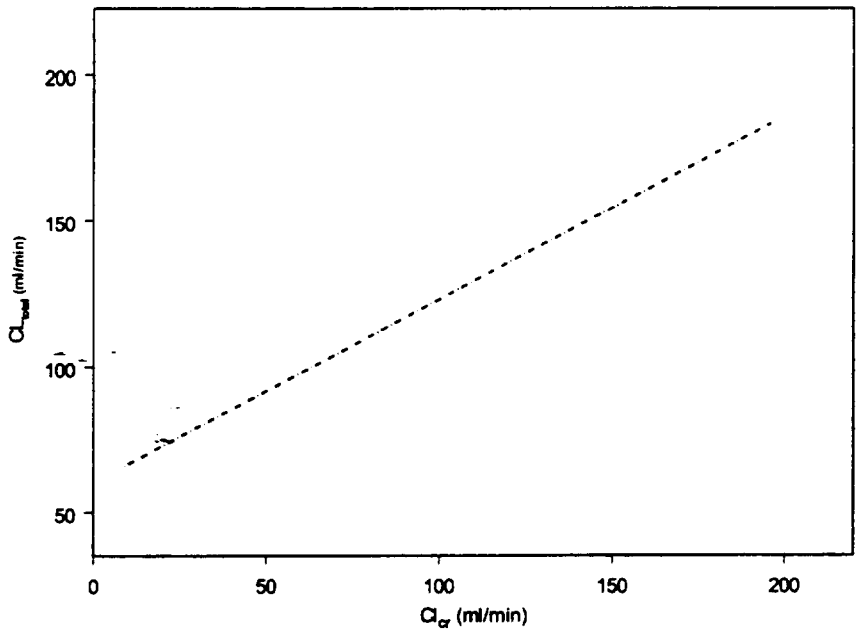

Figure 12. Zometa systemic clearance (CL_{total}) vs creatinine clearance (CL_{cr})

Table 8 shows that a unit increase in AUC leads to doubling of the probability of renal function deterioration. From Figure 13, it can be seen that if the patient is dosed with 4

mg of Zometa, the risk of renal deterioration increases two-fold at the upper limit of severe renal impairment compared to normal Clcr, and three-fold at a Clcr of 10 ml/min. It should be noted that the Zometa AUC in the clinical studies ranged from 0 (control) to 2.3 mg·h/L in patients, indicating that some patients were at an elevated risk of renal deterioration. The modeling also shows that unit increase in Base CLcr results in 1% increase in the hazard. Base CLcr ranges from [redacted] The p-values indicate a very strong relationship.

Table 8. Parameter estimates of the proportional hazard model for the time to renal function deterioration, for combined data from the 3 studies.

Study	Total Observations	Parameter	Estimate (± SE)	P-value	Hazard Ratio
ALL	**2809**	**AUC**	**0.70 ± 0.09**	**<0.0001**	**2.02**
		Base CLcr	**-0.012 ± 0.002**	**<0.0001**	**0.99**

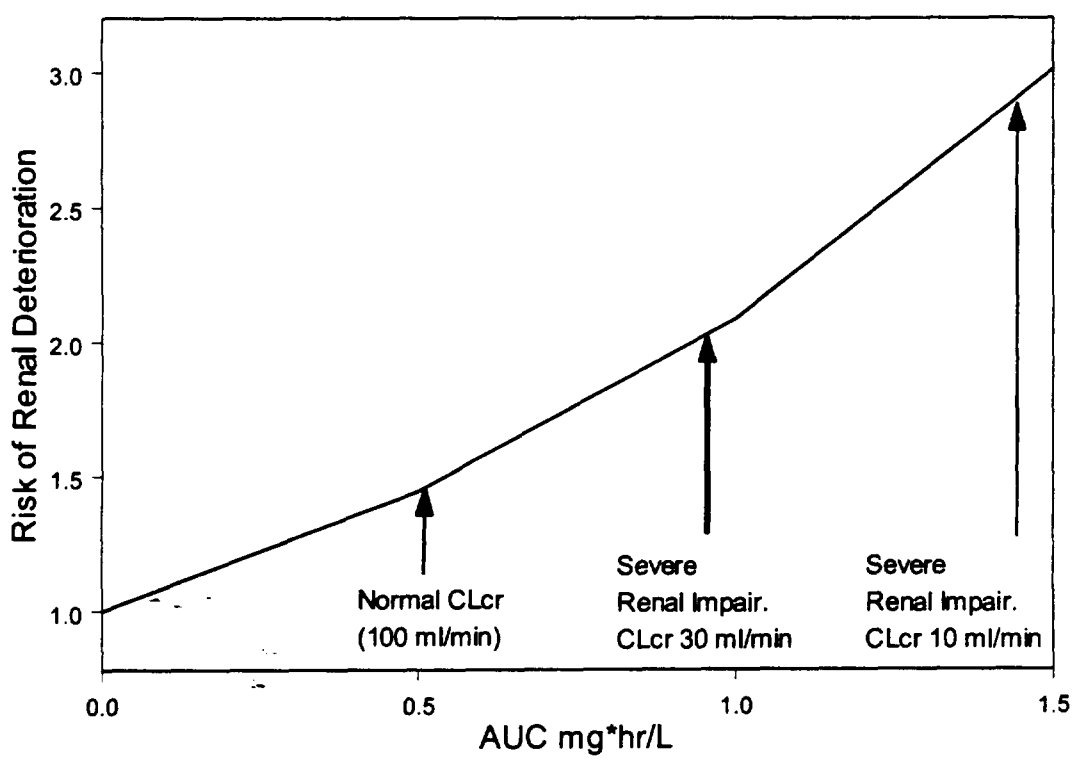

Figure 13. The risk of renal deterioration vs. Zometa AUC

The probability of the renal function deterioration was not higher in the pre- versus post-15 min infusion amendment group. This result also suggests that renal deterioration is

due to cumulative exposure. Further support is provided by an analysis which was repeated with data collected for the first 3 months (before decreasing 8 mg to 4 mg). The probability of renal function deterioration was affected by Base CLcr only and not by AUC. Analysis of the data up to 4 and 6 months, respectively, demonstrated that both AUC and CLcr are important prognostic variables. The relationship became stronger, as indicated by the p-value, with inclusion of data for longer duration. This rudimentary characterization of the time course of toxicity suggests that about 4 months of exposure leads to significant renal function deterioration. Of course, it should be noted that time and overall cumulative exposure (not average) are confounding variables.

Further analysis was performed to test internal consistency of the results. Excluding either the 8/4 or 4 mg dose group (one at a time) did not affect the conclusion that AUC is an important covariate. This inference demonstrates that even within each dose group, primarily due to the varied Base CLcr, the relationship between AUC and renal toxicity is identifiable. Hence it is not enough to simply avoid 8 mg; a more rational approach to Zometa dosing is necessary.

Exposure – Response: Overall Conclusions

1. Zometa treatment affects the measured biomarkers for bone resorption. The time course of the effect could not be determined due lack of appropriate data.
2. Zometa treatment affects the skeletal related event rate. Patients with previous SREs have higher probability of another SRE (50% in studies 039, 011, up to 150% in study 010).
3. Average plasma Zometa AUC and baseline creatinine clearance are well correlated with the renal function deterioration.
4. Although the probability of SREs is not dose-dependent, the question that remains unanswered is how frequently should zometa be administered? The current recommendation is to administer zometa every 3 weeks, for which no rationale was provided. It might be practically impossible to obtain an answer to this very important question with any of the submitted clinical trials. It is unfortunate that the sponsor missed a good opportunity to tease out the offset of the response based on biomaker response.
5. Based on the dosage of 4 mg indicated in the labeling, the following information and dosing recommendations should be included in the label to reduce the risk of renal deterioration. The AUC was determined for 4 mg administered to patients with normal renal function (>80 ml/min). The recommended doses in patients with reduced renal function are normalized to the Zometa AUC observed in normal renal function.

Table 9. Suggested Zometa Dosing Recommendations for Renal Impairment

Renal Function	Cl_{cr} (ml/min)	CL_{total} (L/hr)	Target AUC (mg*hr/L)	Recommended Dose (mg)

Normal	100	6.8	0.588	4.0
Moderate Impairment	50	5.2	0.588	3.0
Severe Impairment	30	4.3	0.588	2.5
Severe Impairment	10	2.8	0.588	1.6

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Exposure –Response: Applicant Rebuttal

An abridged version of the FDA PK/PD modeling report was provided to the applicant for comment. The Applicant's response is appended, and the FDA evaluation of those remarks is detailed in this section.

The applicant expressed interest in the FDA population PK/PD modeling of Zometa, but urged a cautious interpretation of the results. The central argument against the population PK/PD model for Zometa is that a poor understanding of the action of Zometa on the bone. It is clear to FDA and to the Applicant that Zometa's interaction with bone involves binding and inhibition of the osteoclasts, which are believed to mediate bone resorption, and some other binding that can be termed nonspecific. This nonspecific binding could be a collection of interactions or processes that are not yet understood. Neither the applicant nor the FDA was able to model these phenomena. Both FDA and the Applicant used an open three-compartment mammalian model to describe the timecourse of Zometa plasma concentrations. The "deep" compartment ostensibly describes the kinetics of Zometa binding and release from all of the bone tissue. The Applicant indicated that the model was limited because it was incapable of describing all the processes, such as uptake, osteoclast inhibition, and Zometa release, involved in this physiological compartment. The FDA agrees with this limitation of the model. Nonlinear processes could affect the kinetics of Zometa in the bone and the circulation, but the Applicant demonstrated that C_{max} and $AUC_{0\text{-}24h}$ were linear from 2 to 16 mg of Zometa. From this perspective, the usual assumption that plasma concentrations reflect changes of the same magnitude in bone is not unreasonable. Clearly though, the model is insufficient to describe the events involved in the action of Zometa at the bone. In other words, it is not possible to adequately describe the **efficacy** of Zometa in terms of biomarker suppression, SREs or time to SREs. The failure of the FDA population PK/PD modeling to reveal an interaction between Zometa dose, AUC or C_{max} and efficacy endpoints (SREs, time to SREs) could possibly be explained by this model limitation.

The Applicant also indicated that Zometa population PK/PD modeling of **safety** parameters, specifically renal deterioration, is also unreliable, because of the inability to model drug action at the level of the bone. The FDA disagrees with the Applicant's interpretation for the following reasons

1. It can be assumed that the Zometa molecules bound to bone can not directly affect the kidney, and cause renal deterioration.
2. Secondly, Zometa, like other bisphosphonates, is avidly bound to the bone. The release of the Zometa from the bone back into the circulation is extremely slow. The estimated half-life total elimination of Zometa and other bisphosphonates is estimated to be months to years. Measurements of Zometa in plasma 24 hours post administration are generally at the limit of quantification. Therefore, it can be assumed that the release of Zometa from bone is insignificant and does not contribute significantly to plasma concentrations or renal deterioration.
3. Therefore, the plasma exposure of the drug is the only apparent source of drug available to mediate renal deterioration, and the shortcomings in modeling bone-Zometa processes is not relevant to assessing **Zometa's saftey.**

4. The population PK model for Zometa is based on plasma concentrations of the drug. Both the model proposed by the Applicant and the model proposed by the FDA accurately characterize the systemic concentrations of Zometa. In the case of the FDA model, which depends only on creatinine clearance, accurate predictions of the Zometa exposure can be made if dose and creatinine clearance are known.
5. The Cox regression analysis of Zometa plasma $AUC_{0\text{-}24h}$ vs. renal deterioration was highly significant, ($P<0.0001$; HR 2.02).

Therefore, FDA concludes that the population PK modeling and the correlation with renal deterioration that was determined for Zometa based on plasma $AUC_{0\text{-}24h}$ are valid, irrespective of its inability to distinguish between osteoclast binding and nonspecific binding in the bone.

I. Issues of Disagreement Between FDA and the Applicant Regarding the PopulationPK/PD Modeling of Zometa

In this section is a list of arguments made by the Applicant that critiques of the FDA PK/PD modeling of Zometa. The FDA disagrees with these arguments. Each of the arguments in this section relates to limitations of Zometa bone processes. The FDA responded to all of these arguments in the section above, and no individual explanation is supplied for each individual point raised here.

1. Novartis General Comment:
Novartis agrees with FDA's assessment that "...although the model supplied by the applicant may be 'best' fit by NONMEM, it appears not to be physiologically 'best'." In fact, the 3-compartment open pharmacokinetic model used for the data analyses is an imperfect representation of the physiological processes involved in bisphosphonate disposition, given that after an intravenous dose approximately 60% of drug is sequestered in bone and not released over the model timescale (e.g. >5 terminal half-lives). In a physiological sense bone is essentially a storage organ for bisphosphonates, and the deep but reversible compartment used in the pharmacokinetic model is an imperfect description of skeletal uptake of drug. This becomes apparent when simultaneously fitting the zoledronic acid urine and plasma concentration data, which necessitates accounting for an approximately 60% "loss" of drug over the timescale of the 3-compartment model parameters. Using higher order compartment models may in principle better express the prolonged slow release of bisphosphonate from bone, but the practical difficulties of assessing a true terminal elimination phase, with a half-life likely to be substantially greater than 6 months, negates such models' value. It is also possible that the linear PK processes, where rate is proportional to concentration, and which are operative in the earlier time frame post bisphosphonate administration, may not apply to the release of drug from bone.

Novartis' attempts to use physiologically based PK modeling to address the complicated interplay of different PK processes have not been uniformly successful to date. The effect of metastatic disease processes on bisphosphonate pharmacokinetics is not known, but may be speculated to result in greater rate and extent of uptake of drug by hydroxyapatite

at exposed, active sites of bone resorption. A therapeutic effect by zoledronic acid on the metastatic oncolytic processes would in turn affect its disposition. While we believe that the 3-compartment open model chosen for the population pharmacokinetic analysis should be adequate to provide an overall, useful assessment of how demographic and other covariates affect drug disposition, the modeling results with zoledronic acid must be qualified in light of the characteristic pharmacokinetic and physiologic processes of bisphosphonates.

2. Limitations of analytical sensitivity prevented Novartis from obtaining a greater body of zoledronic acid concentration data at time points late post dose, which could have helped to refine the models. In addition, our attempts, in study 506, to use low-level radioactive (^{14}C) dose of zoledronic acid to achieve a better characterization of the late elimination phases, unfortunately were unsuccessful, due to the interference of natural abundance ^{14}C in the environment. Therefore, although good model fits were obtained, application of the model to the clinical safety and efficacy data to examine exposure – response must take into consideration a potential lack of robustness of the model.

3. FDA comment:
The pivotal trials did not include any Zometa plasma concentration measurements. However, the population pharmacokinetic (pop PK) model from the preceding section, based on data collected in studies J001, 503, and 506 predicts the plasma concentration very well. Hence, the pop PK model and its parameters were used to predict the typical AUC values given the dosing regimen in the clinical studies. The AUC represents the average overall exposure in these patients.

Novartis response:
The application of the model to the clinical studies represents an interesting and potentially valuable approach. However, based on the above concern of model robustness, any conclusions of this exercise should be viewed with caution.

4. FDA comment:
...it is hypothesized that cumulative exposure, rather than acute increases in concentration of circulating Zometa might result in a gradual deterioration of the kidney function. A separate analysis of the 3 studies consistently indicated that AUC and baseline creatinine clearance (Base CLcr) are important predictors of renal deterioration, which is not surprising given the relationship between CLcr and Zometa CL_{total} (see Figure 12).

Novartis response:
The hypothesis of gradual deterioration in kidney function is interesting and deserves further study. As shown in FDA's Figure 12, total clearance substantially exceeds creatinine clearance, which is consistent with the previously discussed total clearance representing a composite of renal clearance and uptake by bone. Therefore, establishing relationships of plasma AUC with safety with inferences regarding risk of renal dysfunction may be problematic without simultaneous consideration of other factors affecting total body clearance.

II. Issues of Mutual Agreement

In this section, the responses by the applicant to the FDA population PK/PD modeling of Zometa are issues that FDA believes are clarifications, issues that both groups agree with, or are minor disagreements of scientific opinion that do not affect the interpretation of the population PK/PD modeling. Issues that FDA disagrees with are explained, but items without any notation should be interpreted to mean agreement between both groups.

1. Novartis response to FDA's comments on applicant's model analysis

1. FDA comments on model specific issues

1. FDA comment:

The standard errors on the θ's for body weight, age and dose were at least 80% (and as high as 300%) and the reliability of using these characteristics as covariates on clearance estimation is questionable.

Novartis response:

We agree with FDA regarding the magnitude of standard error for the covariates body weight, age, and dose, but believe that our overall conclusions, i.e. that there are no relevant effects by these covariates on zoledronic acid clearance, are consistent with the data. The model predicted effects were small , representing changes in clearance of 13% over the weight range 40 to 120 kg, 47% over the age range 40 to 90 years, and 29% over the dose range 2 to 16 mg. As the target population is typically well within these weight and age ranges, and the clinical dose is fixed at 4 mg, no relevant impact of the model-predicted changes in clearance would be expected.

Clarification

2. FDA comment:

The applicant's error model was designed to switch from a proportional error model to an additive error model if the plasma concentration fell below the limit of quantification (LOQ [redacted] An examination of the database indicated that none of the concentrations were below the LOQ. The applicant did not provide any justification for this unconventional residual error model.

Novartis response:

Concentration values below LOQ were set to zero. In the concentration data set used for Novartis' initial analysis, several positive values below LOQ were included, leading to the dual approach in error modeling. This approach was inadvertently maintained when analyzing the final data set, which excluded all values below LOQ.

Clarification

3. FDA comment:

The results reported by the applicant could not be reproduced with the control stream and dataset supplied. This appears to result from differences in the [redacted] compiler used by

the applicant and the FDA. The FDA uses a Digital Fortran Compiler, version 6.1. The Agency is looking into a means of procuring benchmark datasets for qualifying the installation and usage of NONMEM. The applicant is encouraged to do the same, as this is mutually beneficial.

Novartis response:
We are very interested in working with the agency to achieve consistent results with NONMEM across different sites with different compilers using benchmark datasets.

Agreement

4.FDA comment:
The applicant used first order estimation method in NONMEM (FO). However, the database consisted of full pharmacokinetic profiles (dense data), and conventional wisdom indicates the use of first order conditional estimation (FOCE) with interaction because a proportional residual error model was employed. While it is sometimes not possible to use FCOE [sic]methods, the applicant did not provide any explanation for using FO instead.

Novartis response:
FO was used to analyze the earlier data set in the original NDA (NDA 21-223) and we applied the same method to the extended data set in the present submission for consistency. When using the FOCE+INTERACTION method on the model elaborated with FO, we failed to achieve convergence.

Clarification

FDA comments on physiological relevance of model

5. FDA comment:
Zometa clearance decreases as the patient's weight increases. Typically, as weight increases, so does clearance, and it is not clear why that paradigm would not be true for Zometa as well.

Novartis response:
The relationship of body weight with clearance obtained by Novartis' model analysis indicates very small changes in clearance over a wide range of body weight. The direction of this change may be counter-intuitive based on standard allometric assumptions. However, Zometa total body clearance is a composite of different processes, including uptake by bone and renal clearance, which might result in unanticipated patterns in the modeling results.

Minor disagreement

6. FDA comment:

Zometa clearance increases as the patient ages. Generally we expect renal clearance of drugs to decrease with age.

Novartis response:
The relationship of age with clearance obtained by Novartis model analysis indicated only very small differences in clearance over a wide age range, as discussed above. Given that bone structural quality and metabolism do change with age, some effect by age on bone uptake by zoledronic acid can by hypothesized. The metastatic disease processes prevalent in the population investigated also will have an impact on bone uptake of bisphosphonate, further complicating an interpretation of differences in clearance.

Minor disagreement

7. FDA comment:
Zometa clearance decreases with increasing dose. The applicant supplied figures in the report to study 503/503E as well as J001 that indicated graphically that Zometa clearance and Cmax were proportional to dose.
Novartis response:
The change in clearance with doses over the range 2 mg to 16 mg obtained by the Novartis model analysis was small. As discussed above, a contributing factor may have been the presence of a greater number of concentration values above LOQ, particularly at the 16 mg dose, leading to the model result of an apparent slight non-linearity.

Minor disagreement

8. FDA comment:
The applicant did not explore relationships between any of the pharmacokinetic parameters, other than systemic clearance, with any covariates. Biology dictates that volume of distribution is dependent upon body size. Therefore, the omission of this relationship from the model requires a strong defense, which the applicant did not make.

Novartis response:
We agree with FDA regarding the relevance of V_1. This term was included in the original model analysis of NDA 21-223 (Zometa in the treatment of hypercalcemia of malignancy). However, in the present submission we focussed on clearance as the principal variable to characterize average exposure.

Clarification

Novartis comments on FDA model

9. FDA comment:
The 15-minute sample for subject 2109 (10050 ng/ml) was 3 to 4 times greater than other samples at corresponding timepoints in patients treated with the same dose. This datum

was removed from the analysis because it appeared to be either a typographical error or data outlier.

Novartis response:
The concentration reported is accurate. We agree that it is an outlier and speculate that the unusually high concentration may have resulted from cross-contamination with the infusion solution, given that this blood sample was taken at the end of infusion. However, inquiry at the clinical site could not confirm that this did in fact occur. Therefore, we retained the value in our analysis, although a case can be made to remove the outlier, given that the concentration values for the subsequent timepoints in patient 2109 appear less anomalous, and more in line with those from the other patients.

Clarification

10. FDA comment:
The several concentrations of Zometa in patient 1102 were over 100 ng/ml 10 to 24 hours after drug administration. In other patients treated at the same dose (16 mg), these plasma concentrations were less than 1 ng/ml. These data may have been outliers or typographical errors, and they were excluded from the analysis. These data are

Time (hrs)	Concentration (µg/L)

Novartis response:
The concentrations are reported accurately and there is no reason to suspect an analytical error.

Clarification

11. FDA comment:
Both the individually predicted and population predicted concentrations of Zometa appear to be well described by the model (see Figure 4). The WRES plot indicates a small bias that is not likely important (see Figure 5). However, even at the low concentrations, the model seems to accurately predict the concentrations of Zometa (see Figure 6). This [was] also observed from the applicant's model. These specific data corresponded predominantly to late observations in cycles 2 or 3 of therapy, and may represent release of drug from bone back into the circulation.

Novartis response:
We agree with FDA's comment regarding the good agreement of actual with model-predicted data, including those obtained at the low concentrations at later times post dose. However, when re-running the data set excluding the data points from patient 2109 and 1102, using Novartis' model adapted with the FDA suggested error function, we obtained an MOF of 7074, which is very similar to the minimum objective function value for the FDA model analyses. This suggests that both Novartis and FDA models are sensitive to the amount and magnitude of data at the later time points post dose and that, with more

data at the later time points, other models presently not considered might provide similar or better fits.

Agreement

Novartis comments on FDA investigations of exposure – response

12. FDA comment:
Initially, biomarker data from studies J001, 503 and 506 were considered for modeling. Based on the mechanism of action of the drug, attempts were made to describe the time course of effect of Zometa on the biomarkers using indirect response models. The first biomarker observation collected during these trials was at 24 h after the dosing. Maximal change in the biomarker occurred by 24 h. Further, no samples after the last dose were collected.

Novartis response:
Biomarkers were measured in serum and urine. Several urine markers were measured in studies J001 and 503. The first measurement for the urine markers was day 7 post dose, at which time maximal declines from baseline were observed. Serum CTX, measured in study 503, showed significant, nearly maximal declines from baseline already at the first measurement, 24 hours post 4 mg zoledronic acid dose, showing a nadir on day 8 post dose, the second measurement. The pharmacologic effect was maintained for the entire 28-day dosing interval (see Fig 7-15 in study 503 report). No urine markers were measured in study 506, but serum CTX and NTX were obtained after three doses of zoledronic acid (see Figures 7-17 and 7-18 in study 506 report) from 24 h after the first dose to day 84, i.e. up to 28 days after the third dose.

Clarification

13. FDA comment:
In all studies neither Zometa dose nor AUC influenced the SREs (see Figure 10). It may be argued that the plasma AUC, which was used in this analysis, is the incorrect covariate for correlations because the mechanism of action is due to drug activity at the bone. However, it should be noted that the linear, 3-compartment PK model ensures that the AUC of Zometa in plasma and bone are in a constant proportion. Therefore, the plasma AUC is a reasonable surrogate for bone AUC.

Novartis response:
We disagree that the 3-compartment linear model ensures that AUC in bone and plasma are in constant proportion. The deep compartment of the model is a mathematical construction that may or may not have any direct correspondence to physiological bone space. As discussed above, the time scale of the 3-compartment linear model is much shorter than the time scale of drug traffic through bone. Bone absorption and elimination may not be linear. Based on the above discussions on the retention of drug in bone and the imperfect description of actual physiologic processes by this model, the plasma AUC may not perform optimally as a surrogate for response.

Partial Agreement. FDA agrees that the model does not ensure bone AUC of Zometa. This was a poor choice of wording. More correctly phrased, it is a model assumption that the plasma AUC reflects similar changes in the bone. In general, it is possible that drug absorption or elimination from bone could be nonlinear processes, in which case plasma AUC would be a poor choice of surrogate for bone. However, the applicant has demonstrated that the pharmacokinetic characteristics of Zometa are linear from 2 to 16 mg. Therefore, the attempts to model efficacy of Zometa with plasma AUC was not unreasonable.

14. FDA comment:
The probability of the renal function deterioration was not higher in the pre- versus post-15 min infusion amendment group.

Novartis response:
This finding is not consistent with the Novartis' analysis of the pre-amendment versus post-amendment data of the clinical trials 10, 11, and 39. In all three studies, the hazard ratio for time to first creatinine increase was substantially lowered as a consequence of the 15-minute infusion amendment, for both dose groups.

Clarification: The FDA analysis was a Cox regression analysis of Time To Event, which does not show any effect related to pre- or post 15 minute amendment. A logistic regression analysis of total events does indicate a difference between the pre- and post amendment.

15. FDA comment:
Hence it is not enough to simply avoid 8 mg; a more rational approach to Zometa dosing is necessary.

Novartis response:
The clinical experience with Zometa, spanning up to 19 months of treatment, indicates that the 4 mg dose is safe and provides a desirable benefit versus risk. Novartis remains interested in identifying practical approaches that may further enhance the safety of Zometa in clinical use.

Agreement

Appendix 3

1. NONMEM Control Stream for the final FDA Model (CRTC on CL/WT on V)

```
THETA:    TVCL      TVV1      Q2        V2        Q3        V3        7CCR
ETA:
ERR:
ZOMETACRTC.lst        7107.219          eval=381 sig=3.0 sub=64 obs=1419 CCIL=NNNN NV1.1
PIV1.1
THETA   = 6.53      7.86      3.43      173       7.86      8.43      0.387
ETASD   = 0.307571  0.262679  0.244745  0.167033  0c        0.169115
ERRSD   = 0.292404  0.319374

MINIMIZATION SUCCESSFUL

 user 1:22        real 1:22tcl 0:3.24

$PRO ZOLEDRONATE POPULATION PK
$INPUT ID TIME DV RATE AMT DSL WT HT AGE SEX RACE BMI CRTC CMT UVOL EVID

$DATA ..\final1.csv IGNORE=C

$SUB ADVAN11 TRANS4

$PK

 FWT = WT/70
 AGE1 = AGE/60
 CCR1 = CRTC/90
 FEM = SEX - 1
 DSL1 = DSL/4
 TVC1 = CCR1**THETA(7)
 TVCL = THETA(1)*TVC1
 CL  = TVCL * EXP(ETA(1))

 TVV1 = THETA(2)*FWT
 V1  = TVV1*EXP(ETA(2))

 TVQ2 = THETA(3)*FWT**0.75
 Q2  = TVQ2*EXP(ETA(3))

 V2  = THETA(4)*FWT*EXP(ETA(4))

 TVQ3 = THETA(5)*FWT**0.75
 Q3  = TVQ3*EXP(ETA(5))

 V3  = THETA(6)*FWT*EXP(ETA(6))

K = CL/V1
K12 = Q2/V1
K21 = Q2/V2
K13 = Q3/V1
K31 = Q3/V3
S1 = V1

$ERROR
```

```
Y = F*EXP(ERR(1)) + ERR(2)

$THETA
(0,4,30) ;1 TVCL
(0,6,30) ;2 TVV1
(0,3,10) ;3 Q2
(0,70,400) ;4 V2
(0,15,30) ;5 Q3
(0,10,30) ;6 V3
0.1 ;7CCR

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0  FIX

$OMEGA 0.09

$SIGMA 0.02 0.04

$EST POSTHOC METHOD=0 MAXEVAL=9999 PRINT=10 NOABORT

;$COV

$TABLE ID TIME DSL PRED Y CL V1 ETA1 ETA2 WT HT AGE SEX
RACE BMI CRTC CMT EVID NOPRINT ONEHEADER FILE=zometacrtc.fitzometa.fit
```

2. NONMEM control stream for FDA Base Model

```
THETA:    TVCL      TVV1      Q2        V2        Q3        V3
ETA:
ERR:
zometabase.lst    7221.854          eval=359 sig=3.1 sub=64 obs=1419 CCIL=NNNN NV1.1 PIV1.1
THETA    = 6.11      8.18      3.61      170       8.64      9.21
ETASD    = 0.3755    0.352136  0.279643  0.0892749 0c        0.192094
ERRSD    = 0.289137  0.336155

MINIMIZATION SUCCESSFUL

  user 1:17.06     real 1:17.06       tcl 0:2.69

$PRO ZOLEDRONATE POPULATION PK
$INPUT ID TIME DV RATE AMT DSL WT HT AGE SEX RACE BMI CRTC CMT UVOL EVID

$DATA ..\final1.csv IGNORE=C

$SUB ADVAN11 TRANS4

$PK
```

```
 FWT  = WT/70
 AGE1 = AGE/60
 CCR1 = CRTC/90
 FEM  = SEX - 1
 DSL1 = DSL/4

 TVCL = THETA(1)
 CL   = TVCL * EXP(ETA(1))

 TVV1 = THETA(2)
 V1   = TVV1*EXP(ETA(2))

 Q2   = THETA(3)*EXP(ETA(3))
 V2   = THETA(4)*EXP(ETA(4))
 Q3   = THETA(5)*EXP(ETA(5))
 V3   = THETA(6)*EXP(ETA(6))

K = CL/V1
K12 = Q2/V1
K21 = Q2/V2
K13 = Q3/V1
K31 = Q3/V3
S1 = V1

$ERROR

Y = F*EXP(ERR(1)) + ERR(2)

$THETA
(0,4,30) ;1 TVCL
(0,6,30) ;2 TVV1
(0,3,10) ;3 Q2
(0,70,400) ;4 V2
(0,15,30) ;5 Q3
(0,10,30) ;6 V3

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0.09

$OMEGA 0 FIX

$OMEGA 0.09

$SIGMA 0.04 0.04

$EST POSTHOC METHOD=0 MAXEVAL=9999 PRINT=10 NOABORT

;$COV

$TABLE ID TIME DSL PRED Y CL V1 ETA1 ETA2 ETA3 ETA4 ETA5 ETA6
WT HT AGE SEX
```

RACE BMI CRTC CMT EVID NOPRINT ONEHEADER FILE=zometabase.fitzometa.fit

3. NONMEM Control Stream for the Applicant's model

```
$PRO ZOLEDRONATE POPULATION PK
$INP ID TIME DV RATE AMT DSL WT HT AGE SEX RACE BMI CRTC CMT UVOL EVID
$DAT final.csv IGNORE=c
$SUB ADVAN11 TRANS4
$PK
WT1 = WT/75
AGE1 = AGE/60
CCR1 = CRTC/90
FEM = SEX - 1
DSL1 = DSL/4
TVC1 = CCR1**THETA(7)*WT1**THETA(8)
TVC2 = AGE1**THETA(9)*THETA(10)**FEM*DSL1**THETA(11)
TVCL = THETA(1)*TVC1*TVC2
CL = TVCL * EXP(ETA(1))
V1 = THETA(2)*EXP(ETA(2))
Q2 = THETA(3)*EXP(ETA(3))
V2 = THETA(4)
Q3 = THETA(5)
V3 = THETA(6)
K = CL/V1
K12 = Q2/V1
K21 = Q2/V2
K13 = Q3/V1
K31 = Q3/V3
S1 = V1
$ERR
W = F
IF (F.EQ.0) W = 0.001
X1 = 0
IF (EVID.EQ.0.AND.DV.GT.0.4) X1 = 1
IPRE= F
IRES= DV - IPRE
IWRE= IRES/W
Y = X1*F*EXP(ERR(1)) + (1-X1)*ERR(2)
$THE
(0,4,100) ;1 TVCL
(0,6,100) ;2 TVV1
(0,5,100) ;3 Q2
(0,500) ;4 V2
(0,15) ;5 Q3
(0,15) ;6 V3
0.1 ;7 CLcr on CL
0.1 ;8 Wt on CL
0.1 ;9 Age on CL.1.0 ;10 Female on CL
-0.1 ;11 Dose
$OME BLOCK(2) 0.2
0.01 0.2
$OME 0.2
$SIG 0.4 0.04 FIXED
$EST POSTHOC METHOD=0 MAXEVAL=9999 PRINT=10 NOABORT
$COV
$TAB ID TIME DSL PRED IPRE IWRE CL V1 ETA1 ETA2 WT HT AGE SEX
RACE BMI CRTC CMT EVID NOPRINT FILE=../my.final.txt ONEHEADER
$TAB ID RACE SEX DSL CL V1 K12 K21 WT AGE CRTC FILE="listing.txt"
NOPRINT ONEHEADER
$TAB ID K K12 K21 K13 K31 EVID FILE="RateConst.txt"  NOPRINT ONEHEADER
```

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

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