CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-223 / N-000	**SUBMISSION DATE: 21-DEC-99, 11-FEB-00(BB), 18-MAY-00(BB), 25-MAY-00(BB)**
BRAND NAME:	**Zometa**
GENERIC NAME:	**Zoledronic acid for injection, 4mg lyophilized**
REVIEWER:	**Robert M. Shore, Pharm.D. Sam Haidar, Ph.D., Pharmacometrics Consultant**
SPONSOR:	**Novartis Pharmaceuticals Corp., East Hanover, NJ**
TYPE OF SUBMISSION:	**NME ; Code: 1P**

TERMS AND ABBREVIATIONS:

λ_z : Terminal elimination rate constant. The value was calculated from the slope of the linear regression of the terminal 3 points, which were the log-linear part of the plasma concentration versus time profile.

C_{end} : Measured plasma concentration at the end of infusion.

$t_{1/2}$: Elimination half-life, determined by $\ln 2/\lambda_z$

AUC_{0-t}: Area under the concentration-time curve (AUC) from time zero to the last measurable sampling time (described as t), calculated by the linear trapezoidal method.

AUC_{0-24}: AUC from time zero to 24 hours, calculated by the linear trapezoidal method.

AUC_{∞} : AUC from time zero to infinity. This corresponds to $AUC_{0-t} + C_t/\lambda_z$, where C_t is the concentration at time t.

CL : Plasma clearance, calculated by Dose/AUC

V_z : Volume of distribution in the terminal phase, calculated by Dose/(AUC*λ_z)

Ae_{0-24} : Cumulative amount of drug excreted into the urine from time 0 to 24 hour.

Ae_{∞} : Cumulative amount of drug excreted into the urine from time 0 to infinity. This corresponds to Ae_{0-t} + $(dAe/dt)/\lambda_z$. Ae_{0-t} is the cumulative amount of drug excreted into the urine from time 0 to time t, and $(dAe/dt)/\lambda_z$ is the residual amount of excretion from time t to infinity. dAe/dt was the urinary excretion rate at time t.

$\%\ dose_{urine}$: Urinary excretion (% of dose), calculated by Ae_{∞}/Dose*100

CL_R : Renal clearance, calculated by Ae_{∞}/AUC

SYNOPSIS:

Zometa is proposed for the treatment of tumor induced hypercalcemia (TIH). It would be the sixth bisphosphonate to be approved and the third for use in hypercalcemia associated with malignancy (pamidronate and etidronate are already approved). the sponsor has submitted two pharmacokinetic studies in cancer patients with bone metastases along with a population pharmacokinetic analysis of these two studies. No relevant pharmacodynamic data were collected in these two studies. Since zoledronate

is cleared mostly renally and the pharmacokinetics of zoledronate in renally impaired patients has not been determined, the sponsor needs to determine an appropriate dosing regimen in this patient population.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-223/N-000 submitted 21-DEC-99, 11-FEB-00, 18-MAY-00, and 25-MAY-00. The overall Human Pharmacokinetic Section is acceptable to OCPB. However, the sponsor needs to further define the dosing regimen for renally impaired patients in a Phase 4 commitment. This recommendation, comments (p. 11), and labeling comments (p. 11) should be sent to the sponsor as appropriate.

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(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Zoledronic acid is a member of the amino-bisphosphonates which inhibit osteoclastic bone resorption leading to a reduction in calcium blood levels. Zometa is a lyophilized formulation of the substance for intravenous injection proposed for the treatment of tumor induced hypercalcemia. The proposed dosing regimen is a single 4mg IV infusion over — minutes with one retreatment after at least 7 days if normocalcemia is not achieved or maintained; the retreatment dose is ——At the time this submission was made zoledronic acid was not marketed in any other country.

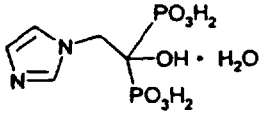
STUDY SUMMARY INDEX

Protocol Number	Title	Page
J001	Phase 1 clinical trial of CGP42446 for injection in cancer patients with bone metastases	p. 32
503	An open-label, single intravenous infusion dose study to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of zoledronate in cancer patients with bone metastases	p. 35

DRUG FORMULATION:

What is Zometa?

Zometa is zoledronic acid, which is a white crystalline powder. It's structure is shown below.



$C_5H_{10}N_2O_7P_2.H_2O$

The table below indicates the contents of one vial of Zometa.

Ingredient	Amount (mg)*	Function	Reference to standards
Zoledronic acid anhydrous**	4.000 mg	Drug substance	Novartis Monograph
Mannitol	[redacted]	[redacted] bulking agent	Ph. Eur., USP
Sodium citrate	[redacted]	[redacted] buffering agent	Ph. Eur., USP
Water for injection***	–	Solvent (removed during lyophilization)	Ph. Eur., USP
[redacted]		[redacted]	[redacted]

* Zoledronic acid anhydrous is added in form of Zoledronic acid monohydrous. 4.000 mg Zoledronic acid anhydrous corresponds to the amount of 4.264 mg Zoledronic acid monohydrate.
*** removed during lyophilisation

The to-be-marketed formulation is the same as that used in the two pharmacokinetic studies as well as the clinical trial and is manufactured at Novartis Pharma AG, Basel, Switzerland. The product is reconstituted with sterile water, further diluted in 50mL of sodium chloride or dextrose, and then intravenously infused over [redacted]

ANALYTICAL METHODOLOGY:

[redacted]

HUMAN BIOAVAILABILITY AND PHARMACOKINETICS STUDIES:

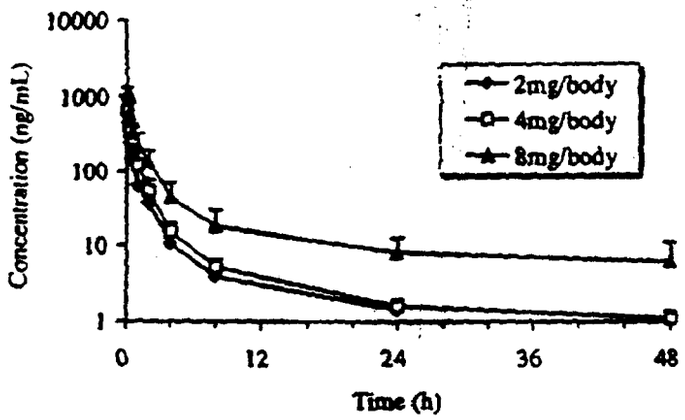
I. Bioavailability/Pharmacokinetics

What are the pharmacokinetic parameters of Zometa after IV infusion?
Is there dose proportionality regarding pharmacokinetic parameters?

Two pharmacokinetic studies were conducted by the sponsor, studies J001 and 503. Both studies were conducted in cancer patients with bone metastases. Study J001 was conducted in Japan and used a 5 minute IV infusion (50mL) of 2, 4, or 8mg Zometa (N=3 different patients in each dosing group) while study 503 used 5 minute IV infusion (50mL) of 4mg (N=3) or 15 minute IV infusions (50mL) of 4 (N=4), 8 (N=8), and 16mg (N=8) Zometa in different patients. Plasma and urine sample were collected from patients in both studies. The most relevant biomarker for TIH is serum corrected calcium, which was not monitored in either of these studies.

Non-compartmental as well as modeled pharmacokinetic parameters were determined from zoledronate concentrations (full consult review for NonMEM compartmental analysis can be found in Appendix).

From study J001:
Maximal plasma concentrations of zoledronate were observed immediately after the end of infusion (5 minutes). There was a rapid decline in concentrations followed by a slower phase. Zoledronate concentrations were low but detectable at 48 hours post dose. The figure below shows the average plasma concentration-time profiles for the 3 different doses.

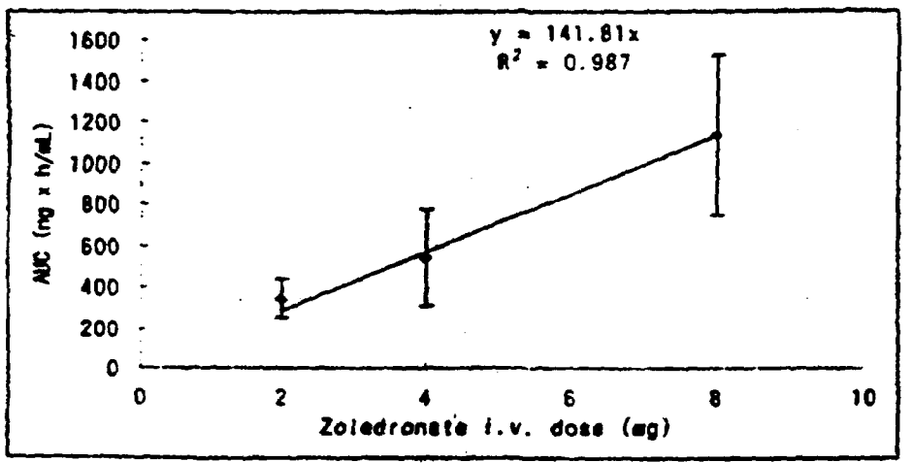


The table below summarizes the plasma pharmacokinetic parameters (mean+-SD) from the non-compartmental analysis of each dose group (N=3/dose).

Dose	Cmax ng/mL	AUC_{0-24} ng*h/mL	AUC_{0-t} [1] ng*h/mL
2mg/body	453 ± 162	344 ± 98	344 ± 98
4mg/body	668 ± 251	540 ± 232	572 ± 236
8mg/body	1142 ± 190	1133 ± 386	1299 ± 483

1) 2mg group; t=24hrs. 4 and 8mg group; t=48hrs.

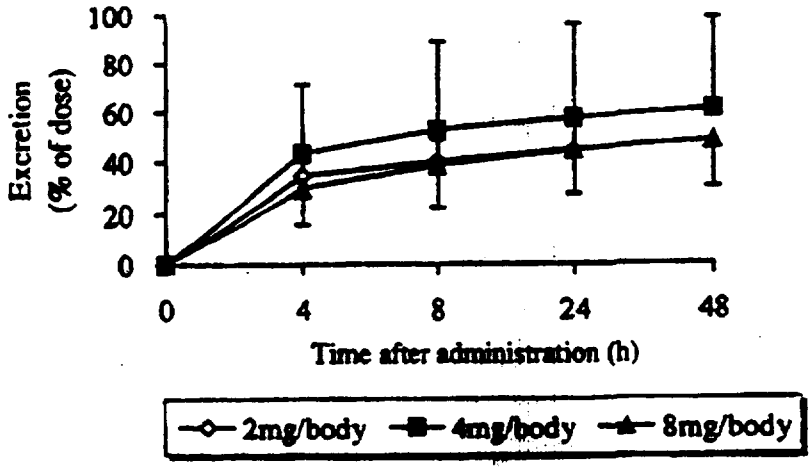
The relationship of dose to AUC (mean +-SD) is shown below.



Note: CGP42446 is zoledronate.

This plot indicates that there is generally dose proportionality for AUC from 2 to 8mg of Zometa although there is also large variability in the pharmacokinetic parameters.

The figure and table below show the cumulative urinary excretion of zoledronate after the three different doses and summarize (mean +-SD) the pharmacokinetic parameters.

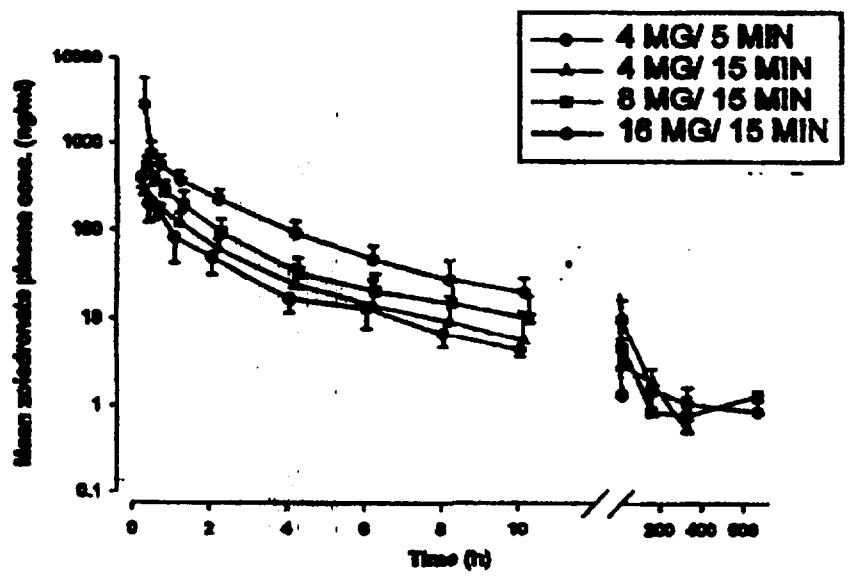


Dose	Quantity excreted in urine $_{0-24}$ µg	Quantity excreted in urine $_{0-\infty}$ µg	Urinary excretion rate $_{1)}$ %	CL_R [1] L/h
2mg/body	883±213	968±245	48.2±12.2	3.14±1.75
4mg/body	2279±1539	2693±1753	67.2±43.8	4.63±3.37
8mg/body	3531±1364	4872±1565	60.9±19.6	3.61±1.68

1) Calculated from quantity excreted in urine until infinity.

From the estimate of urinary excretion it can be seen that about 30-50% of the dose remains in the body for an extended period of time, probably in bone.

Study 503:
Data from 23 patients were used for this pharmacokinetic study. The semi-log plot below shows the mean (+-SD) zoledronate plasma concentration-time profiles following IV infusion of 4, 8, and 16mg Zometa over 5 or 15 minutes.



The table below summarizes the mean (+-SD) zoledronate plasma pharmacokinetic parameters following IV administration of Zometa.

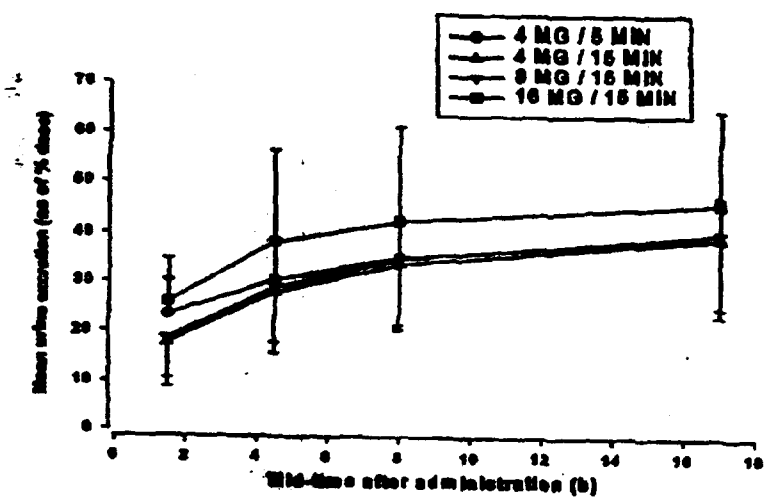
PK parameter	AUC_{0-24} (ng-h/ml)	AUC_{0-last} (ng-h/ml)	C_{last} (ng/ml)
4 mg/5 min	411 ± 107 (N = 3)	412 ± 107 (N = 3)	293 ± 100 (N = 3)
4 mg/15 min	496 ± 212 (N = 4)	689 ± 596 (N = 4)	257 ± 41 (N = 4)
4 mg (pooled)	460 ± 168 (N = 7)	570 ± 451 (N = 7)	321 ± 93 (N = 7)
8 mg/15 min	816 ± 297 (N = 8)	1182 ± 770 (N = 8)	528 ± 165 (N = 8)
16 mg/15 min	2139 ± 585 (N = 8)	3328 ± 1102 (N = 8)	2759 ± 3077 (N = 8)

The median C_{end} value for the 16mg group was 1706ng/mL and the mean of 2759ng/mL was due to one patient having a value of 10,050ng/mL.

After a 15 minutes infusion of 4 mg the C_{end} is about 30% lower than after a 4mg infusion administered over 5 minutes but the AUC_{0-24} are not significantly different. Of interest is that the AUC_{0-last} for the 15 minutes infusion is about 70% higher than the 5 minutes infusion. The clinical dosing will be over 5 minutes.

The plot and table below summarize the renal excretion data.

Mean (±SD) cumulative urine excretion (as % of dose) of zoledronate vs. mid-time following intravenous administration of 4 mg, 8 mg or 16 mg of zoledronate



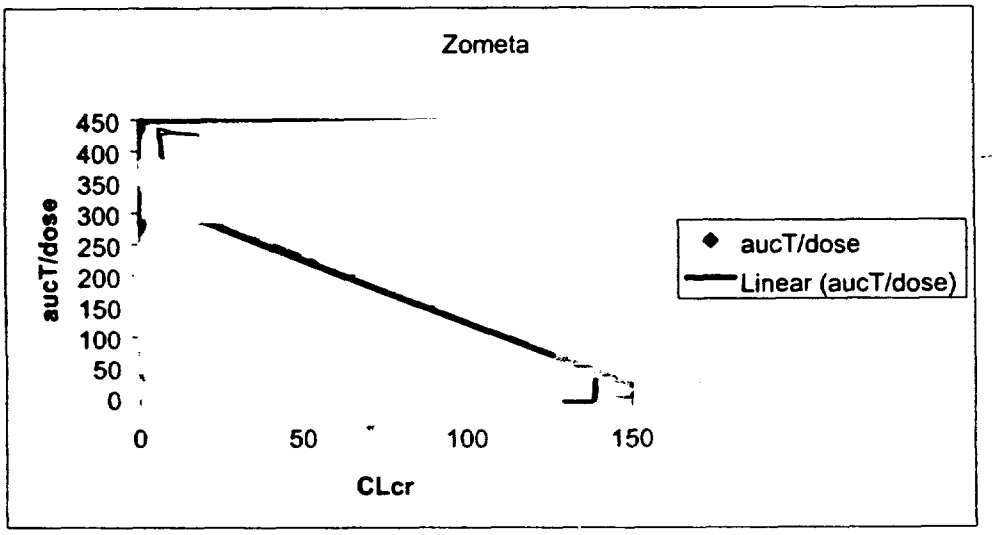
Mean (±SD) zoledronate urine PK parameters following intravenous administration of zoledronate

PK parameter	% excretion (0-24h)	CL_R* (l/h)
4 mg/5 min	39.5 ± 8.1 (N = 3)	4.1 ± 1.8 (N = 3)
4 mg/15 min	39.4 ± 14.3 (N = 3)	3.5 ± 2.0 (N = 3)
4 mg (pooled)	39.5 ± 10.4 (N = 6)	3.8 ± 1.7 (N = 6)
8 mg/15 min	40.6 ± 17.1 (N = 8)	4.7 ± 2.9 (N = 8)
16 mg/15 min	48.2 ± 16.7 (N = 6)	4.1 ± 2.5 (N = 6)

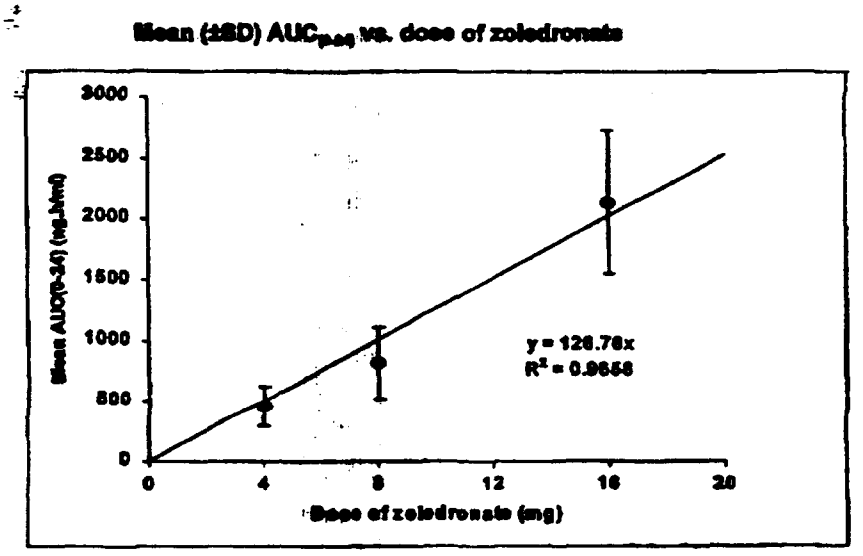
* CL_R is calculated by Ae_{0-24}/AUC_{0-24}, where Ae_{0-24} is cumulative amount of drug excreted up to 24 hours post-dose.

These CL_R estimates are in agreement with study J001.

The plot below shows the relationship between dose-normalized $AUC_{0\text{-last}}$ and CLcr (with linear trend line) in patients from study 503. As expected, the exposure increases as CLcr decreases. However, no exposure-response relationship has been determined so specific dosing changes based on CLcr are difficult to make at this time.



Dose proportionality was assessed from 4 to 16mg in the plot below.



Although there is considerable variability in $AUC_{0\text{-}24}$ there does seem to be dose proportionality.

II. Metabolism

Does zoledronate inhibit the metabolism of other drugs?

An *in vitro* human microsome study demonstrated that zoledronate did not inhibit the following P450 CYP enzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11. *In vitro* drug interaction studies were not conducted.

IV. Special Populations

Does the dosing of Zometa need to be altered in special populations?

Renal

Zometa is proposed for administration as a single, and in some patients a repeat, dose. Even in patients with impaired renal function it seems unlikely that zoledronate would accumulate; there is also no established pharmacokinetic / pharmacodynamic (safety or efficacy) relationship on which to base dose adjustments. The labeling includes a precaution that Zometa has not been tested in patients with serum creatinine greater than 4.5mg/dL and that its benefits should outweigh the risks to such patients.

Hepatic

No pharmacokinetic studies in hepatically impaired patients have been conducted.

V. Protein Binding

To what extent does zoledronate bind to components in blood?

In vitro studies indicated that the mean human plasma protein binding of zoledronate is 22% while the

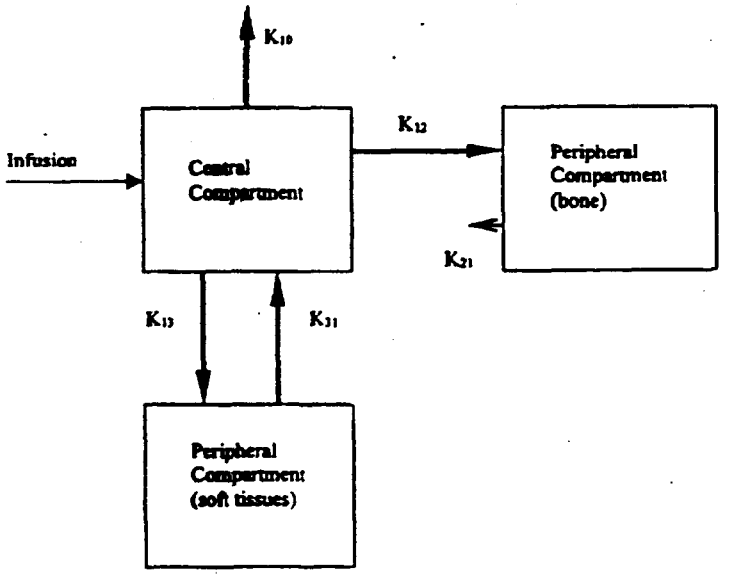
VI. Population Pharmacokinetics

What are the pharmacokinetic parameters from the POP PK analysis?
Are there any covariates that might affect dosing?

(Note: the population pharmacokinetic analysis was reviewed by the Pharmacometrics group and the full review can be found in the appendix)

A population pharmacokinetic analysis was conducted using the following model:

Illustration of three-compartment linear model



This model was found to be valid and the pharmacokinetic parameters estimated from it are listed in the table below.

Population pharmacokinetic parameter estimates of ZOL obtained using NONMEM based on the final covariate model (first-order conditional estimation method)

Parameters	Estimates	
	Parameters	CV%
Estimates of population parameters (fixed effects)		
θ_1 (L/h)	3.57	14.5
θ_3 (L)	7.71	8.4
Q_2 (L/h)	4.58	7.7
V_2 (L)	381	10.8
Q_3 (L/h)	6.70	19.1
V_3 (L)	7.52	12.2
θ_2	0.904	24.2
θ_4	1.01	25.4
$t_{1/2\alpha}$ (h)	0.23	-
$t_{1/2\beta}$ (h)	1.75	-
$t_{1/2\gamma}$ (h)	167	-
Estimates of variability (random effects)		
Intersubject variability (%)		
CL	61.1	40.2
V1	32.4	49.7
Residual variability (%)	28.2	31.9

V_1: volume of distribution in central compartment; V_2 and V_3: volumes of distribution in two peripheral compartments; CL: clearance from central compartment; Q_2 and Q_3: intercompartment clearance between peripheral compartments and central compartment; $t_{1/2\alpha}$, $t_{1/2\beta}$ and $t_{1/2\gamma}$ half-life in fast distribution phase, slow distribution phase and elimination phase, respectively, estimated as secondary parameters

where $CL = \theta_1 \cdot (CL_{cr}/82.6)^{\theta_2} \cdot \exp(\eta_1)$ and $V_1 = \theta_3 \cdot (BW/69.4)^{\theta_4} \cdot \exp(\eta_2)$.

The conclusions of the analysis were that body weight is a covariate for central volume of distribution, individual creatinine clearance is a covariate for total plasma clearance, and total plasma clearance is not affected by body weight, body mass index, age, gender, or race.

VII. Pharmacokinetic / Pharmacodynamic Relationships

The most relevant pharmacodynamic endpoint/biomarker for TIH is serum corrected calcium which was collected in neither study J001 nor 503.

DISCUSSION:

The pharmacokinetic parameters of zoledronate have been established in cancer patients with bone metastases. The recommended dosing regimen is 4mg infused over ——— with a single repeat dose of — as needed based on response. No pharmacokinetic data were collected after a second dose. At this time it is unknown if dosing adjustments will be needed in this patient population based on renal function. Since the kidneys handle the majority of the total clearance of zoledronate, it is reasonable to assume that dosing changes will be needed in renally impaired patients. However, since Zometa is dosed only once or twice in TIH patients, there is perhaps less concern in this patient population regarding accumulation of zoledronate in the body than in other populations which might receive many multiple doses.

The issue of renal adverse effects (perhaps toxicity) has been brought up in discussions with Dr. Colman and the potential relationship of these AEs to exposure of zoledronate has been discussed. However, until there is a better understanding of the exposure-response and/or exposure-toxicity relationship it is difficult to suggest dosing guidelines based on renal function. Currently, AE/safety data is under review by DMEDP and the labeling does indicate that renally impaired patients should be treated if the benefits outweigh the risks. One suggestion is that, before an — re-treatment, a patient's renal function should be checked. Collaboration between DMEDP and OCPB on this issue will continue.

COMMENTS TO BE SENT TO SPONSOR:

1) [ ]

2) The sponsor should re-format the pharmacokinetic section of the labeling into the following sections: Distribution, Metabolism, Excretion, Special Populations.

3) In a Phase 4 commitment the sponsor should pursue the development of rational dosing guidelines in renally impaired patients. The sponsor should pursue defining an exposure (probably AUC-related) that shows efficacy and develop a dosing regimen based on creatinine clearance that would result in that exposure at different creatinine clearances. All study designs should be submitted for review before the sponsor proceeds with these studies.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double <u>underlined text</u> should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

[ ]

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Labeling

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 24-MAY-00

CPB Briefing 26-MAY-00
attendees: Hunt, Selen, Johnson, Haidar, Wang, Ahn

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 6/6/00

CC: NDA 21-223/N-000 (orig.,1 copy), HFD-510(Hedin), HFD-870(Ahn, HuangS), HFD-850(Lesko) CDR.

DFS Code: AE

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Appendix 1. Draft labeling

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Labeling

Appendix 2. Study summaries

Study J001
Blood sampling at pre-dose and 5min (end of infusion), 15 min, 0.5h, 1h, 2h, 4h, 8h, 24 h for all three dose levels and at 48h for the 4mg and 8mg doses. Urinary excretion was assessed at 0-4h, 4-8h, 8-24h, and 24-48h for all doses.

1. Title Page

Title of clinical trial	Phase I Clinical Trial of — 42446 for Injection in Cancer Patients with Bone Metastases
Name of investigational product	CGP42446 (Zoledronate)
Clinical trial subjects	Cancer patients with metastatic bone lesions
Design • comparator product • trial duration • dose • study population	Design: Open-label, cohort, dose-escalating trial Comparator product: None Trial duration: 3-week cycles of single dose intravenous treatment that include a period of follow-up observation (maximum of 4 cycles) Doses: 2 mg, 4 mg, and 8 mg Study population: Cancer patients with metastatic bone lesions
Clinical trial sponsor	Novartis Pharma K.K.
Clinical trial protocol identification code	ZOLJ001
Development phase	Phase I clinical study
Start of trial	26 August 1998 (enrollment of first subject)
Early termination of trial	None
Completion of trial	30 April 1999 (final day of observation of last subject)
Medical expert	[redacted]
Study director (for sponsor) Manager contact information	Director: H. Kawakami, Chief, Clinical Development Division Managers: N. Yokota and T. Suzuki, Clinical Pharmacology Group, Clinical Development Division Novartis Pharma K.K. 4-17-30 Nishi Azabu, Minato-ku, Tokyo TEL: 03-3797-8578 FAX: 03-3797-4472
Declaration of GCP compliance	This study was conducted in compliance with "Good Clinical Practice [GCP]" (Ministerial Ordinance No. 28 by the Japanese Ministry of Health and Welfare, dated 27 March 1997). All clinical trial documents and data are appropriately archived by the respective study directors. Director of auditing: [redacted]
Date of report preparation	October 12, 1999

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2. Summary

Clinical trial sponsor: Novartis Pharma K.K.	Summary sheet for each clinical trial	(For use by review official)
Name of product:	Location in application summary	
Name of active ingredient: —'42446 (Zoledronate)	Volume No: Page:	

Title of clinical trial: Phase I Clinical Trial of CGP42446 for Injection in Cancer Patients with Bone Metastases	
Names of medical institutions and investigators: Department of Internal Medicine, (Chemotherapy Division), National Cancer Center Higashi Hospital: Y. Sasaki Department of Surgery, National Hospital Shikoku Cancer Center: T. Saeki	
Publications: None at this time (Manuscripts to be submitted)	
Study period: From: 26 August 1998 (enrollment of first subject) To: 30 April 1999 (final day of observation of last subject)	Development phase: Phase I clinical trial
Objective: The primary objective of this study was to evaluate the tolerability and safety of intravenous (IV) administration of CGP42446 when given to cancer patients with metastatic bone lesions. Secondary objectives of this study included estimation of clinical dose ranges, evaluation of CGP42446 efficacy using improvement in various metabolic bone parameters as a guide, and assessment of the pharmacokinetics of CGP42446.	
Study methodology: We conducted this clinical trial as a cohort, dose-escalating study. CGP42446 was given intravenously at an initial dose of 2 mg. We then increased the IV dose to 4 mg and 8 mg while monitoring treatment safety. Each treatment group consisted of 3 to 6 patients. One cycle of therapy, including single dose IV administration of the trial drug and a period of follow-up observation, lasted 3 weeks. A maximum of 4 cycles of therapy were administered.	
Number of subjects: Number stipulated in protocol, 9 to 18; number who received treatment, 9.	
Diagnosis and primary eligibility criteria: Cancer patients with metastatic bone lesions who were at least 20 years of age and gave voluntary written consent to participate in this study. All eligible subjects had a performance status (PS) of 2 or less (however, patients without metastases to a major organ but a PS of 3 due to bony metastases were eligible) and an expected survival time of at least 3 months.	
Trial drug, dosage and administration, and lot number: Each vial contained 4.16 mg of lyophilized —42446 as the anhydride form. The product was reconstituted with 5 ml of solution for injection (water for injection) at the time of use. Lot numbers: Lot No. J0030298 (CGP42446) and Lot No. J0130398 (water for injection).	
Duration of treatment (observation): 3-week cycles of treatment that included single dose IV administration of the trial drug, followed by a period of observation (maximum of 4 cycles).	
Comparator product, dosage and administration, and lot number: None	
Evaluation criteria: Safety: We evaluated tolerability and safety on the basis of symptoms, vital signs, other physical examination findings, general laboratory studies, and electrocardiogram. With respect to tolerability, grade 3 and 4 adverse events for which a causal relationship with the trial drug could not be excluded were considered to represent "dose limiting toxicity" (DLT). If DLT was present in at least 3 patients within one cohort, the protocol stipulated that the study not be continued to the subsequent cohort, and that the lower dose be considered as the "maximum tolerated dose" (MTD). Efficacy: We evaluated treatment efficacy on the basis of metabolic bone markers, bone pain scores, required use of analgesics, PS, bone related clinical manifestations, and whenever possible, bone imaging studies. Therapeutic efficacy based on the results of bone imaging studies was assessed using the same evaluation criteria as in trials conducted overseas.	

Clinical trial sponsor: Novartis Pharma K.K.	Summary sheet for each clinical trial	(For use by review official)
Name of product:	Location in application summary	
Name of active ingredient: CGP42446 (Zoledronate)	Volume No: Page:	

Statistical analysis: The data was analyzed from all evaluable cases in which at least the first treatment cycle was completed. For safety and efficacy evaluation parameters, we prepared a list of the data for each dose group and performed a descriptive analysis. The data are depicted graphically whenever necessary.

Summary and conclusions:

Results of safety evaluation: Of the 9 patients who received treatment with the trial drug, one patient in the 2 mg group died soon after the observation period during the second cycle of treatment had been completed. Clinical findings (neurologic signs and diabetes insipidus) and imaging studies in this patient strongly suggested the presence of brain metastases. However, a causal relationship of these findings with the trial drug "could not be excluded." Symptoms and signs classified as grade 3 or greater developed in 4 patients. These findings were attributed to the underlying disease and/or concomitantly administered anticancer agents in these patients. There was "no causal relationship" with the study drug. Grade 3 or greater laboratory abnormalities occurred in 7 patients. These events included lymphopenia in 5 patients (56%), decreased serum phosphorus in 3 patients (33%), and a prolonged APTT in 1 patient (11%). These laboratory abnormalities were probably related to treatment with the trial drug, but all were transient, did not produce any clinical symptoms, and did not influence patient tolerability of the trial drug. Other symptoms and signs during treatment that could not be excluded as being causally related to the trial drug included: fever in 5 patients (56%); headache and local pain at the injection site each in 3 patients (33%); nausea, anorexia, and fatigue each in 2 patients (22%); and dizziness, tremors, drowsiness, vomiting, stomatitis, diabetes insipidus, ear congestion, flushing, erythema of the hands and feet, and bone pain each in 1 patient (11%). All of these findings were classified as grade 1 in severity, with the exception of grade 2 severity of the tremors and diabetes insipidus in the patient suspected of having brain metastases.

Results of efficacy evaluation: Efficacy was evaluated primarily on the basis of metabolic bone parameters, which generally reflect the state of bone resorption and bone formation. Treatment with CGP42446 reduced metabolic bone marker levels from pretreatment baseline values. This suggested that CGP42446 inhibits bone metabolism, but there were no dose-dependent differences. Other efficacy parameters such as pain scores, amounts of analgesic drugs required, PS, and development of bone related symptoms were generally assessed in those patients whose overall condition was satisfactory at the time of study enrollment. Thus, the efficacy of [redacted]42446 could be not adequately judged from these latter parameters. Bone imaging studies performed before and after treatment showed no changes (NC) in 8 cases with evaluable bone lesions. However, bone imaging studies did show a trend towards some improvement in one case each from the 4 mg and 8 mg dose groups, without concomitant administration of any other antineoplastic agents.

Results of pharmacokinetic studies: After IV administration, there was rapid elimination of CGP42446 from the blood, followed by a more gradual elimination phase. Increasing the dose of CGP42446 produced higher drug blood concentrations, but the elimination profile remained unchanged. The results of analysis using a compartment model suggested rapid uptake and gradual release of the trial drug in bone. There were variations in urinary drug excretion among all patients. The cumulative excretion rate at the time of final evaluation varied from less than 20% to more than 90%, but this variation was not dose dependent. These variations in urinary drug excretion rate may be due to the severity of the bone metastases because they showed a correlation with baseline type I collagen telopeptide (ICTP) values.

The above findings demonstrate adequate tolerability of a 8 mg/body dose of CGP42446 given as an IV infusion over [redacted] They also suggest that CGP42446 is effective soon after administration in light of the fact we saw decreases in bone metabolism markers and a tendency toward improvement in bone lesions on images without the use of other anticancer therapies.

Date of report:
October 12, 1999

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Study synopsis

Title of study: An open-label, single intravenous infusion dose study to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of zoledronate in cancer patients with bone metastases

Investigators:

James R. Berenson, M.D.
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Publication(s): None

Study period: first subject dosed at 29-Jun-99 Interim subjects completed at 15-Oct-99

Objectives: The primary objective of the study was to characterize the PK and PD of a single dose of 4 mg zoledronate administered by a 5 minute intravenous infusion, and 4 mg, 8 mg, and 16 mg zoledronate administered by a 15 minute intravenous infusion in cancer patients with bone metastases. Secondary objectives were to characterize the relationship between PK and PD measurements and to evaluate the relationship between adverse events and PK measurements. This interim report does not address the latter of the secondary objective.

Design: This was a randomized, open-label, single dose study. Zoledronate naive cancer patients with bone metastases were randomized to one of the following four treatment schedules if the patients met all inclusion/exclusion criteria: 4 mg zoledronate with a [redacted] infusion, 4 mg zoledronate with a [redacted] minute infusion, 8 mg zoledronate with a [redacted] usion, or 16 mg zoledronate with a [redacted] infusion. Patients were admitted to the study center on the morning of dosing and received a single infusion of zoledronate. Sequential plasma and urine PK samples were obtained for 24 hours post-infusion. Additional plasma and urine PK/PD samples were obtained on days 8, 15, and 29 post-infusion. An end-of-study evaluation was performed after the final PK/PD sampling on day 29. If in the investigator's judgment there was a clinical benefit from the initial zoledronate treatment, the patient could consent to enroll in an extension of study 503 (i.e., ZOL446 0503E) to receive additional zoledronate administrations. This interim report covers the results for the core study 503 for all patients enrolled by the cut-off date of September 15, 1999.

Number of subjects: The study population comprises all patients enrolled by the pre-determined cut-off date of September 15, 1999; twenty-three patients were enrolled and had received a single infusion of zoledronate by this date. The cut-off date for data collection for this interim evaluation was October 15, 1999.

Criteria for inclusion: Patients at least 18 years of age with a histological diagnosis of cancer and metastatic disease to the bone were included in this study. Patients who had received previous treatment with zoledronate or another bisphosphonate were not eligible. Patients who received an investigational agent within 30 days, the non-bisphosphonate anti-hypercalcemia medications calcitonin, gallium nitrate or mithramycin within 14 days, or chemotherapy within 7 days of zoledronate administration were not eligible. Patients with liver disease or a confirmed diagnosis of HIV infection were also excluded from this study.

Investigational drug: Zoledronic acid, 4.16 mg per vial, batch numbers: Y011 0298, Y115 1198, and Y021 0698

Comparator drug: None

Duration of treatment: Single dose of zoledronate with a 4-week follow-up period

Criteria for evaluation:

Safety and tolerability: Assessment of adverse events, laboratory evaluations including hematology and blood chemistry, vital signs, and physical examinations were used to ensure patients safety. Safety variables other than serious adverse events are not itemized and discussed in this report.

Pharmacokinetics:

- Plasma concentrations of zoledronate: $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24h)}$, and C_{end}
- Urine concentrations of zoledronate: % excretion (0-24h), CL_R

Pharmacodynamics: The magnitude and duration of changes in PD measurements (serum bone alkaline phosphatase (BAP), urine N-telopeptide (NTX)/creatinine ratio, urine calcium/creatinine ratio, urine (deoxy)pyridinoline/creatinine ratio, and urine hydroxyproline/creatinine ratio as a consequence of zoledronate administration were assessed. Exploratory evaluations of the relationships between PK and PD were performed.

Statistical methods: Descriptive statistics for demographics, PK, and PD parameters. Dose proportionality was assessed using ANOVA and power model approaches. Exploratory analysis of PK/PD relationships was performed using ANCOVA model.

Results: Of the 23 patients enrolled (13 male, 10 female, mean age 58 years, range 45 to 80 years), 21 completed all PK and PD evaluations. Two patients (patient numbers 503-104 and 503-106), withdrew from the trial prior to completion of all scheduled PK and PD sampling on days 15 and 29. One patient (503-106) was removed due to progression of disease, while a second patient (503-104) did not return to the site after visit 3 (day 8 post-infusion), and was lost to study follow-up. Both patients provided PK and PD collections up to and including day 8.

All patients had confirmed bone metastases and multiple myeloma (n=11), breast cancer (n=4), prostate cancer (n=3), carcinoma of unknown origin (n=2), or cancer of the lung (n=1), colon (n=1), or head and neck (n=1).

Safety and tolerability: The investigators reported five serious adverse events in 23 patients. None of these events were considered to be related to study drug.

Pharmacokinetics: Zoledronate concentrations peaked immediately post end-of-infusion (C_{end}), showing a rapid decline to less than 10% of C_{end} after 4 hours and less than 1% of C_{end} after 24 hours, followed by prolonged extremely low concentrations to day 29. These were about 0.1% of C_{end}, passing below the limit of bioanalytical quantitation for the lower doses, precluding assessment of individual patients' terminal zoledronate half-lives. The distribution of patients receiving 4, 8, and 16 mg doses infused and the mean systemic exposure to drug for each dose group are tabulated below:

Zoledronate dose	$AUC_{(0\text{-}24)}$ (ng·h/ml)	C_{end} (ng/ml)
	411 ± 107 (N = 3)	
4 mg/15 min	496 ± 212 (N = 4)	
	460 ± 168 (N = 7)	
	816 ± 297 (N = 8)	
	2139 ± 585 (N = 8)	

Statistical analysis showed that C_{end}, $AUC_{(0-24h)}$, and $AUC_{(0-tau)}$ behave consistently with the assumption of dose proportionality. Increasing the infusion period from 5 to 15 minutes caused an approximately 30% decrease in C_{end} but produced no statistically significant difference in the systemic exposure (AUC).

Approximately 40-46% of zoledronate dose was excreted in urine up to 24 hours post-dose, with a renal clearance of ——— Dosing regimen had no appreciable effect on renal clearance and urinary excretion of zoledronate. The mean (±std. dev.) urinary excretion and renal clearance, CL_R, of zoledronate are tabulated below:

Zoledronate dose	Urinary excretion 0-24 h (% of dose) [$Ae_{(0-24h)}$ / dose]	CL_R (L/h) [$Ae_{(0-24h)}$ / $AUC_{(0-24h)}$]
———	39.5 ± 8.1 (N = 3)	4.1 ± 1.8 (N = 3)
4 mg/15 min	39.4 ± 14.3 (N = 3)	3.5 ± 2.0 (N = 3)
	39.5 ± 10.4 (N = 6)	3.8 ± 1.7 (N = 6)
	40.6 ± 17.1 (N = 6)	4.7 ± 2.9 (N = 6)
	46.2 ± 18.7 (N = 6)	4.1 ± 2.5 (N = 6)

Pharmacodynamics: Statistically significant decreases from baseline were observed in all urinary PD bone markers after zoledronate infusion, consistent with the drug's inhibitory effects on bone resorption. Serum bone specific alkaline phosphatase tended to increase but the changes were not significant for this marker of bone formation.

Marker	N	Mean[3]	Std. Err[3]	p-value
NTX/creatinine[1]	21	-35.62	6.69	<0.01
Hydroxyproline/creatinine[1]	21	-6.78	2.32	0.01
Pyridinoline/creatinine[1]	20	-11.41	4.47	0.02
Deoxypyridinoline/creatinine[1]	20	-5.15	1.84	0.01
Calcium/creatinine[1]	20	-59.95	15.64	<0.01
Bone alkaline phosphatase[2]	20	25.05	14.57	0.10

1 urine
2 serum
3 mean ± std. error of differences between baseline and day 8, 15, and 29 average values

Multiplicative statistical model analysis showed no significant impact of time post dose (days 8, 15, 29) on any of the bone marker values, reflecting a long duration of the effect of a single zoledronate infusion. However, the analysis also identified the 8 mg dose as producing significantly different changes in NTX/creatinine, hydroxyproline/creatinine, and deoxypyridinoline/creatinine than either the 4 mg or 16 mg dose. The failure to demonstrate a traditional dose dependency, i.e. effect of 4 mg < 8 mg < 16 mg is unclear but may be due to interpatient differences in the effects of zoledronate and to the high dose range investigated.

There were no significant differences in serum creatinine between baseline and 24 hours post dose, suggesting absence of an acute effect by zoledronate on renal function.

Pharmacokinetic-pharmacodynamic relationship: A statistically significant correlation of the change in bone marker with the parameter [dose - $Ae_{(0-24)}$]; i.e., reflecting zoledronate retained in the body at 24 h post infusion, was found for calcium/creatinine (negative correlation) and for bone alkaline phosphatase (positive correlation). These associations may reflect that the targeting of zoledronate to bone and resulting effect on bone resorption is influenced by disease status.

Conclusions:

- Following intravenous dosing zoledronate plasma concentrations show a rapid decline, followed by prolonged, but very low concentrations to day 29 post dose. The pharmacokinetics of zoledronate are consistent with dose proportionality over the dose range 4 mg to 16 mg.
- Approximately 40% of zoledronate is excreted in urine within 24 hours post infusion irrespective of dosing regimen.
- Zoledronate produces statistically significant reductions from baseline in urinary pharmacodynamic markers of bone resorption, but an increasing trend in serum bone alkaline phosphatase, a marker of bone formation. The changes in the bone markers are consistent over the time period day 8 to day 29 post dose, reflecting a long duration of effect from a single infusion of drug.
- Zoledronate in the dose range 4 mg to 16 mg does not show a typical dose dependency of effects, 8 mg producing the greatest changes in bone markers.
- Zoledronate retained in the body after 24 hours post dose was significantly negatively correlated with changes from baseline in urinary calcium and significantly positively correlated with changes from baseline in serum bone alkaline phosphatase.

Date of the report: 01-Dec-99

Appendix 3. POP PK Review

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Division of Pharmaceutical Evaluation II

NDA:	**21-223**
Generic	**Zoledronic Acid for Injection**
(Brand®)	**Zometa®**
Submission Date:	**December 21, 1999**
Sponsor:	**Novartis Pharmaceuticals**
Consult:	
Pharmacometrics Scientist:	**Sam H. Haidar**

Background

NDA 21-223 for zoledronic acid injection (Zometa®) was submitted by Novartis on December 21, 1999. The proposed indication for Zometa is the treatment of tumor induced hypercalcemia (TIH, also known as hypercalcemia of malignancy), a serious and potentially life-threatening metabolic complication of cancer.

According to the sponsor, Zometa is a third generation bisphosphonate (new molecular entity) which is one of the most potent inhibitors of bone resorption known.

This pharmacometric consult evaluated the population pharmacokinetic analysis performed on data from two pharmacokinetic studies (ZOL J001 and ZOL 503), which were conducted in cancer patients with bone metastases. Study designs and results are given below.

Title:

Objectives:

1. Build a population Pharmacokinetic (PK) model for ZOL
2. Identify significant covariates on ZOL's pharmacokinetics
3. Assess the dose-proportionality of ZOL over the dose range of 2 to 16 mg
4. Compare the pharmacokinetics of ZOL among different populations

Methods:

Data from two PK studies (listed below) in cancer patients with bone metastases were used to develop a population pharmacokinetic model.

Study ZOLJ001:

Title: Open-label, fixed ascending, dose ranging, safety trial of rapid intravenous infusion of — 42446 in any cancer patients with bone metastases. This study was conducted in Japan in 9 patients (4 males, 5 females). Blood samples were collected at predose, 5, 15, and 30 minutes,

and 1, 2, 4, 8, and 24 hours after the start of drug infusion. Six patients (4 mg & 8 mg treatment groups) had an additional sample point at 48 hours, for a total of 10 samples.

Study ZOL503:
Title: An open-label, single intravenous infusion dose study to determine the pharmacokinetics and pharmacodynamics of zoledronate in cancer patients with bone metastases. This study was conducted in the US and it included 23 patients (13 male, 10 female). Blood samples were collected predose, and at 5, 15, and 30 minutes, and 1, 2, 4, 6, 8, 10, and 24 hours. Additional samples were collected on Day 8, Day 15, and Day 29.

Plasma levels of ZOL from the above studies were used to develop a population PK model using _____ The structural model was selected after comparing two-compartment and three-compartment models with zero order input and first order elimination from the central compartment. The linear three-compartment model was parameterized according to the following:

- Total body clearance (CL)
- Intercompartmental clearance between central and 1st peripheral compartment (Q_1)
- Intercompartmental clearance between central and 2nd peripheral compartment (Q_2)
- V_1, V_2, and V_3 for volume of distribution for central, 1st peripheral, and 2nd peripheral compartment, respectively

Creatinine clearance, body weight, body mass index, gender, age, dose and Study were assessed as potential covariates for CL and V_1. Intersubject variability for CL and V_1 were modeled using an exponential error, as shown below:

- $CL_i = TVCL \cdot e^{\eta 1}$
- $V_{1i} = TVV_1 \cdot e^{\eta 2}$

where CL_i is clearance in the i^{th} subject, *TVCL*, modeled as a function of creatinine clearance, is the population typical value for clearance, V_{1i} is volume of distribution for the i^{th} subject and TVV_1, modeled as a function of body weight, is the population typical value for volume of distribution. η_1 and η_2 are the intersubject variability (normal distribution with a mean of zero) for clearance and volume of distribution, respectively. Residual variability, which includes intrasubject variability and model misspecification and other errors, was also modeled with an exponential error structure. Attachment A contains the control file (code) used for the final model.

Results:

According to the sponsor, the three-compartment model (Figure 1) provided a significantly improved fit of the data. This was based on a large decrease in the objective function, examination of residual plots, as well as evaluation of correlation plots of predicted versus observed plasma concentrations. Additionally, assignment of intersubject variability to both CL and V_1 in the model provided the best fits. Figure 2 illustrates observed Cp (plasma levels) vs. predicted values around the line of unity. The concentration-time profiles (observed and model predicted) for a representative number of patients are shown in Figure 3. Table I lists the PK parameters obtained following the population PK analysis of the two groups of patients.

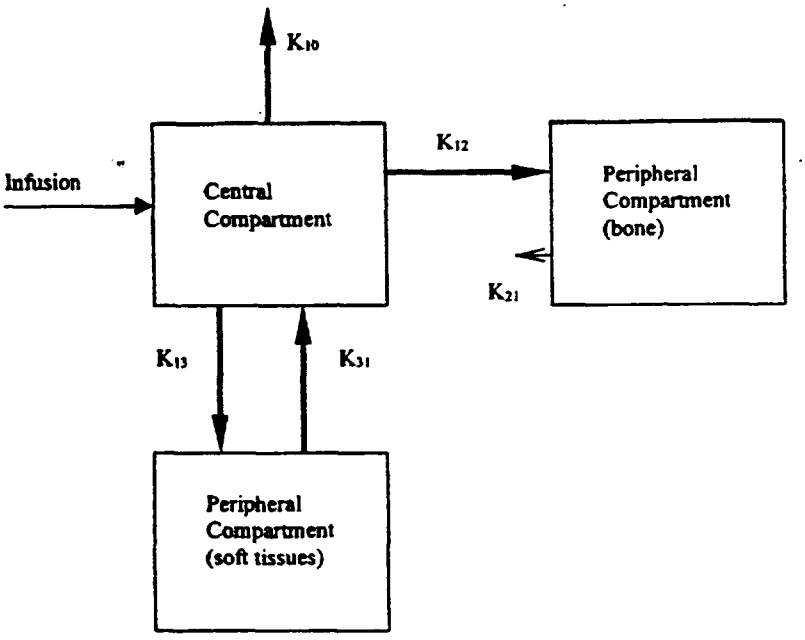

Figure 1. Illustration of the three compartment model used to fit the combined data sets of ZOL plasma levels from Study ZOLJ001 and Study ZOL503.

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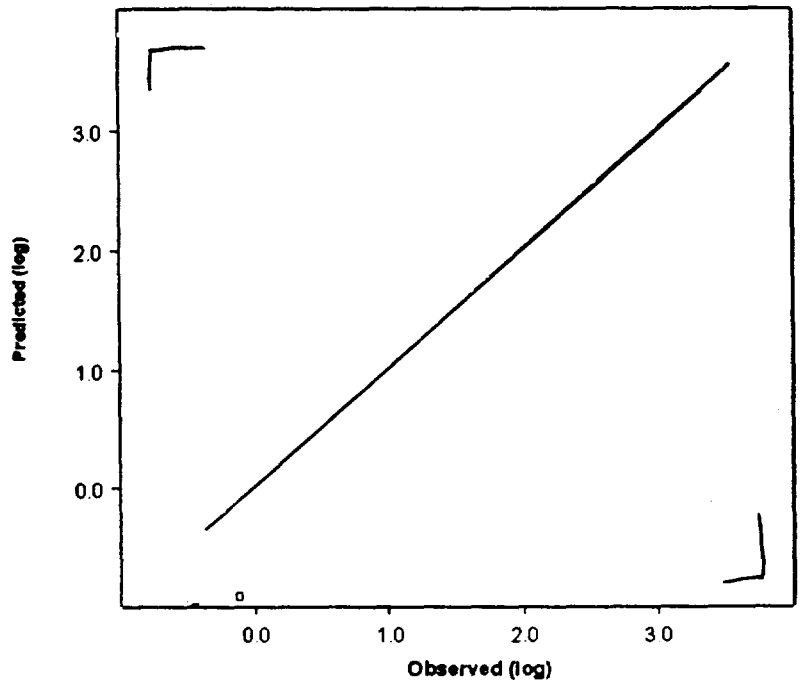

Figure 2. Observed versus model predicted plasma levels of ZOL, log transformed.

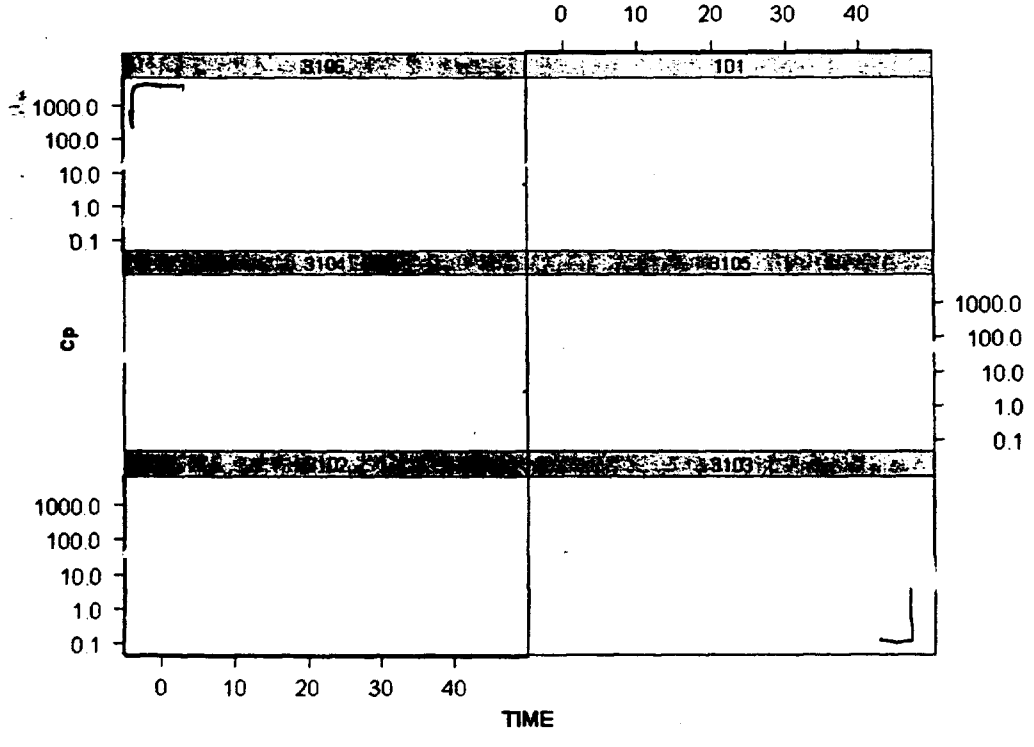

Figure 3. Observed (symbols) and model predicted (line) concentration over time profiles for a representative number of patients used in the population PK analysis.

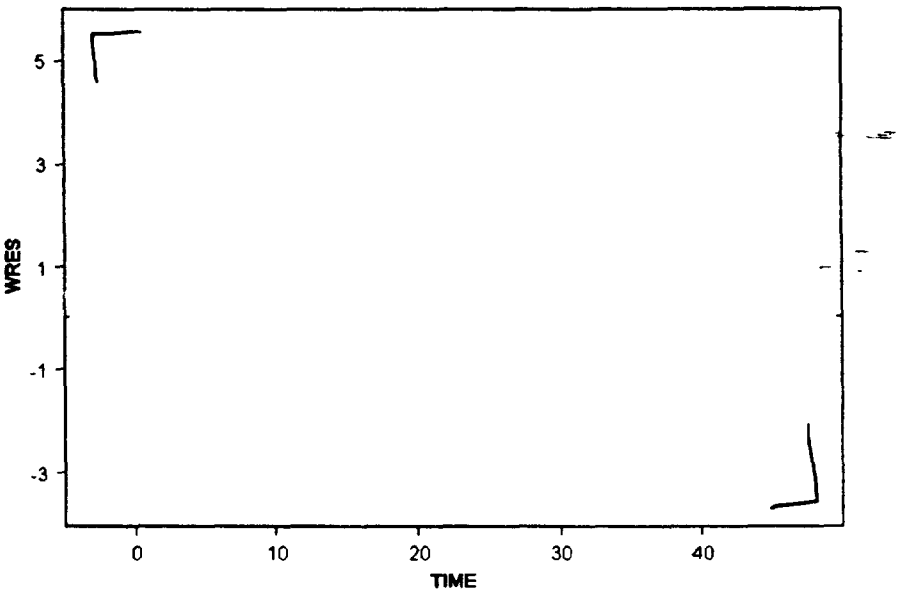

Figure 4. Weighted residuals versus Time, suggesting low or no bias in the model predictions.

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ID	RACE	DOSE (mg)	CL (L/h)	V1 (L)	CL*(70/BW)	K12/K21	BW (kg)	HT (cm)	AGE (year)	SEX	BMI	CLcr (mL/min)
Mean			6.26	10.0	5.6	41.4	78.03	170	56.8		26.56	79.2
SD			2.49	2.2	2.1	17.0	17.17	7.96	7.35		5.15	31.3
CV%			39.8	21.8	36.6	41.0	22.0	4.7	12.9		19.4	39.5
ID	RACE	DOSE (mg)	CL (L/h)	V1 (L)	CL*(70/BW)	K12/K21	BW (kg)	HT (cm)	AGE (year)	SEX	BMI	CLcr (mL/min)
Mean			5.26	10.8	4.4	38.7	61.50	171	59		28.14	75.7
SD			2.73	3.3	1.8	13.3	15.00	13	13		4.68	21.4
CV%			51.9	30.4	40.7	34.3	18.4	7.8	21.2		16.6	28.2
ID	RACE	DOSE (mg)	CL (L/h)	V1 (L)	CL*(70/BW)	K12/K21	BW (kg)	HT (cm)	AGE (year)	SEX	BMI	CLcr (mL/min)
Mean			4.50	6.1	5.4	66.3	57.5	156	56		23.9	89.3
SD			2.19	1.4	2.1	17.3	7.9	10	11		4.6	34.9
CV%			48.6	23.5	39.8	26.1	13.7	6.5	20.1		19.2	39.1
Overall Mean			5.55	9.0	5.3	47.8	73.0	166	57		26.2	81.3
Overall SD			2.51	2.9	2.0	19.8	17.4	12	10		5.0	30.1
Overall CV%			45.2	32.4	38.4	41.3	23.8	7.0	16.7		19.1	37.0

Table I. PK Parameter estimates and demographics of the patient population used in the analysis.

Reviewer's Comments:

1. The population PK model and analysis are acceptable.

2. Creatinine clearance is identified as a significant covariate for clearance as follows:

$$CL = 3.57*(CRT/82.55)^{0.9}$$

(This is supported by the fact that ZOL is eliminated mainly by the kidneys.) Based on this a dosing strategy based upon CrCl would decrease the variability associated with dosing and provide a more predictable response and avoid inadvertent under or over dosing.

3. Body weight is another significant covariate, which appears to impact the volume of distribution of the central compartment (V_1).

4. The average value of V_1 in Oriental patients was about 40% lower than that for Caucasian or Black patients. This is probably related to the lower body weight seen in Oriental patients. The clinical implications of this difference may need to be considered.

5. In the proposed labeling under **Special Populations**, the following changes should be made:

Hepatic Insufficiency:

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Peer reviewed by Dan Wang, Ph.D.

cc:
NDA 21-223
HFD-870 (Huang S-M, Shore R, Ahn H-Y, Haidar S)
HFD-880 (Wang D)
HFD-850 (Lee P)
CDR (Barbara Murphy For Drug)

Attachment A

NDA 21-223

NONMEM Control File

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Attachment B

NDA 21-223

Proposed Labeling: Product Description and Clinical Pharmacology sections

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Draft

Labeling

Appendix 4. Data

Individual and mean noncompartmental pharmacokinetic parameters

Study J001

Study	Pt. ID	Dose (mg)	Infusion time (h)	C_{end} (ng/mL)	C_{end}/dose (ng/mL/mg)	$AUC_{(0-24h)}$ (ng•h/mL)	$AUC_{(0-24h)}$ /dose (ng•h/mL/mg)	$Ae_{(0-24\ h)}$ (µg)	dose in urine$_{(0-24h)}$ (%)	CL_P (L/h)	CL_R (L/h)	CL_{tot} (mL/min)	CL_R/CL_{tot} (%)
J001	[												]
J001													
J001													
Group mean				453	227	344	172	883	44.17	6.1	2.8	86.4	58
std. dev.				162	81	98	49	213	10.67	1.7	1.5	35.6	27
J001	[												]
J001													
J001													
Group mean				668	167	540	135	2279	56.97	8.3	4.3	95.9	67
std. dev.				251	63	232	58	1539	38.47	3.0	3.3	44.0	23
J001	[												]
J001													
J001													
Group mean				1142	143	1133	142	3531	44.14	7.8	3.3	85.5	66
std. dev.				190	24	386	48	1364	17.06	3.3	1.4	39.6	17
Study mean					179		150		48.43	7.4	3.5	89.3	64
std. dev.					66		48		22.63	2.8	2.0	34.9	20

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Individual and mean noncompartmental pharmacokinetic parameters

Study 503

Study	Pt. ID	Dose (mg)	Infusion time (h)	C_{max} (ng/mL)	C_{max}/dose (ng/mL/mg)	$AUC_{(0-24h)}$ (ng•h/mL)	$AUC_{(0-24h)}$/dose (ng•h/mL/mg)	$Ae_{(0-24h)}$ (µg)	dose in $urine_{(0-24h)}$ (%)	CL_F (L/h)	CL_R (L/h)	CL_{cr} (mL/min)	CL_R/CL_{cr} (%)
503	[redacted]												
503													
503													
Group mean				393	99	411	103	1580	39.80	10.2	4.1	74.4	91
std. dev.				100	25	107	27	326	8.14	2.6	1.7	24.0	18
503	[redacted]												
503													
503													
503													
Group mean				267	67	497	124	1878	39.45	8.9	3.5	83.7	66
std. dev.				40	10	212	53	570	14.26	2.8	2.0	29.4	22
503	[redacted]												
503													
503													
503													
503													
503													
503													
503													
Group mean				526	66	816	102	3251	40.64	11.1	4.7	79.2	99
std. dev.				164	20	297	37	1367	17.09	4.5	2.9	27.1	50

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Individual and mean noncompartmental pharmacokinetic parameters

Study 503

Study	ID	Dose (mg)	Infusion time (h)	C_{end} (ng/mL)	C_{end}/dose (ng/mL/mg)	$AUC_{(0-24)}$ (ng•h/mL)	$AUC_{(0-24)}$/dose (ng•h/mL/mg)	$A_{(0-24\ h)}$ (µg)	dose in urine$_{(0-24)}$ (%)	CL_P (L/h)	CL_R (L/h)	CL_{tot} (mL/min)	CL_R/CL_{tot} (%)
503	[redacted]												
503													
503													
503													
503													
503													
503													
503													
Group mean				2759	172	2139	134	7394	46.22	8.0	4.1	76.7	90
std. dev.				3077	192	585	36	2992	18.70	2.6	2.5	34.6	120
Study mean					109		117		41.96	9.5	4.3	78.2	90
std. dev.					129		39		16.38	3.5	2.4	28.2	36
Across study mean (J001 and 503)							126		43.97	8.9	4.0	81.3	82
std dev.							44		17.78	3.3	2.3	30.1	36
min.							[redacted]						
max.													