CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-399

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21,399/S-000
Date of Submission:	December 12, 2002
Drug Name:	IRESSA (Gefitinib, ZD1839)
Dosage Form:	250 mg Film-Coated Oral Tablets
Sponsor:	AstraZeneca Pharmaceuticals LP
Reviewer:	Sophia Abraham, Ph.D.
Type of Submission:	Meeting Request

AstraZeneca requested a teleconference on February 6, 2003 to discuss their three Phase 3 clinical trials that were proposed to satisfy Subpart H Phase 4 Commitments for the use of IRESSA (gefitinib, ZD1839) in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). In response to the teleconference held on January 23, 2003, AstraZeneca submits a draft protocol for a survival trial (#709), to facilitate the review of these Phase 4 Commitments. Trial #709 is entitled "A Randomized Phase 3 Survival Study Comparing ZD1839 (IRESSA) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Subjects with Advanced NSCLC who have received One or Two Prior Regimens and Are Refractory or Intolerant to Their Most Recent Regimen".

IRESSA (Gefitinib, ZD1839), a novel synthetic anilinoquinazoline, is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. *In vitro*, ZD1839 inhibited tyrosine kinase activity of EGFR isolated from human EGFR-over-expressing squamous carcinoma cells with an IC_{50} value of 0.023-0.079 µmol/L (10-35 ng/ml). It is proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy. The proposed commercial formulation of IRESSA is a 250-mg round, brown, film-coated oral tablet. The proposed dosage regimen is one tablet daily with or without food.

No clinical pharmacology and biopharmaceutics issues were discussed during the teleconference on February 6, 2003.

RECOMMENDATION

No action is indicated.

/S/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-399
HFD-150/Division file
HFD-150/ Baird, Cohen, Farrell
HFD-860/Mehta, Sahajwella, Rahman, Abraham
CDR/Biopharm

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sophia Abraham
2/12/03 02:01:50 PM
BIOPHARMACEUTICS

Atiqur Rahman
2/12/03 04:17:21 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21,399
Date of Submission:	October 4, 2002
Drug name:	IRESSA (Gefitinib, ZD1839)
Dosage Form:	250 mg Oral Tablets
Applicant:	AstraZeneca Pharmaceuticals LP Wilmington, DE
Reviewer:	Sophia Abraham, Ph.D.
Type of Submission:	NDA (general)

This is a review of a response to FDA Request for information sent to Astra-Zeneca by facsimile on September 30, 2002. The information is in regard whether AstraZeneca assessed the plasma levels of the major active metabolite, O-desmethyl ZD1839, in Study ZD1839/0032. This study is designed to evaluate the pharmacokinetics of ZD1839 in patients with impaired hepatic function.

In response, Study ZD1839/0032 does not include the assessment of ZD1839 metabolites in patients with hepatic impairment. The study will be submitted prior to December 2002 to the Agency.

RECOMMENDATION

We recommend that if you still have the blood samples from Study ZD1839/IL0032, you analyze these samples for the O-despmethyl metabolite ((M523595) and determine its plasma pharmacokinetics. The data for this O-desmethyl metabolite should be included in the study report when it is submitted to the Agency for review.

Please forward the above Recommendation to the Applicant.

/S/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-399
HFD-150/Division file
HFD-150/Baird, Williams, Cohn
HFD-860/Mehta, Sahajwella, Rahman, Abraham
CDR/Biopharm

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sophia Abraham
10/11/02 01:38:23 PM
BIOPHARMACEUTICS

Atiqur Rahman
10/17/02 04:23:19 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW	
BRAND NAME:	IRESSA
GENERIC NAME:	Gefitinib (ZD1839)
DOSAGE FORM/STRENGTH:	250 mg Oral Tablets
NDA:	21-399
INDICATION:	Advanced Non-Small Cell Lung Cancer
SUBMISSION TYPE:	NDA (NME)
APPLICANT:	AstraZeneca Pharmaceuticals
SUBMISSION DATES:	August 02, 2002 October 07, 2002
OCPB DIVISION:	DPE-1 (HFD-860)
OND DIVISION:	DODP (HFD-150)
OCPB REVIEWER:	Sophia Abraham, Ph.D.
OCPB TEAM LEADER:	Atiqur Rahman, Ph.D.
PHARMACOMETRICS REVIEWER:	Brian Booth, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Joga Gobburu, Ph.D.

I. Executive Summary

The Applicant seeks approval for IRESSA (gefitinib, ZD1839) 250 mg oral Tablet to be used in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy. The proposed oral dose of IRESSA is one 250 mg tablet once daily with or without food.

A. Recommendations

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant for NDA 21-399 (IRESSA 250 mg Tablets) is acceptable. The Applicant should address the Phase 4 Commitments below and incorporate the OCPB's labeling recommendations as outlined in Section VI of this review (pp. 41) in IRESSA package insert. We recommend the following dissolution method and specifications for IRESSA 250 mg commercial brown, round, biconvex, film-coated tablets:

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	50 rpm
Medium	1000 ml of Tween 80 (5% v/v) in water
Temperature	37 °C
Proposed Specifications	[redacted]% dissolved in 45 minutes

Please forward the above Recommendations and Comments 1 and 2 to the firm (pp. 2).

B. Phase 4 Commitments

1. During clinical trials, some patients developed an elevation in their International Normalized Ratios (INR) and/or bleeding events when given IRESSA in combination with warfarin. We recommend that you conduct a pharmacokinetic study in patients taking IRESSA in combination with warfarin to explore the mechanism that caused such an increase in INR and/or occurrence of bleeding events.

2. You are required to submit the study report and individual data for Trial 32, entitled "An Open, Non-Randomized, Multicenter, Phase I Study to Compare the Pharmacokinetics and Tolerability of Multiple Oral Doses of ZD1839 (IRESSA) in Patients with Solid Tumors and Normal, Moderate or Severe Hepatic Impairment", to provide proper dosage adjustment for this patient population in the package insert for IRESSA.

C. Comments

To the Applicant:

1. In future Clinical Pharmacology studies, we recommend that you determine the plasma profiles of both parent drug, ZD1839 and its major pharmacologically active metabolite, O-desmethyl ZD1839.

2. We also recommend that you to assess the plasma protein binding of the O-desmethyl metabolite alone and in the presence of ZD1839.

To the Medical Reviewer:

3. A study is underway to assess the effect of hepatic impairment on the pharmacokinetics of ZD1839 (Trial 32). No specific dosing recommendations could be included in the labeling for IRESSA for this special population. The label should include a precaution for the use of IRESSA in hepatically impaired patients until the study is completed and submitted to the Agency for review.

4. ZD1839 undergoes metabolism in humans to several active metabolites. Of the five circulating metabolites identified in plasma, the major one was the O-desmethyl ZD1839. O-desmethyl ZD1839 has comparable plasma levels and EGFR-TK inhibition activity as the parent drug (mean IC_{50}=0.036 μM and 0.033 μM, respectively). The pharmacokinetics of the O-desmethyl metabolite were not determined in all Clinical Pharmacology and Biopharmaceutics studies. Specific dosage recommendations for drug-drug interactions and for patients with organ dysfunction can not be made in the absence of the pharmacokinetics of the O-desmethyl metabolite.

II. Table of Contents

III. List of Abbreviations

AUC	Area under the concentration-time curve from time zero to infinity
AUC(0-24h)	Area under the concentration-time curve from time zero to 24 hours
CI	Confidence interval
CL	Total plasma clearance
C_{max}	Peak plasma concentration
C_{min}	Trough plasma concentration
CYP	Cytochrome P450 enzymes
%CV	Coefficient of variation (CV=SD/mean x100)
DPE	Division of Pharmaceutical Evaluation
DODP	Division of Oncology Drug Products
EGFR	Epidermal growth factor receptor
F_{abs}	Absolute bioavailability
h	Hour
HPLC	High performance liquid chromatography
IC_{50}	Concentration at which 50% inhibition of enzyme activity occurs
IV	Intravenous
LOQ	limit of quantification
MAPK	Mitogen-activated protein kinase
MW	Molecular weight
n	number of subjects
NSCLC	Non-small cell lung cancer
NDA	New Drug Application
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
OND	Office of New Drugs
PK	Pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
q.s.	Quantity sufficient
SD	Standard deviation
SN	Serial number
$t_{1/2}$	Elimination half-life
TK	Tyrosine kinase
T_{max}	Time to C_{max}
V_{ss}	Steady state volume of distribution
vs	versus

IV. Summary of Clinical Pharmacology and Biopharmaceutics Findings

IRESSA (Gefitinib, ZD1839) is an anilinoquinazoline with the chemical name of N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazoline-4-amine and molecular weight of 447. ZD1839 is an inhibitor of the epidermal growth factor receptor tyrosine kinase activity (EGFR-TK). It blocks EGFR autophosphorylation and, consequently, blocks signal transduction from the EGFR at a mean IC_{50} value of 0.033 μM (16.5 ng/ml); steady state trough plasma levels ranged from 30-1070 ng/ml following daily 250 mg oral doses to cancer patients.

IRESSA (Gefitinib, ZD1839) is proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy. The proposed dosage regimen is one tablet once daily with or without food. The proposed commercial formulation of IRESSA is a 250-mg round, biconvex, brown, film-coated oral tablet manufactured at Macclesfield, UK.

According to the Applicant, no obvious relationship was found between dose and response and/or ZD1839 trough plasma concentrations and response. The selection of dose for the Phase 2 Trials 39 (pivotal) and 16 (supportive) was based on maximally tolerated dose determined in Phase 1 Trials 11 and 12. In Trials 11 and 12, escalating oral doses of 150 mg to 1000 mg of ZD1839 were administered once daily for 28 days to patients with solid tumors. Based on the results from these two Phase 1 trials, two dose levels of ZD1839, 250 mg/day and 500 mg/day, were selected to be evaluated in patients with NSCLC in the Phase 2 Trials 39 and 16. In Trial 39, according to the Applicant, the objective tumor response rate is 11.8% and 8.8% after the 250 mg and 500 mg doses, respectively. The disease-related symptom improvement rate is 43.1% and 35.1% after the 250 mg and 500 mg doses, respectively. Dose reduction due toxicity occurred in 1% of patients at the 250 mg/day dose versus 8.8% of patients at the 500 mg/day dose. The mean (± SE) population predicted trough plasma concentration is 261 ± 11.5 ng/ml for the 250 mg dose and 512±73.6 ng/ml for the 500 mg dose. Because the 250 mg/day dose provided an acceptable safety profile than the 500 mg/day dose, the Applicant selected the 250 mg/ day dose to support the proposed indication for use of IRESSA in the treatment of patients with locally advanced or metastatic NSCLC.

Following single-dose oral administration, the absorption of ZD1839 is moderately slow with peak plasma concentrations (C_{max}) achieved within 3-7 hours after dosing. Cancer patients have 2-fold higher exposure to ZD1839 than healthy volunteers at the same dose level. Absolute bioavailability of ZD1839 is 60% in both healthy volunteers and in cancer patients. In overall Clinical Pharmacology trials, variability in AUC is comparable between healthy volunteers and cancer patients following oral administration, CV=60-68%, n=177 and CV=45-70%, n=74, respectively. However, following IV administration, variability in AUC is higher in cancer patients (CV=52%, n=19) than in healthy volunteers (CV=22%, n=4). ZD1839 exhibits linear kinetics over the therapeutic dosing range in both healthy volunteers and cancer patients.

Administration of a single 250 mg oral dose to healthy male volunteers after a high-fat breakfast increased ZD1839 AUC and C_{max} by about 30%. This food effect may not be clinically significant and patients could be administered IRESSA with or without a meal; although patients during clinical trials took ZD1839 tablets in the morning on an empty stomach (250 mg and 500 mg once daily). Concomitant administration of a single 250 mg oral dose of ZD1839 with a high dose of ranitidine (to sustain the pH level above pH 5.0) decreased ZD1839 AUC by 44% and C_{max} by 70% in healthy male volunteers. The Applicant included a precaution statement in IRESSA labeling that drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of IRESSA and therefore potentially may reduce efficacy.

ZD1839 is widely distributed throughout the body with a mean steady state volume of distribution of 1400 ±504 L after a single 50 mg IV bolus dose to cancer patients. ZD1839 is 91% bound to human plasma proteins over the concentrations of 50-8000 ng/ml. It is 83% bound to serum albumin and 82-64% bound to alpha1-acid glycoprotein at ZD1839

concentrations of 50-8000 ng/ml. The plasma protein binding of the major active metabolite, O-desmethyl ZD1839, has not been determined.

ZD1839 is extensively metabolized in the liver. The identified metabolic pathways include O-demethylation, dealkylation, and oxidative defluorination. CYP3A4 is the major cytochrome P450 enzyme responsible for ZD1839 metabolism. Five pharmacologically active metabolites were identified in human plasma following oral administration of ZD1839 to cancer patients. The major identified metabolite is the O-desmethyl metabolite. It has comparable exposure and EGFR-TK inhibition activity as the parent drug (IC_{50}= 0.036 μM *vs* 0.033 μM, respectively). Unchanged ZD1839 was the only active drug moiety measured in Clinical Pharmacology studies and used to assess the pharmacokinetic parameters and concentration/response relationships. About 90% of the radioactive orally administered dose recovered in urine and feces over 10 days, 86% of dose recovered in the feces with less than 4% of the dose in the urine. The radioactivity identified in feces was unchanged parent drug (12.1%), carboxypropyl metabolite (12.1%), O-desmethyl metabolite (26.3%), aldehyde metabolite (12.1%), and other (unidentified) metabolites (37.4%). Total plasma clearance and elimination half-life of ZD1839 average 595±358 ml/min and 48±27 hours, respectively, after a single 50 mg IV bolus dose to cancer patients.

Following oral administration of 50 mg to 700 mg daily doses of ZD1839 to cancer patients, steady state reaches within 10 days after dosing with steady state plasma levels two-fold higher than those achieved following single doses.

Age appears to have no significant effects on the exposure to ZD1839. Exposure to ZD1839 is 27% higher in females than males (normalized to body weight); this is not clinically significant.

There were insufficient data available from different racial and ethnic groups other than Caucasians to investigate potential pharmacokinetic differences between these groups. A cross-study comparison showed that Japanese and Caucasian patients have comparable exposure to ZD1839.

A study is underway to assess the effect of hepatic impairment on the pharmacokinetics of ZD1839. No specific dosing recommendations could be included in the label for this special population. Since ZD1839 is primarily eliminated in the liver, the label will also include a precaution for the use of IRESSA in hepatically impaired patients until the study is completed and submitted to the Agency (Phase Commitment 2).

As renal clearance is not a major route of excretion for ZD1839 (<4% of dose in urine), the Applicant has not conducted a formal renal impairment study. However, the label will include a precaution for patients with severe renal impairment.

No data are currently available on the pharmacokinetics of ZD1839 in pediatric patients.

There is no information regarding the use of IRESSA in pregnant or lactating women.

In vitro studies with human liver microsomes indicate that ZD1839 at concentrations ranging from 0.004 to 11.2 μM (2 to 5000 ng/ml) has a little inhibitory potential on CYP1A2, CYP2C9, and CYP3A4 activities; the %inhibition is less than 10%. Inhibition of CYP2C19 and CYP2D6 activity, however, is more pronounced with %inhibition of 23.7% and 43%,

respectively, at the highest ZD1839 concentration (11.2 μM). These results indicate ZD1839 may have a potential to inhibit the metabolism of drugs that are substrates of CYP2C19 and CYP2D6. In addition, ZD1839 is a substrate of CYP3A4; and drugs that are substrates and/or inhibitors of this enzyme are expected to inhibit its metabolism.

Concomitant itraconazole administration (200 mg QD for 12 days), an inhibitor of CYP3A4, with ZD1839 (250 mg single dose) increased the mean ZD1839 C_{max} and AUC by 55% and 88% respectively, compared to ZD1839 alone treatment to healthy male volunteers. The increase in exposure to ZD1839 may be clinically relevant and patients may experience adverse events when ZD1389 is concomitantly administered with drugs that are substrates and/or inhibitors of CYP3A4.

Rifampicin (600 mg daily), an inducer of CYP3A4, reduced mean C_{max} and AUC of ZD1839 by about 60% and 85%, respectively, when given in combination with ZD1839 (500 mg single dose) to healthy male volunteers. This may be clinically significant; the efficacy of ZD1389 may be reduced when it is concomitantly administered with drugs that induce CYP3A4.

Exposure to metoprolol (50 mg single dose), a substrate of CYP2D6, increased by 30% when given in combination with ZD1839 (500 mg QD for 28 days), an inhibitor of CYP2D6 in patients with solid tumors. This may not be clinically significant and no dosing reduction is warranted for metoprolol when given in combination with ZD1839.

During clinical trials with ZD1839, elevations in the International Normalized Ratio (INR) and/or bleeding events were reported in some patients taking warfarin while on ZD1839 therapy (Overall NDA Summary). A formal drug interaction study with warfarin may explain the mechanism that caused such increase in INR and/or occurrence of bleeding events (see Phase 4 Commitment 1). The Applicant included a precaution statement in the labeling for IRESSA that patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

ZD1839 can be categorized as a "Low Solubility-High Permeability" (Class 3) drug.

The Applicant proposes the following dissolution method and specifications for IRESSA 250 mg commercial brown, round, convex, film-coated tablets:

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	50 rpm
Medium	1000 ml of Tween 80 (5% v/v) in water
Temperature	37 °C
Proposed Specifications	[redacted]% dissolved in 45 minutes

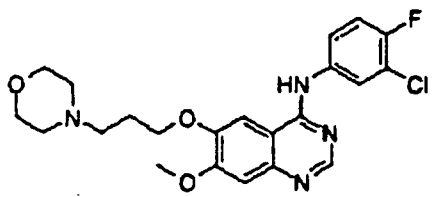
We recommend specifications of [redacted]% dissolved in 45 minutes.

V. 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?

ZD1839 is a novel synthetic anilinoquinazoline with a chemical name of N- (3-chloro-4-fluorophenyl)-7-methoxy-6- (3-morpholino-propoxy) quinazoline-4-amine ($C_{22}H_{24}ClFN_4O_3$) and molecular weight of 447. It is a free base with two pK_a values of 5.4 and 7.2. It is highly soluble at pH 1.0 (21 mg/ml), but is practically insoluble at pH 7 (<0.001 mg/ml)), with the solubility dropping sharply between pH 4 and pH 5 (2.6-0.17 mg/ml). ZD1839 is freely soluble in glacial acetic acid and dimethylsulfoxide; soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, and acetonitrile. The log n-octanol/water partition coefficient is 4.15, indicating that it is a lipophilic compound. ZD1839 has the following structural formula:



The proposed commercial formulation of IRESSA is a 250-mg round, biconvex, brown, film-coated oral tablet manufactured at Macclesfield, UK. The composition of the commercial tablet formulation is as follows:

Ingredient	**Amount (mg/tablet)**
Tablet core	
ZD1839	250.0
Lactose monohydrate	
Microcrystalline cellulose	
Croscarmellose sodium	
Povidone	
Sodium lauryl sulfate	
Magnesium stearate	
Nominal core tablet weight	
Tablet coating	
Hydroxypropyl methylcellulose	
Polyethylene glycol 300	
Red ferric oxide	
Yellow ferric oxide	
Titanium dioxide	
Nominal coated tablet weight	511.45

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

IRESSA (Gefitinib, ZD1839) is an inhibitor of the epidermal growth factor receptor tyrosine kinase activity (EGFR-TK) which is commonly expressed in solid human tumors of epithelial origin. EGFR is a 170-kd plasma membrane glycoprotein that belongs to the ErbB receptor tyrosine kinase family. *In vitro*, ZD1839 inhibited the EGFR-TK activity isolated from human EGFR-over-expressing squamous carcinoma cells at a mean IC_{50} value of 0.033 μM (16.5 ng/ml). Inhibition of EGFR-TK activity by ZD1839 decreases tumor growth, metastasis, and angiogenesis and increases cell apoptosis.

IRESSA (Gefitinib, ZD1839) is proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy.

What is the proposed dosage and route of administration?

The proposed dosage is one tablet (250'mg) orally daily with or without food.

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

Efficacy and safety information was collected from Phase 2 Trials 39 (pivotal) and 16 (supportive). These trials evaluated the efficacy and safety of once daily oral doses of 250 mg and 500 mg ZD1839 in patients with locally advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. Both trials were multi-center, randomized, two-dose, double-blind, parallel-group Phase 2 trials.

- Trial 39 was conducted in the United States with 216 patients (30 to 84 years of age, 93 Females; 123 Males, 196 White; 7 Black, 5 Hispanic, 4 Asian, 4 Others) received trial treatment (102 patients had 250 mg/day and 114 patients had 500 mg/day).

- Trial 16 was conducted in Europe, Australia, South Africa, and Japan with 209 patients (28 to 85 years of age, 62 Females, 148 Males, 102 White, 102 Japanese, 2 Black; 2 Hispanic, one Oriental, 1 Maltese) received trial treatment (103 patients had 250 mg/ day, and 106 patients had 500 mg/day).

In Trial 39, patients had to have previously received at least two chemotherapy regimens that contained platinum and docetaxel given concurrently or sequentially.

In Trial 16, patients had to have previously received either one or a maximum of two chemotherapy regimens, one of which contained platinum. Apart from these differences, the design of these two trials was very similar.

The primary efficacy endpoints in the Phase 2 trials (Trials 39 and 16) were objective tumor response rate and disease-related symptom improvement rate (as measured weekly using the Lung Cancer Subscale [LCS]). Objective responses were seen in both trials at 250 mg/ day and 500 mg/day doses by Day 28 and continued to occur up to 4 months. Improvement in disease-related symptom rates was also seen in both trials at both doses. A summary of these efficacy findings from Trials 39 and 16 are presented below:

[Applicant's Table]

Summary of key efficacy findings in pivotal Trial 39 and supportive Trial 16

Efficacy endpoint	Trial 39		Trial 16	
	250-mg/day group (N=102)	500-mg/day group (N=114)	250-mg/day group (N=103)	500-mg/day group (N=106)
Objective tumor response rate, %	11.8	8.3	18.4	19.0
95%CI	6.2 - 19.7%	4.3-15.5	11.5-27.3	12.1-27.9
Duration of objective response, range (months)	1+ - 7+	2+ - 4+	1+ - 5+	1+ - 6+
Symptom improvement rate, %	43.1	35.1	40.3[a]	37.0[a]
95% CI	33.4 - 53.3	26.4 - 44.6	28.5 - 53.0	26.0 - 49.1
Median time to symptom improvement (days)	10	9	8[a]	8[a]
95% CI	8 - 22	9 - 16	7 - 10	8 - 15
Disease control rate[b], %	42.2	36.0	54.4	51.4
95% CI	32.4 - 52.3	27.2 - 45.5	44.3 - 64.2	41.5 - 61.3
Median duration of disease control (months)	4.1	3.6	3.2	4.6
95% CI	2.8 - 4.7	2.8 - 4.5	2.8 - NC	3.2 - NC
Median PFS (months)	1.9	2.0	2.7	2.8
95%CI	1.8 - 2.8	1.6 - 2.2	2.0 - 2.8	1.9-5.8
Median survival (months)	6.1	6.0	NC	NC
95% CI	4.8 - 7.7	4.3 - 7.2	5.3 - NC	6.1-NC

[a] Based on patients evaluable for symptom improvement 250-mg (n=67); 500-mg (n=73)).
[b] Disease control = Partial response + partial response in non-measurable disease + stable disease 56 days.
+ = data are ongoing as of data cutoff.
NC Not calculable.
PFS Progression-free survival.

Drug-related adverse events experienced were diarrhea, rash, acne, dry skin, nausea, and vomiting. The Applicant performed population PK analysis on the combined trough plasma data for Trials 39 and 16 [974 trough plasma concentrations from 353 patients]. The mean (± SE) population predicted trough concentration is 261 ± 11.5 ng/ml for the 250 mg dose and 512±73.6 ng/ml for the 500 mg dose. Interpatient variability in trough levels is 55% for the 250 mg dose and 59% for the 500 mg dose. Intrapatient variability is 29.6% for Trial 39 and 22% for Trial 16. No obvious relationship is observed between objective response rate and the predicted steady state trough concentrations.

In conclusion, both trials demonstrate the 250 mg/day dose has comparable efficacy to the 500-mg dose but with favorable safety profile than the 500 mg/day dose.

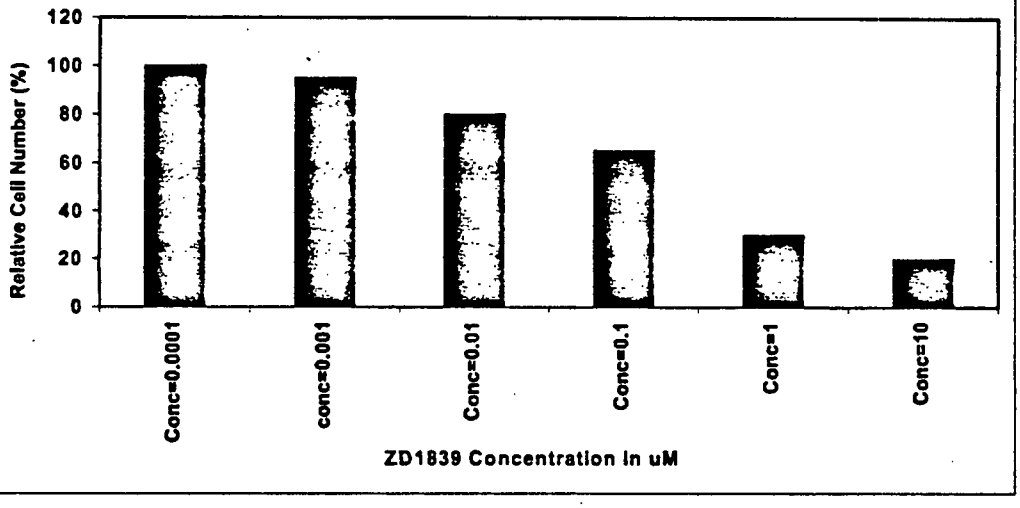
B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

In vitro studies explored the potential surrogate markers of ZD1839 efficacy such as the inhibition of activated (phosphorlyated) EGFR and downstream receptor-dependent molecules such as mitogen-activated protein kinase (MAPK).

The possible correlations between inhibition of EGFR phosphorlyation and inhibition of receptor transduction pathways such as the Ras-Raf-mitogen-activated protein kinase (MAPK) pathways, and effects on receptor-dependent processes such as tumor cell proliferation or apoptosis were examined *in vitro* using human EGFR-over-expressing human squamous carcinoma and adenocarcinoma cell lines. A dose-dependent inhibition of cell proliferation in monolayer cultures for the EGFR-over-expressing squamous carcinoma cells was observed at ZD1839 *in vitro* concentrations ranging from 0.0001-10 μM (Fig. 1).

Fig. 1. Correlation between inhibition of cell growth and ZD1839 concentrations

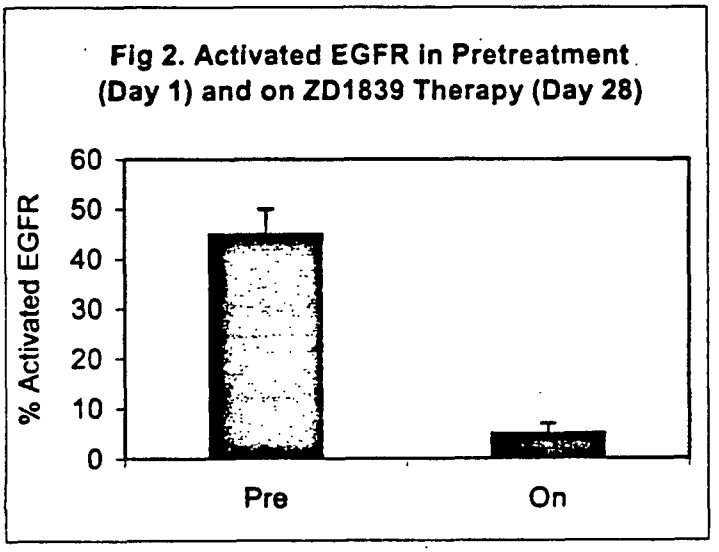


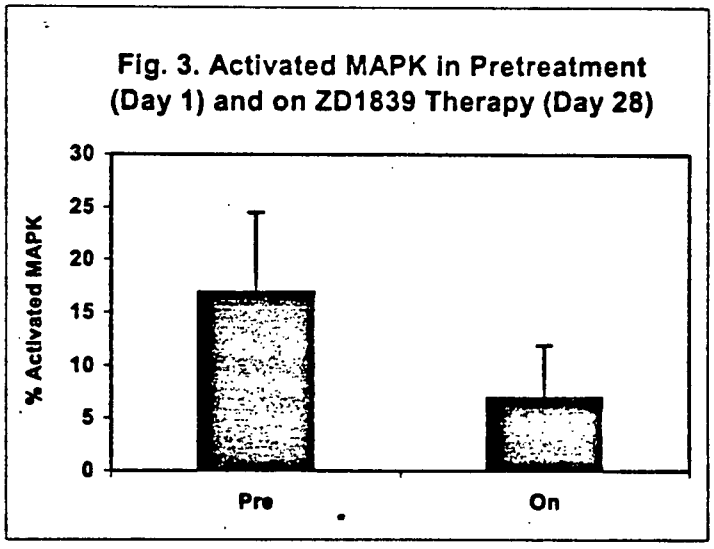
A mean IC_{50} value of 0.033 µM (16.5 ng/ml) was obtained indicating that ZD1839 is an inhibitor of EGFR-TK activity. ZD1839 also decreased the activated (phosphorylated) MAPK staining and shifted the total (phosphorylation-dependent) MAPK staining to a mainly cytoplasmic localization at same ZD1839 concentrations that inhibited tumor cell growth.

Because of correlations between inhibition of tumor cell growth and ZD1839 concentrations, and inhibition of activated EGFR or MAPK and ZD1839 concentrations, these two surrogate markers (EGFR and MAPK inhibition) were assessed in skin biopsies from patients treated with ZD1839 in Phase 1 Trials 11 and 12.

Phase 1 Trials 11 and 12 assessed the pharmacodynamics (PD) endpoints ((EGFR and MAPK inhibition) using skin biopsies to measure the biological effects of ZD1839. Both trials were multicenter, open-label, randomized, parallel-group, dose-ranging trials

conducted in United States (Trial 11) and Europe/Australia (Trial 12) in patients with metastatic or advanced tumors with no standard therapy for non-small cell lung cancer (NSCLC), head and neck cancer, colorectal cancer, prostate cancer, or ovarian cancer. In Trial 11, sixty-nine (69) patients (ranging in age from 27 to 90 years) received trial medication. In Trial 12, eighty-eight (88) patients (ranging in age from 33 to 81 years) received trial medication. Escalating oral doses of ZD1839 (150, 225, 300, 400, 600, 800, or 1000 mg) were administered once daily for 28 days (14 patients per dose level). Normal skin biopsy samples (n=104) were collected from consenting patients (n=65) two weeks before treatment with ZD1839 and on day 28 after dosing. The skin was chosen because it is easily accessible and has high levels of EGFR-expression. The effect of ZD1839 on EGFR and MAPK activation (phosphorylation) was measured by immunohistochemistry and immunostaining using an antibody specific for activated (phosphorylated) EGFR and MAPK. Trough plasma concentrations of ZD1839 for blood samples collected from the 65 patients on day 28 were analyzed by [redacted] method with [redacted]. The results showed that the decrease in EGFR-expression in epidermal keratinocytes was significant during ZD1839 therapy compared to pre-therapy ($p < 0.001$) (Fig. 2). There was also a significant reduction in the staining for activated MAPK on-therapy with ZD1839 in the basal layer of the epidermis ($p < 0.001$) (Fig. 3).





However, there are no significant correlations between dose levels of ZD1839 and the on-therapy levels of activated EGFR and MAPK. The steady-state trough plasma concentrations obtained on day 28 of therapy correlate with the dose of ZD1839 ($r = 0.63$; $p<0.001$) (Tables I.a and I.b), but there is no significant correlation with the on-therapy levels of activated EGFR. A significant relationship is seen between plasma concentrations and levels of activated MAPK ($r = 0.38$; $p=0.021$). Because of the lack of correlation between these markers of ZD1839 biological activity and dose/concentrations, the Applicant did not use these markers in the selection of dose for Phase 2 trials.

Table I.a Steady-state trough concentrations of ZD1839 on Day 28 (Trial 11)

Statistics	Dose of ZD1839, mg						
	150	225	300	400	600	800	1000
	N = 13	N = 13	N = 13	N = 13	N = 6	N = 6	N = 5
n	12	9	12	5	3	1	0
Gmean, ng/ml	172	190	265	621	774	287	—
CV, %	22	14	21	16	10	10	—
Minimum, ng/ml							
Maximum, ng/ml							

CV Coefficient of variation.
Gmean Geometric mean.
n Number of patients with steady-state plasma concentrations.
N Number of patients.

The geometric mean steady-state trough plasma concentration increased from 172 ng/ml at ZD1839 dose of 150 mg/day to 774 ng/ml at ZD1839 dose of 600 mg/day. Plasma concentrations were obtained from one patient treated at the 800 mg dose level and no patients at the 1000 mg dose.

Table I.b Steady-state trough plasma concentrations of ZD1839 on Day 28 (Trial 12)

Statistics	Dose of ZD1839, mg						
	150	225	300	400	600	800	1000
	N = 6	N = 14	N = 14	N = 14	N = 14	N = 14	N = 12
n	5	12	11	11	10	11	9
Gmean, ng/ml	122	160	247	478	620	736	1099
CV, %	40	56	55	41	43	39	58
Minimum, ng/ml							
Maximum, ng/ml							

CV Coefficient of variation.
Gmean Geometric mean.
n Number of patients with steady-state plasma concentrations.
N Number of patients.

Across the dose range studied, the geometric mean steady state trough plasma concentration increased from 122 ng/ml dose of 150 mg/day to 1099 ng/ml at ZD1839 dose of 600 mg/day.

Are the active moieties in serum appropriately identified and measured to assess pharmacokinetic parameters and exposure/response relationships?

Five metabolites were identified in human plasma following oral administration of ZD1839. Although, the O-desmethyl metabolite (M523595) has comparable exposure and potency as ZD1839 (Fig. 4 and Tables II and IIIa and b), unchanged ZD1839 was the only drug-related entity measured in clinical pharmacology studies and used to assess the pharmacokinetic parameters and exposure/response relationships.

ZD1839 is extensively metabolized in human liver microsomes to several pharmacologically active metabolites (Study KMN012) (Fig. 4). The identified pathways include O-demethylation of the methoxy-substituent on the quinazoline nucleus (M523595), metabolism of the N-propoxymorpholine group (M537194, M527301, M295820), and oxidative defluorination of the halogenated phenyl group (M387783). *In vitro* studies with human liver microsomes indicated that CYP3A4 is the major cytochrome P450 enzyme responsible for ZD1839 metabolism (Study KMX024). The pharmacological activity of potential ZD1839 metabolites was evaluated using *in vitro* kinase and cell growth inhibition assays; the results are summarized below (Table II).

Table II Pharmacological activity of ZD1839 and potential metabolites

Species	MW	Receptor kinase activity inhibition, IC_{50} (μM)				Cell growth inhibition, IC_{50} (μM)	
		EGFR	erB2	KDR	FGFR	EGF-stimulated	Basal
ZD1839	447	0.033	>1.2	>1.2	>33	0.054	8.8
M387783	445	0.199	>3.7	>1.2	>33	0.788	19.9
*M523595	433	0.036	>3.7	>33	>33	0.730	15.1
M537194	421	0.011	>1.2	>1.2	>11	0.375	5.51
M527301	378	0.037	>1.2	>0.4	>33	0.123	12.2
M295820	320	<0.005	>11	>1.2	>33	0.231	23.0

*Major circulating metabolite, O-desmethyl

The mean plasma concentration/time profiles of ZD1839 and its metabolites in cancer patients following daily oral doses of 525 mg ZD1839 are shown in Fig. 5 (Trial 5). Of the five circulating metabolites identified in human plasma, the major one is the O-desmethyl ZD1839 (M523595). It has comparable plasma levels and EGFR-TK inhibition activity as the parent drug (mean IC_{50}=0.036 μM and 0.027 μM, respectively). All metabolites are enzyme inhibitors of the EGFR-TK activity with similar or more potent activity than parent drug. Only parent drug was measured in all clinical pharmacology studies. The Applicant claims that there is no obvious relationship between efficacy and EGFR-TK inhibition.

Fig. 4 Structures of ZD1839 and its metabolites [Applicant's Figure]

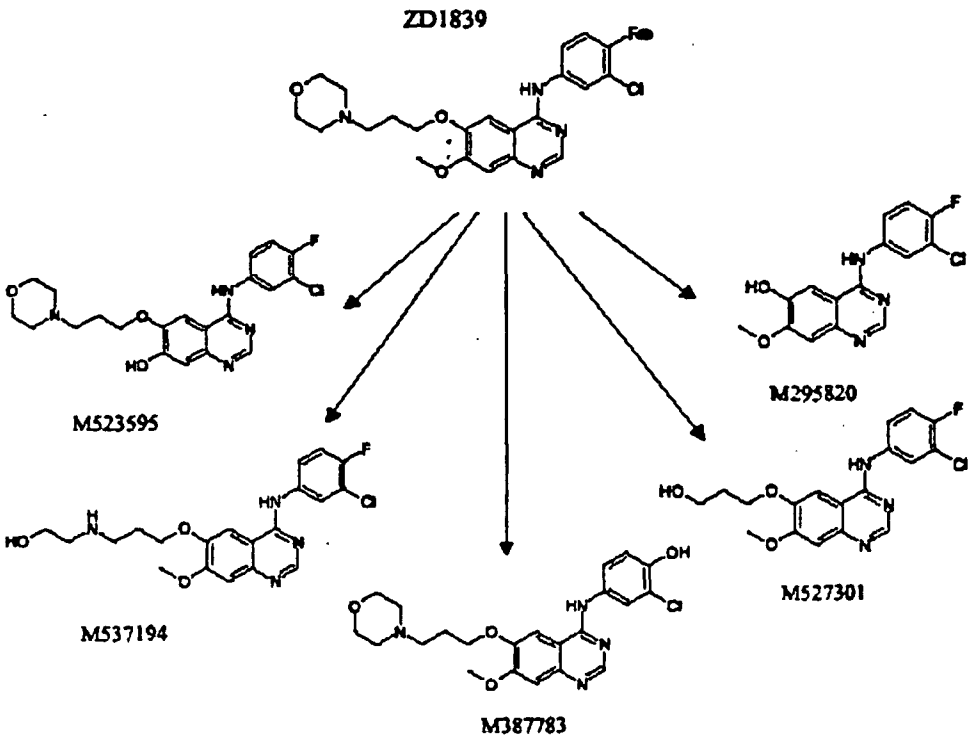


Fig. 5 Mean plasma concentration-time profiles of ZD1839 and metabolites following 14 daily oral doses of 525 mg ZD1839 (n=9 patients)

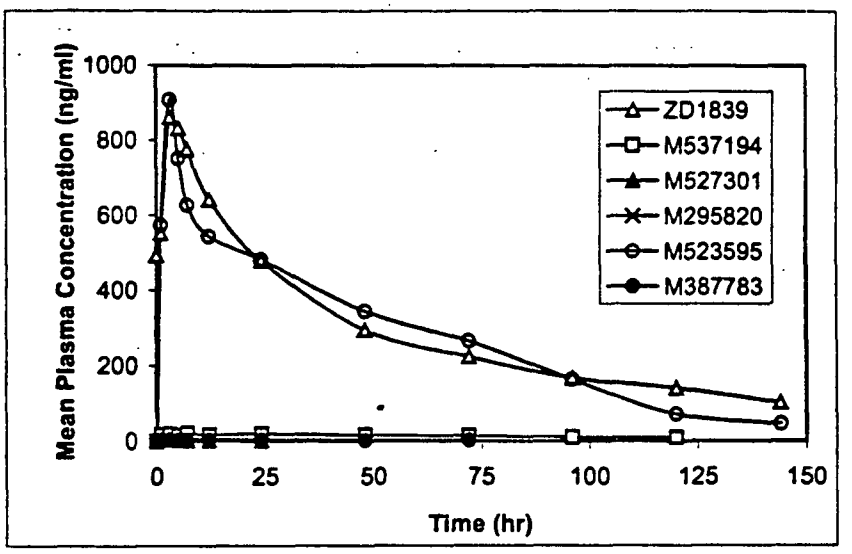


Table IIIa. Steady-state exposure to ZD1839 and its metabolite following 14 daily oral doses of 525 mg to 9 patients (Trial 5)

AUC(0-24) μg.h/ml	ZD1849	M537194	M527301	M295820	*M523595	M387783
Mean±SD	15.7±5.5	0.418±0.322	0.061	0.088, 0.324	14.3±8.5	0.092±0.036
%CV	35%	77%	–	–	59%	39%
n	9	8	1	2	8	6

*Major metabolite, O-desmethyl ZD1839

Table IIIb. Steady-state PK parameters of ZD1839 and O-desmethyl ZD1839 (M523595) following 14 daily oral doses of 225 mg and 525 mg of ZD1839 (Trial 5)

Parameter	225 mg		525 mg	
	ZD1839 (n=8)	M523595 (n=6)	ZD1839 (n=9)	M523595 (n=8)
AUC(0-24), μg.h/ml	6.2±3.9 (63%)	3.01±2.4 (79%)	15.7±5.5 (35%)	14.3±8.5 (59%)
C_{max}, ng/ml	350±175 (50%)	215±88 (41%)	933±241 (26%)	986±820 (83%)
*T_{max}, h	3.0	3.0	5.0	3.0
t½, h	47±23.6 (46%)	48±13.1 (27%)	56±10.9 (20%)	37±25 (68%)

*Median (range)

Following oral administration of 50 mg (175 μCi) of ^{14}C-ZD1839 as a capsule to six male volunteers, 90% of the radioactivity was recovered in urine and feces over 10 days (Trial 3). The majority of the dose, 86%, was eliminated in the feces. Urinary excretion accounted for less than 4% of the dose (see Table below).

[Applicant' Table]

Cumulative percentage dose recovered in urine and feces following oral dosing of 50 mg [^{14}C]-ZD1839 to 6 healthy male volunteers

Time period (hours)	Feces % of Dose Recovered		Urine % of Dose Recovered		Total % of Dose Recovered	
	Mean	SD	Mean	SD	Mean	SD
0 to 24	1.85	1.74	1.88	0.61	3.72	1.61
0 to 48	59.46	12.32	2.47	0.72	61.92	11.94
0 to 72	72.14	12.13	2.79	0.84	74.93	11.75
0 to 96	77.87	9.32	2.97	0.92	80.83	9.05
0 to 120	81.49	8.20	3.06	0.95	84.55	8.09
0 to 144	83.14	7.69	3.18	1.02	86.33	7.63
0 to 168	84.35	7.14	3.26	1.05	87.60	7.16
0 to 192	85.21	6.84	3.32	1.07	88.53	6.95
0 to 216	85.69	7.15	3.36	1.07	89.05	7.25
0 to 240	86.26	6.67	3.39	1.08	89.65	6.82

Radiochemical profiling of pooled fecal samples from six volunteers over 5 days indicate that unchanged ZD1839 in fecal sample is 12.1% with large proportion of radioactivity identified as a carboxypropyl metabolite (12.1%), an O-desmethyl metabolite (26.3%), an aldehyde metabolite (12.1%), and other unidentified metabolites (37.4%) (Trial 3).

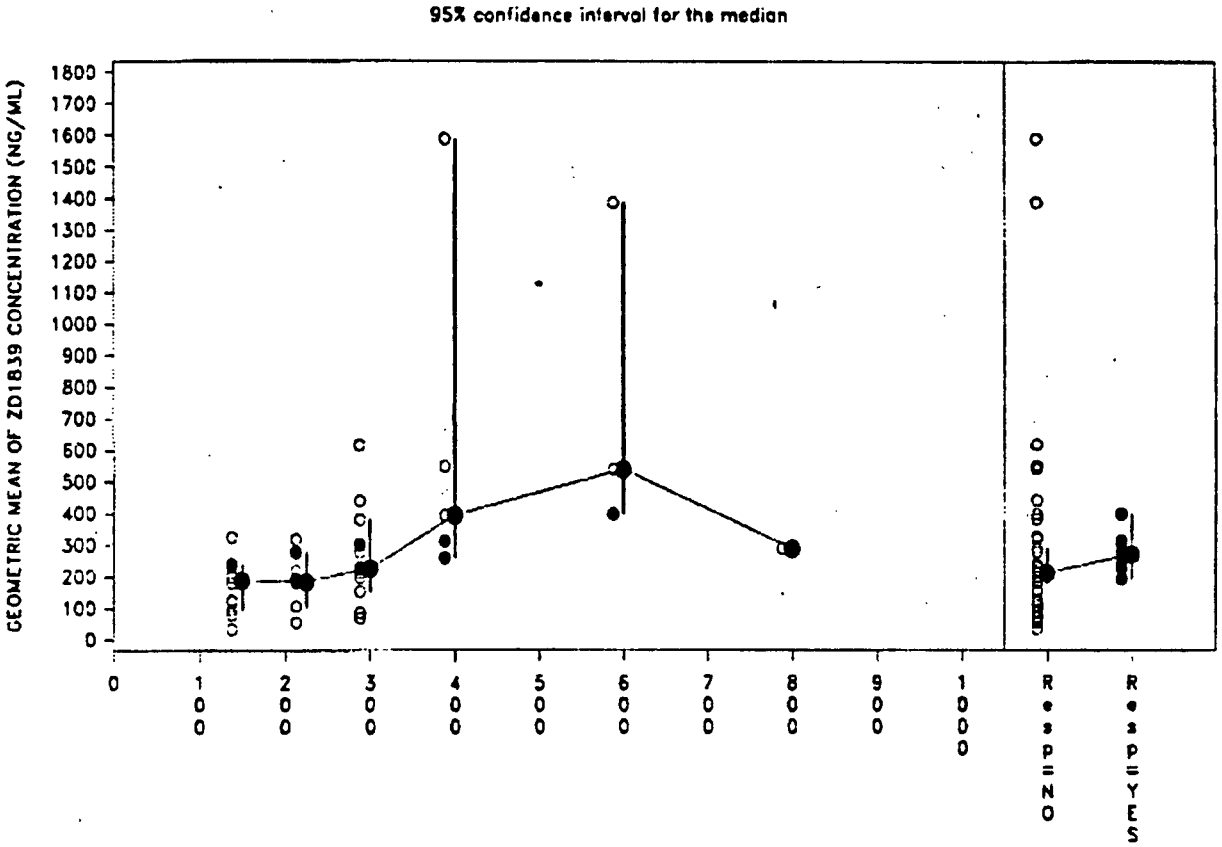
What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- **Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

An anti-tumor activity was seen over the dosing range of 150-1000 mg/day in more than 10% of the patients in the two dose-escalation Phase I Trials 11 and 12 for ZD1839 as a monotherapy in advanced solid tumors, including NSCLC (Figures below).

[Applicant's Figure]

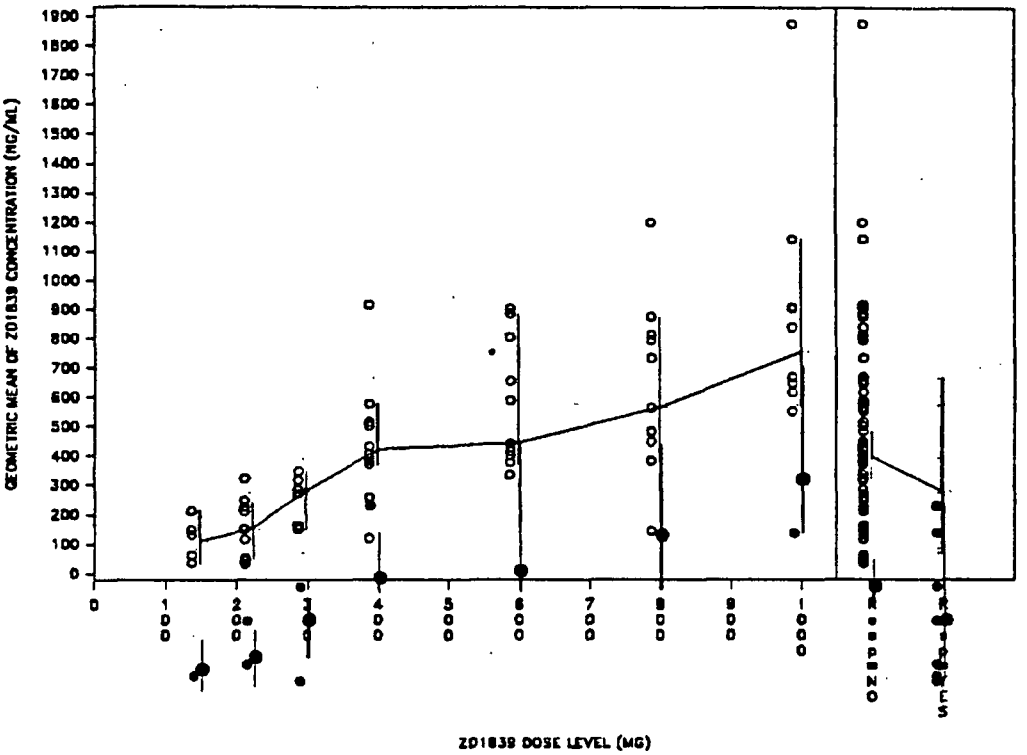
Geometric mean ZD1839 plasma concentrations versus dose level and tumor response (Trial 11)



Response is defined 'YES' if patient had a best overall response of CR, PR, or SD for 6 or more treatment periods

[Applicant's Figure]

Geometric mean ZD1839 plasma concentrations versus dose level and tumor response (Trial 12)



Open circles: Patients who did not have a best overall response of complete response, partial response, or stable disease for at least 6 treatment periods.
Smaller solid circles: Patients who had a best overall response of complete response, partial response, or stable disease for at least 6 treatment periods.
Larger solid circles: Median geometric mean concentrations for dose level or response group. Error bars represent 95% confidence intervals of median geometric mean concentrations.

Therefore, on the basis of this anti-tumor activity, development of ZD1839 was taken into the pivotal (Trial 39) and supportive (Trial 16) trials at dosing levels of 250 mg/day and 500 mg/day. As it is seen, there is no apparent relationship between tumor response and dose or plasma concentrations. The selection of dose for the Phase 2 Trials 39 and 16 was based on Maximum Tolerated Dose (MTD) determined in Phase 1 Trials 11 and 12, although the activated levels of EGFR and MAPK were significantly lower during ZD1839 therapy, compared to pretreatment levels.

- ***Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?***

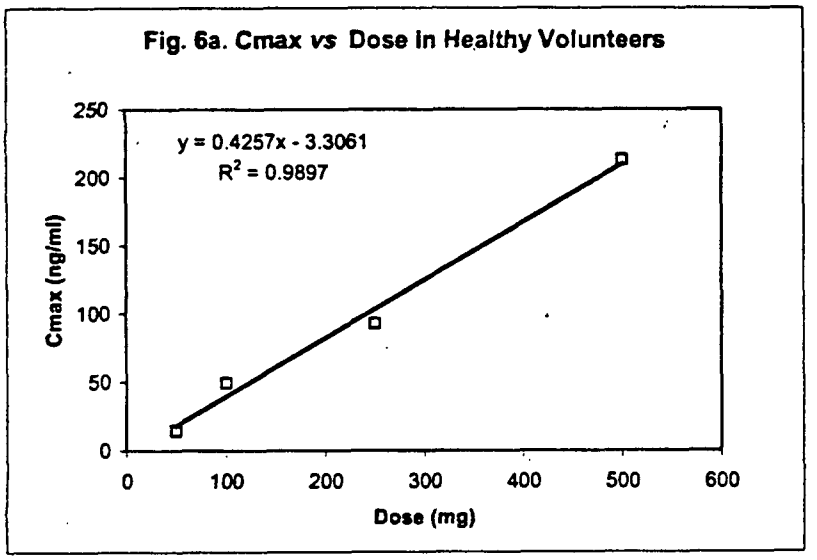
ZD1839 exhibits linear kinetics in healthy volunteers over the single oral doses of 50 mg to 500 mg (Trial 33). Table IV.a. summarizes the mean pharmacokinetic parameters for ZD1839 following single oral doses of 50, 100, 250, and 500 mg. Fig. 6a and Fig. 6b

graphically compares mean C_{max} and AUC values following these doses. Fig. 7 illustrates mean concentration/time profiles for these doses.

Table IV.a **Mean±SD (%CV) PK parameters of ZD1839 following single oral doses to 15 healthy male volunteers (Trial 33)**

Parameter	Dose of ZD1839			
	50 mg	100 mg	250 mg	500 mg
C_{max} (ng/ml)	14.7±8.7 (59%)	49.4±33.5 (67%)	92.8±52 (56%)	213±108 (51%)
*T_{max} (h)	5.0 (3.0-7.0)	3.0 (3.0-7.0)	5.0 (3.0-7.0)	3.0 (3.0-6.0)
AUC (ng.h/ml)	570±397 (69%)	1119±850 (75%)	3345±3232 (97%)	6181±4897 (79%)
t½ (h)	31.2±17.5 (56%)	22.7±13.6 (60%)	32.4±21.9 (67%)	28.2±17.9 (63%)

*Median (Maximum-Minimum)



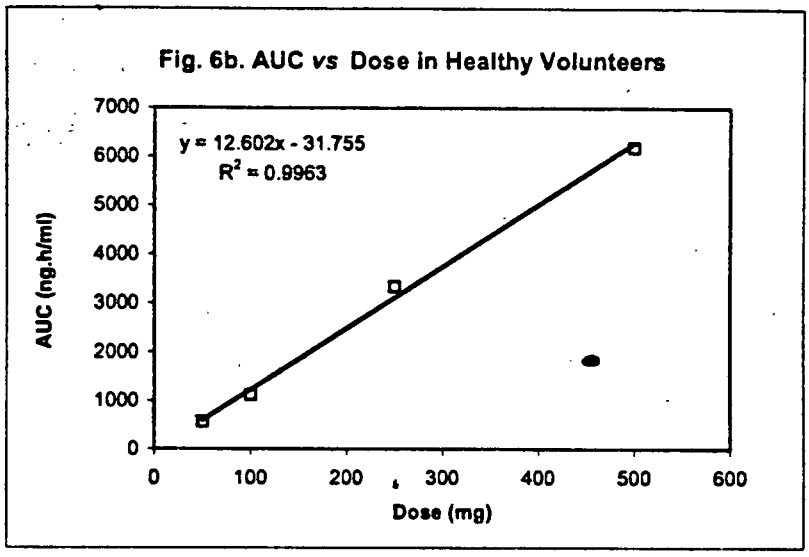


Fig. 6b. AUC vs Dose in Healthy Volunteers
y = 12.602x - 31.755
R² = 0.9963
AUC (ng.h/ml)
Dose (mg)
0
1000
2000
3000
4000
5000
6000
7000
0
100
200
300
400
500
600

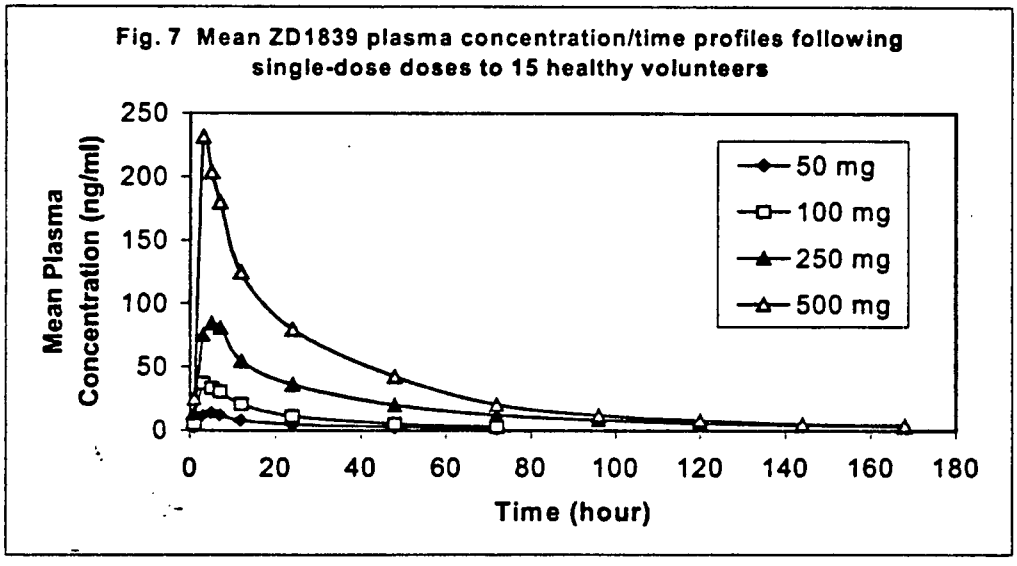


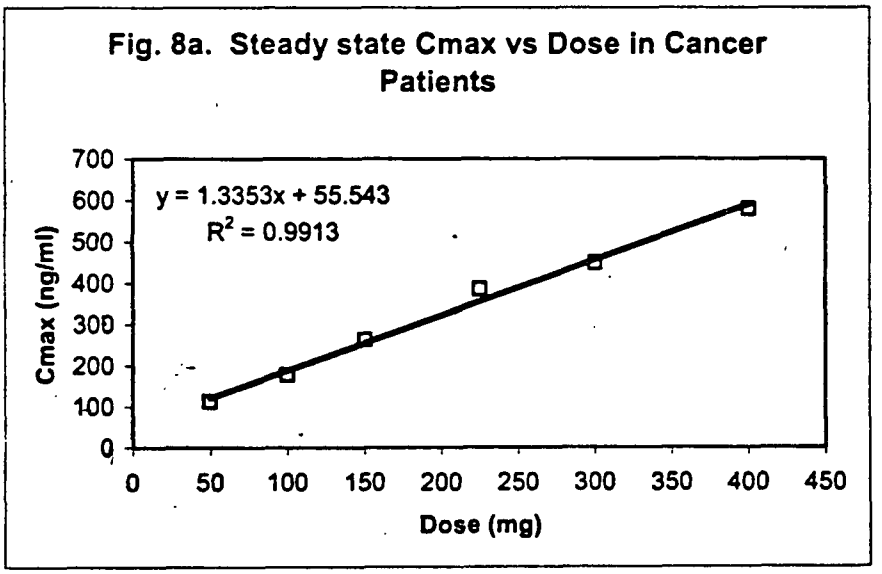
Fig. 7 Mean ZD1839 plasma concentration/time profiles following single-dose doses to 15 healthy volunteers
Mean Plasma Concentration (ng/ml)
Time (hour)
50 mg
100 mg
250 mg
500 mg
0
50
100
150
200
250
0
20
40
60
80
100
120
140
160
180

In cancer patients, ZD1839 also exhibits linear kinetics (Trial 5); mean C_{max} and AUC_{0-24h} were dose-proportional at the daily oral doses of 50-400 mg. However, over the daily oral doses of 50-700 mg, ZD1839 exhibits nonlinear kinetics. Trial 5 was an open-label, dose-rising, single- and multiple-dose, Phase I study in 64 patients with solid malignant tumors. Fig. 8a and 8b graphically compare mean steady state C_{max} and AUC(0-24) values following daily oral doses of 50, 100, 150, 225, 300, and 400 mg. Table V summarizes the mean PK parameters in cancer patients following daily oral doses (Trial 5). Fig. 8c and Fig. 8d graphically compare mean steady state C_{max} and AUC(0-24) values following daily oral doses of 50, 100, 150, 225, 300, 400, 525, and 700 mg.

Table IV.b Mean±SD (%CV) PK parameters of ZD1839 on Day 14 following once daily doses for 14 consecutive days to cancer patients (Trial 5)

Parameter	ZD1839 Doses							
	[c]50 mg	100 mg	150 mg	225 mg	300 mg	400 mg	525 mg	700 mg
N	8	7	7	6	8	6	9	6
C_{max} (ng/ml)	113±44.8 (40%)	178±100 (56%)	264±152 (57%)	386±169 (44%)	449±276 (61%)	579±206 (36%)	1009±169 (17%)	2160±931 (43%)
[*]T_{max} (h)								
AUC(0-24) (ng.h/ml)	1823±832 (45%)	2985±1846 (62%)	4765±2327 (48%)	6998±4122 (59%)	7087±5474 (77%)	10026±2853 (28%)	17454±5061 (29%)	42314±12004 (28%)
AUC (ng.h/ml)	4517±2006 (61%)	NC	NC	NC	NC	NC	NC	NC
t½ (h)	37.3±5.9 (16%)	55.2±14.9 (27%)	40.5±3.1 (7.6%)	46.6±12.4 (27%)	46.05±14.7 (32%)	38.1±8.3 (22%)	55.9±11.2 (20%)	72.9±14.1 (19%)
[$]Accumula-tion ratio	3.35±1.9 (56%)	6.1±4.9 (81%)	2.9±1.8 (60%)	5.1±5.0 (98%)	2.1±2.0 (97%)	2.9±2.2 (77%)	3.7±2.3 (64%)	6.0±3.9 (65%)

[c](For the 50 mg dose, PK assessed on Day 22, for other doses on Day 14)
[*](Maximum-Minimum)
[$] Accumulation ratio=AUC(0-24)(day 14)/AUC(0-24)(day 1)



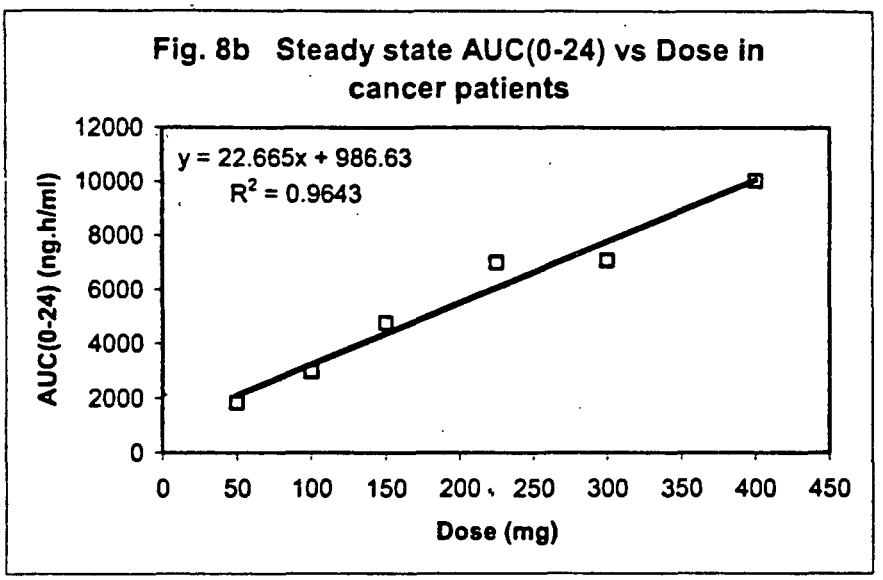


Fig. 8b Steady state AUC(0-24) vs Dose in cancer patients
y = 22.665x + 986.63
R2 = 0.9643
AUC(0-24) (ng.h/ml)
12000
10000
8000
6000
4000
2000
0
0
50
100
150
200
250
300
350
400
450
Dose (mg)

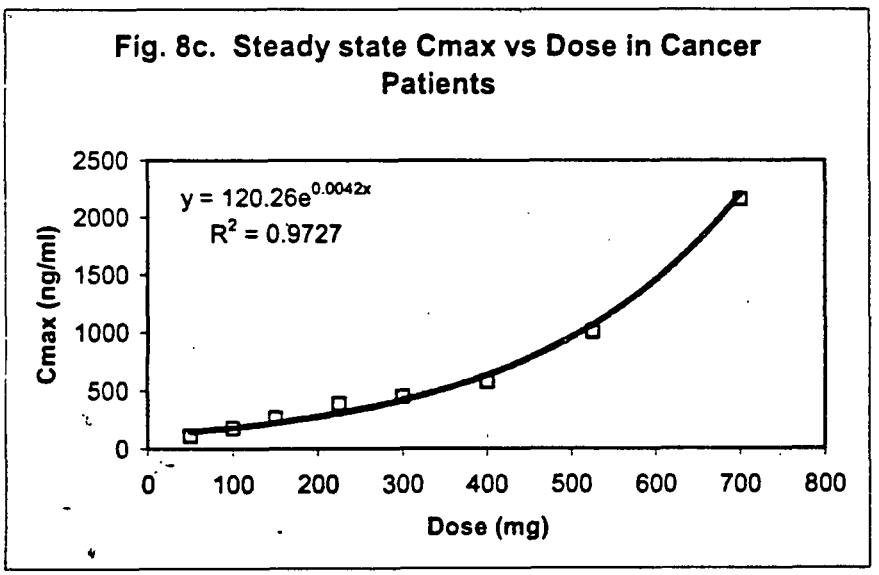
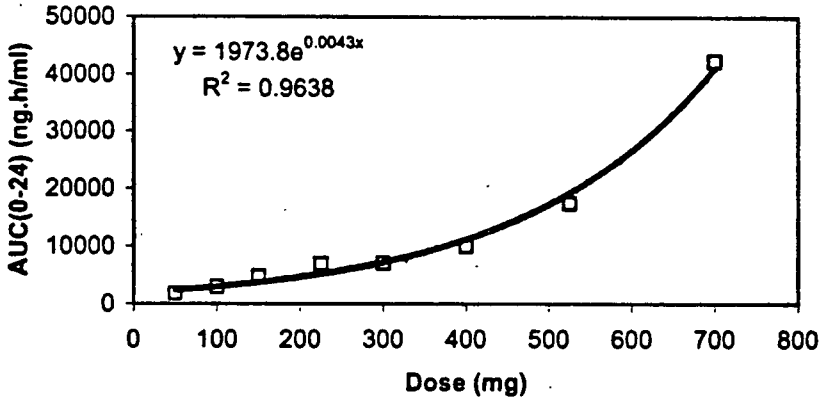


Fig. 8c. Steady state Cmax vs Dose in Cancer Patients
y = 120.26e0.0042x
R2 = 0.9727
Cmax (ng/ml)
2500
2000
1500
1000
500
0
0
100
200
300
400
500
600
700
800
Dose (mg)

Fig. 8d. Steady state AUC(0-24) vs Dose in Cancer Patients



In conclusion, ZD1839 exhibits linear kinetics over the therapeutic dosing range in both healthy volunteers and cancer patients.

Plasma protein binding is independent of ZD1839 concentrations over the range of 50-8000 ng/ml. *In vitro* binding studies indicate that ZD1839 is highly bound to human plasma proteins, mean %bound is 91±0.7% (Report KPJ013). The binding of ZD1839 to human serum albumin is 83% and is independent of drug concentrations (Report KPJ013). At low and normal alpha-1-acid glycoprotein (AGP) concentrations (0.4 and 0.8 mg/ml), the binding of ZD1839 to the protein is saturable, 52-31% and 82-64%, respectively, at ZD1839 concentrations of 50-8000 ng/ml (KPJ046). At an elevated concentration of alpha-1-AGP (3.2 mg/ml), which is usually observed in cancer patients, the binding is 96% and is independent of ZD1839 concentrations over the range of 50-8000 ng/ml (KPJ046). The plasma protein binding of the major pharmacologically active metabolite, O-desmethyl ZD1839, was not assessed in the study.

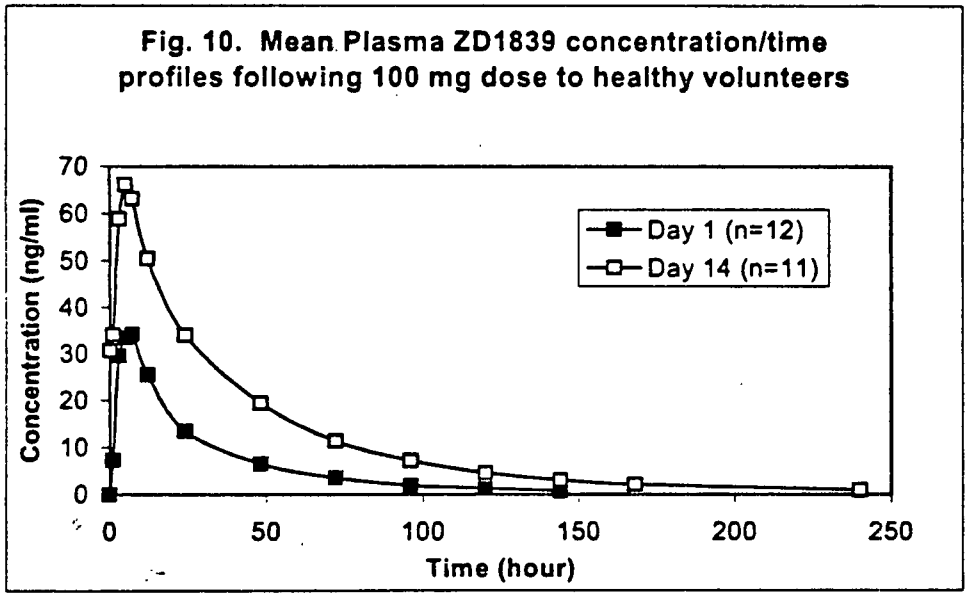
- ***How do PK parameters change with time following chronic dosing?***

Following oral administration of 100 mg daily doses to 12 healthy volunteers for 14 days, steady state reaches within 3 to 5 days of the start of dosing with steady state plasma levels 1.8-2.0- fold higher than those observed after single-dose administration (Table V) (Trial 34).

Table V. Mean±SD (%CV) PK parameters following either a single 100 mg dose or once daily 100 mg doses for 14 days to healthy male volunteers (Trial 34)

Parameter	Day 1 (Single-Dose) (n=12)	Day 14 (Multiple-Dose) (n=11)
C_{max} (ng/ml)	38.4±11.1 (29%)	68.1±30.2 (44%)
*T_{max} (h)	5	5
C_{min} (ng/ml)	–	34 ±0.68 (2%)
AUC(0-24) (ng.h/ml)	557±195 (35%)	1172±594 (50%)
AUC (ng.h/ml)	1085±484 (45%)	2871±1780 (62%)
t½ (h)	27.7±8.7 (31%)	38.02±15.8 (42%)
#Accumulation Ratio	–	2.01±0.64 (32%)

*Median (Maximum-Minimum)
#Accumulation Ratio=AUC(0-24)(day 14)/AUC(0-24)(day 1)



Following oral administration of daily 100-700 mg doses of ZD1839 to cancer patients for 14 days, steady state reaches within 10 days of the start of dosing with steady state plasma levels 2-fold higher than those achieved following single doses (Tables VI.a and VI.b) (Trial 5).

Table VI.a. Mean±SD (%CV) PK parameters of ZD1839 on Day 1 following single doses to cancer patients (Trial 5)

Parameter	ZD1839 Doses							
	50 mg	100 mg	150 mg	225 mg	300 mg	400 mg	525 mg	700 mg
N	8	7	8	7	8	6	10	7
C_{max} (ng/ml)	44.6±13.1 (29%)	45.6±23.5 (51%)	142±60 (42%)	150±57 (38%)	240±111 (46%)	398±204 (51%)	469±204 (43%)	834±379 (45%)
*T_{max} (h)								
AUC(0-24) (ng.h/ml)	586±179 (30%)	572±258 (45%)	1965±843 (43%)	1900±861 (45%)	3493±1694 (48%)	4577±2559 (56%)	5659±2336 (41%)	10958±7731 (70%)
AUC (ng.h/ml)	1302±480 (37%)	*NC	NC	NC	NC	NC	NC	NC
t½ (h)	33.9±7.6 (22%)	NC	NC	NC	NC	NC	NC	NC

*Median (Maximum-Minimum) *NC (Not calculated)

Table VI.b. Mean±SD (%CV) PK parameters of ZD1839 on Day 14 following once daily doses for 14 consecutive days to cancer patients (Trial 5)

Parameter	ZD1839 Doses							
	@50 mg	100 mg	150 mg	225 mg	300 mg	400 mg	525 mg	700 mg
N	8	7	7	6	8	6	9	6
C_{max} (ng/ml)	113±44.8 (40%)	178±100 (56%)	264±152 (57%)	386±169 (44%)	449±276 (61%)	579±206 (36%)	1009±169 (17%)	2160±931 (43%)
*T_{max} (h)								
AUC(0-24) (ng.h/ml)	1823±832 (45%)	2985±1846 (62%)	4765±2327 (48%)	6998±4122 (59%)	7087±5474 (77%)	10026±2853 (28%)	17454±5061 (29%)	42314±12004 (28%)
AUC (ng.h/ml)	4517±2006 (61%)	NC	NC	NC	NC	NC	NC	NC
t½ (h)	37.3±5.9 (16%)	55.2±14.9 (27%)	40.5±3.1 (7.6%)	46.6±12.4 (27%)	46.05±14.7 (32%)	38.1±8.3 (22%)	55.9±11.2 (20%)	72.9±14.1 (19%)
$Accumulation ratio	3.35±1.9 (56%)	6.1±4.9 (81%)	2.9±1.8 (60%)	5.1±5.0 (98%)	2.1±2.0 (97%)	2.9±2.2 (77%)	3.7±2.3 (64%)	6.0±3.9 (65%)

@(For the 50 mg dose, PK assessed on Day 22, for other doses on Day 14)
*Median (Range)
$ Accumulation ratio=AUC(0-24)(day 14)/AUC(0-24)(day 1)

How does the PK of ZD1839 in healthy volunteers compare to that in patients? What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following oral administration of 250 mg ZD1839, mean AUC and C_{max} are 2-fold higher in cancer patients than those in healthy male volunteers (Table VII and Fig. 10). Mean absolute bioavailability is comparable in both populations (F_{abs}=60%). ZD1839 is moderately absorbed reaching peak plasma concentrations in 3-7 hours following oral administration of a single 250 mg dose to either cancer patients or healthy volunteers.

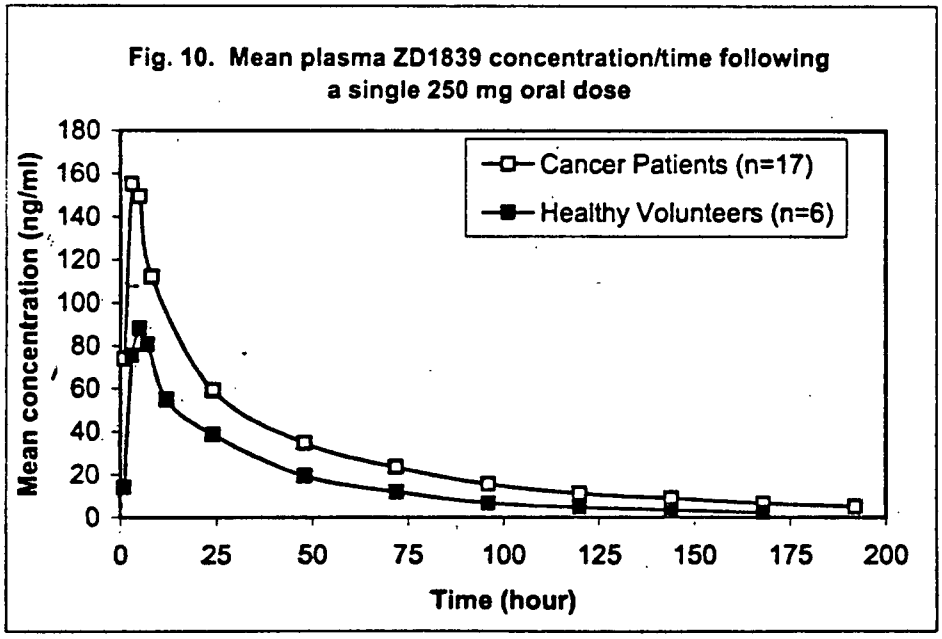
Following IV administration of ZD1839, cancer patients have smaller total clearance and longer terminal half-life than healthy volunteers (CL=8.1 ml/min/kg *vs* 11.6 ml/min/kg and t½=48 hours *vs* 34 hours, respectively). Steady-state volume of distribution is similar in both population (V_{ss}=17.2 L/kg). ZD1839 plasma concentrations decline in a biphasic manner with a mean terminal half-life of 48 hours in cancer patients and 40 hours in healthy volunteers (Table VII and Fig. 10).

Following IV administration, variability in AUC is higher in cancer patients (%CV=52%) than in healthy volunteers (%CV=22%). This variability may be due to differences in the ability to metabolize ZD1839 between healthy subjects and patients. In overall clinical pharmacology trials, variability in AUC is comparable between healthy volunteers (CV=60-68%, n=177) and cancer patients (%CV=28-70%, n=74) following oral administration.

Table VII. Mean±SD (%CV) PK parameters following a single IV dose and a single oral dose to cancer patients and healthy male volunteers

Parameter	Cancer Patients (Trial 35)		Healthy Volunteers (Trial 31)	
	*50 mg (n=19)	Oral 250 mg (n=17)	#50 mg (n=4)	Oral 250 mg (n=6)
C_{max} (ng/ml)	2475±1110 (45%)	173±69 (40%)	238±56 (23%)	88±22 (26%)
T_{max} (h)	–	3.0 (0.95-7.0)	1.0	5.0 (5.0-5.0)
AUC (ng.h/ml)	1853±955 (52%)	6038±3321 (55%)	1675±371 (22%)	3150±1333 (42%)
CL (ml/min) (ml/min/kg)	595±358 (60%) 8.1±6.9 (86%)	–	711±175 (25%) 11.6 ±2.2 (19%)	–
V_{ss} (L) (L/kg)	1400±504 (36%) 17.2±5.3 (30%)	–	1697±582 (34%) 17.2±1.2 (7.0%)	–
t½ (h)	48.4±27.3 (56%)	46.7±16.8 (36%)	34.1 ±16 (47%)	39.7 ±21.5 (54%)
F_{abs} (%)	62±17% (27%)		65 ±26% (40%)	

*5-min infusion
#60-min infusion



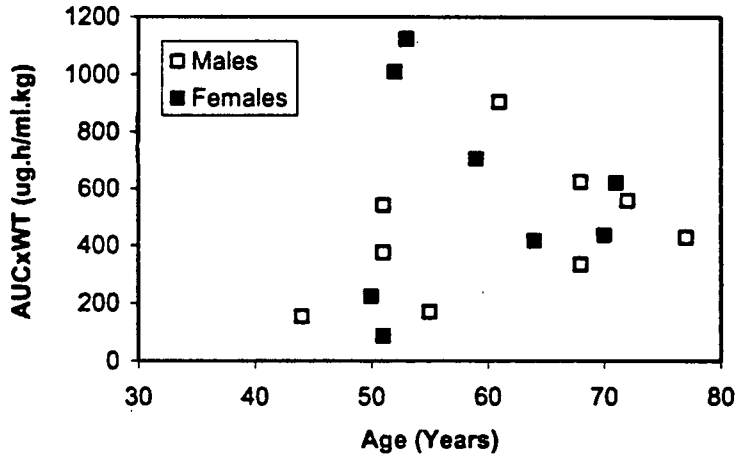
C. Intrinsic Factors and Special Populations

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Are dosage adjustments recommended for any of these subgroups?

a) ***Age:***

It appears that age has no effect on exposure to ZD1839 following a single 250 mg oral dose to 17 Caucasian cancer patients (9 males and 8 females) ranging in age from 44 to 77 years (Trial 35) (Fig. 11).

Fig. 11. Age vs AUCxWT



b) ***Gender:***

Data from Trial 35 indicate that although Caucasian female patients tends to have higher exposure to ZD1839 (about 27%) than Caucasian male patients following a single 250 mg oral dose. This is not clinically important and dosing reduction is not required in female patients.

Table VIII. Effect of gender

Group	n	*AUCxWT (μg.h/ml.kg)	p-value
Males	9	455±235 (51%)	0. 414
Females	8	578±361 (62%)	

*Mean±SD (%CV)

Race: There were insufficient data available from different racial and ethnic groups other than Caucasians to investigate potential pharmacokinetic differences between these groups. Mostly, Caucasian healthy male volunteers and Caucasian male and female cancer patients were included in Phase I trials for ZD1839. A comparison of data obtained from Trial 5 (conducted in Caucasian cancer patients) and Trial V-15-11 (conducted in Japanese cancer

patients) indicates that Japanese and Caucasian patients had comparable exposure to ZD1839. Dose-normalized AUC(0-24) in Japanese patients is not significantly different than that in Caucasian patients (p=0.166) after once daily doses of 100-300 mg of ZD1838.

Table IX. Exposure in Japanese patients vs Caucasian patients

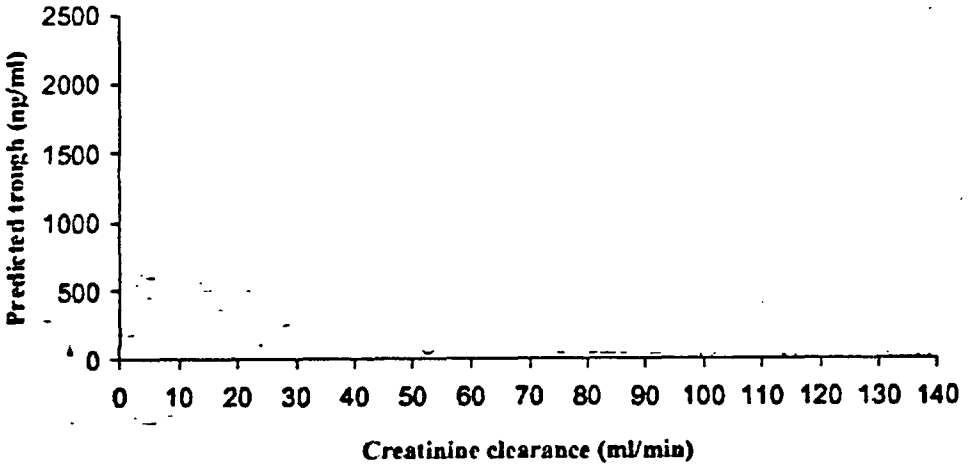
	n	AUC(0-24)/Dose (ng.h/ml)
Caucasian Patients (Trial 5)	24	28.55±17.6 (62%)
Japanese Patients (Trial V-15-11)	10	23.55±11.5 (48%)

*Mean±SD (%CV)

d) ***Hepatic impairment:*** No data are currently available on the pharmacokinetics of ZD1839 in patients with hepatic impairment. A study is underway to assess the effect of hepatic impairment on the pharmacokinetics of ZD1839 (Trial 32). No specific dosing recommendations could be included in the label for this special population. As ZD1839 is primarily eliminated in the liver, the label will also include a precaution for the use of IRESSA in patients with hepatic impairment until the study is completed and submitted to the Agency (see Phase 4 Commitment 2).

e) ***Renal impairment:*** The Applicant did not conduct a formal study in renally impaired patients. Elimination of ZD1839 is mainly via the biliary route, with less than 4% of the dose being excreted via the renal route. Population PK analysis on the combined trough plasma data from Trials 39 and 16 indicate that there is no obvious relationship between predicted trough plasma levels and creatinine clearance values (Median=81 ml/min, range=. ml/min).

[Applicant's Figure]



f) ***Pediatric patients:*** The safety and effectiveness of IRRESA in patients of <18 years of age have not been established.

g) ***Pregnancy or Lactation:*** There is no information regarding the use of IRESSA in pregnant or lactating women.

D. Extrinsic Factors

What extrinsic factors (drugs, herbals, diet, smoking, alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Drug-Drug Interactions

a) ***Is there an in vitro basis to suspect in vivo drug-drug interactions? is the drug a substrate of CYP enzymes? is the drug an inhibitor and/or an inducer of CYP enzymes?***

In vitro studies with human liver microsomes indicate that ZD1839 is a substrate of CYP3A4.

[Applicant's Table]

Effect of selective chemical inhibitors on P450 marker substrate activities

Specific marker substrate activity	Selective Chemical Inhibitor	Inhibitor Concentration (μM)	% of control enzyme activity
Phenacetin	Furafylline	1	64.9
O-deethylase		5	27.5
(CYP1A2)		25	ND
Tolbutamide	Sulphaphenazole	1	66.0
4'-hydroxylase		5	38.1
(CYP2C9)		25	25.3
Dextromethorphan	Quinidine	0.005	99.0
O-demethylase		0.1	61.7
(CYP2D6)		1.0	21.1
S-Mephenytoin	Omeprazole	6	78.4
4-hydroxylase		12	55.7
(CYP2C19)		20	41.2
Testosterone	Ketoconazole	0.04	94.2
6b-hydroxylase		0.1	82.4
(CYP3A4)		1	23.1

ND = not-detected

In vitro Inhibition:

In vitro studies with human liver microsomes indicate that ZD1839 at concentrations ranging from 0.004 to 11.2 µM (~2 to 5000 ng/ml) has a little inhibitory potential on CYP1A2, CYP2C9, and CYP3A4 activity; the %inhibition is less than 10% [Report KMX024]. Inhibition of CYP2C19 and CYP2D6 activities, however, is more pronounced with %inhibition of 23.7% and 43%, respectively, at the highest ZD1839 concentration (11.2 µM).

Table X. Effect of ZD1839 on P450 marker substrate activities

ZD1839 Conc. µM	Specific marker substrate assay (% of control enzyme activity)				
	Phenacetin O-deethylase (CYP1A2)	Tolbutamide 4'-hydroxylase (CYP2C9)	S-Mephenytoin 4-hydroxylase (CYP2C19)	Dextromethorphan O-demethylase (CYP2D6)	Testosterone 6b-hydroxylase (CYP3A4)
0.004	106.4	99.8	88.7	99.0	107.7
0.02	104.7	99.1	78.4	109.1	108.2
0.11	111.7	100.0	82.5	81.3	104.2
0.56	98.3	100.9	82.5	89.0	103.8
2.24	107.6	101.2	80.4	87.1	104.5
11.2	104.7	91.3	76.3	56.9	92.7

These results indicate ZD1839 may have a potential to inhibit the metabolism of drugs that are substrates of CYP2C19 and CYP2D6. In addition, ZD1839 is a substrate of CYP3A4; and drugs that are substrates and/or inhibitors of this enzyme are expected to inhibit its metabolism.

Induction:

There is no evidence of biologically significant induction of hepatic enzymes following daily oral administration of 2, 10, and 40 mg/kg doses of ZD1839 for 14 days to the rats (Overall NDA Summary).

b) ***Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes or other metabolic/transporter pathways that may be important?***

The Applicant did not formally evaluate whether ZD1839 is a substrate, inducer and/or inhibitor of P-gp or other metabolic/transporter pathways using specific probes.

c) ***What other co-medications are likely to be administered to the target patient population (i.e., patients with NSCLC)?***

The following answer to the above question was sought from the Medical Reviewer (Dr. Cohen): "The most common symptoms that lung cancer patients have are shortness of breath, cough, and pain. Thus, they might be expected to be treated with bronchodilators (oral or inhaled), cough suppressants, and narcotic analgesics. Most lung cancer patients are more than 60 years of age so that they frequently have the commodities common to elderly patients, i.e. diabetes, hypertension, heart disease, etc. and they are often on multiple medications for these conditions. In addition they are smokers and often consume considerable alcohol."

d) ***Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?***

Itraconazole: The effect of itraconazole, a CYP3A4 inhibitor, on the PK of ZD1839, a CYP3A4 substrate, was assessed in Trial 51. Trial 51 was an open-label, single-center, randomized, crossover Phase I trial in 24 healthy male volunteers who were administered 200 mg once daily doses of itraconazole on Days 1 through 12 and a single 250 mg ZD1839 dose on Day 1 and on Day 4.

Table XI. Mean±SD (%CV) PK parameters of ZD1839 following coadministration of ZD1839 and itraconazole to 24 healthy male volunteers (Trial 51)

Parameter	250 mg ZD1839 Alone (n=24)	250 mg ZD1839+ 200 mg Itraconazole (*n=23)
C_{max} (ng/ml)	110±41 (45%)	170±76 (40%)
T_{max} (h)	5.0 (3.0-7.0)	5.0 (3.0-7.0)
AUC (ng.h/ml)	3247±1474 (52%)	6113±3767 (55%)
t½ (h)	30.7±10.1 (56%)	38.5±11.3 (36%)

*One volunteers had a decrease in AUC for ZD1839 of 50% when given with itraconazole, no reasons for this finding are apparent.

Concomitant itraconazole administration with ZD1839 results in an increase in mean C_{max} and AUC of ZD1839 by 55% and 88% respectively, compared to ZD1839 alone treatment ($p < 0.05$). The increase in exposure to ZD1839 may be clinically relevant and patients may experience more adverse events when ZD1389 is concomitantly administered with drugs that are known to inhibit CYP3A4.

Metoprolol: The inhibitory effect of ZD1839 on CYP2D6 activity was assessed in Trial 38. Trial 38 was an open-label, non-randomized, Phase I trial assessed the pharmacokinetics of metoprolol, a CYP2D6 substrate, in the presence of ZD1839, a CYP2D6 inhibitor, in 18 patients with solid tumors. All patients received a single oral dose of 50 mg metoprolol, followed two days later by daily administration of ZD1839 for 28 days. Initially, patients received 500 mg twice a day loading doses of ZD1839 (to ensure that steady state levels were reached rapidly). Following the loading doses, 500 mg once daily doses of ZD1839 were given for 27 days with a second 50 mg dose of metoprolol given on Day 15 of the first 28-day treatment cycle.

Table XII. Mean±SD (%CV) PK parameters of Metoprolol following coadministration of ZD1839 and metoprolol to 18 patients with solid tumors (Trial 38)

Parameter	50 mg Metoprolol Alone	50 mg Metoprolol+ 500 mg ZD1839
C_{max} (ng/ml)	73.7±36.7 (49%)	77.2±34.8 (45%)
AUC (ng.h/ml)	383±307 (80%)	496±330 (67%)
t½ (h)	3.7±1.9 (52%)	3.6±2.0 (57%)

The results show that mean exposure to metoprolol (AUC) increases by 30% when given in combination with ZD1839 ($p=0.176$) compared to metoprolol alone treatment; this increase may not be clinically significant. No dosing reduction is warranted for metoprolol when given in combination with ZD1839.

Rifampicin:

The effect of rifampicin, an inducer of CYP3A4, on the pharmacokinetics of a single oral dose ZD1839, a CYP3A4 substrate, was assessed in 18 healthy male volunteers in Trial 30. In this trial, the volunteers were randomized to receive 600 mg rifampicin once daily for 16 days and a single 500 mg ZD1839 on Day 10 (group 1, n=9) and only a single 500 mg ZD1839 on Day 10 (group 2, n=9) during Period 1. In Period 2, the volunteers received the treatment they did not receive in Period 1 after 3-week washout period.

Table XIII. Mean±SD (%CV) PK parameters of ZD1839 following coadministration of ZD1839 and Rifampicin to 18 healthy male volunteers (Trial 30)*

Parameter	500 mg ZD1839 Alone	500 mg ZD1839+ 600 mg Rifampicin
C_{max} (ng/ml)	183±65 (35%)	68±31 (46%)
T_{max} (h)	3.02 (2.98-7.0)	3.0 (1.0-5.0)
AUC (ng.h/ml)	6251±3717 (59%)	953±368 (38%)
t½ (h)	33.8±13.9 (41%)	20.7±7.9 (38%)

*The change in the ratio of urinary-6β–hydroxycortisol to free cortisol was used to assess the induction of CYP3A4 in this trial.

The above results indicate that mean C_{max} and AUC of ZD1839 significantly reduced by about 60% and 85%, respectively, when given in combination with rifampicin compared to ZD1839 alone treatment ($p < 0.05$). Mean terminal half-life of ZD1839 decreased from 34 hours to 21 hours when ZD1839 was given with rifampicin. The reduction in exposure to ZD1839 may be attributed to the increase in the first-pass metabolism and clearance of ZD1839 as a consequence of the induction of CYP3A4 by rifampicin; CYP3A4 is major cytochrome P450 enzyme involving in ZD1839 metabolism. The decrease in ZD1839 exposure may be clinically significant and the efficacy of ZD1839 may be reduced when given in combination with CYP3A4 inducers.

e) ***Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?***

The applicant conducted metabolism, CYP inhibition, and protein binding studies for ZD1839. At this time, there are no unresolved questions related to the metabolism of ZD1839. However, the pharmacokinetics and plasma protein binding of the major pharmacologically active metabolite, O-desmethyl ZD1839, should be assessed (see Comments 1 and 2, pp 2). Related to drug interactions, an elevation in the International Normalized Ratio (INR) and/or bleeding events were reported during clinical trials in some patients taking warfarin while on ZD1839 therapy (Overall NDA Summary). A formal drug interaction study with warfarin may be helpful to explain the mechanism that caused such an increase in INR and/or occurrence of bleeding events (see Phase 4 Commitment 1). The Applicant added a precaution statement in the labeling for IRESSA that patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

f) ***What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?***

The hepatic impairment trial is undergoing (Trial 32), no specific dosing recommendations could be included in the label for this special population until Trial 32 is submitted and reviewed by the Agency. An interaction study between ZD1839 and warfarin is required to explain the increase in INR and/or occurrence of bleeding events observed during clinical trials with ZD1839 and to provide proper dosing for labeling considerations.

E. General Biopharmaceutics

Based on BCS principles, in what class is this drug and dosage form? What solubility, permeability and dissolution data support this classification?

Biopharmaceutical classification (BSC)

Permeability data indicate that the apparent absorptive permeability (P_{app}) of ZD1839 across cultured monolayers of the Caco-2 human cell line at pH 7.4 ranges from cm/sec over a 100-fold (1 to 100 µM) concentration range (CMC Summary).

The 250 mg ZD1839 does not meet the BSC high solubility criteria requiring that the solubility of highest strength should be less than or equal to 250 ml of aqueous media over the pH range of 1 to 8 as shown below:

[Applicant's Table]

Buffer/media	Concentration[a]	pH[b]
0.1 M Hydrochloric acid	1.01	1.2
pH 1.2 Hydrochloric Acid Buffer (USP)	1.03	1.2
pH 2.0 Hydrochloric acid (0.01 M)	1.04	2.2
pH 2.0 Hydrochloric Acid Buffer (USP)	1.06	2.4
pH 3.0 Phosphate buffer	1.02	3.3
pH 3.0 Acetate Buffer (USP)	1.02	3.4
pH 4.0 Acetate Buffer (USP)	0.99	4.2
pH 5.0 Acetate Buffer (USP)	0.43	5.1
pH 6.0 Phosphate Buffer (USP)	0.01	6.0
pH 6.8 Phosphate Buffer (USP)	<0.01	6.8
pH 8.0 Phosphate Buffer (USP)	<0.01	7.9

[a] Measured as mg/ml at 37°C.

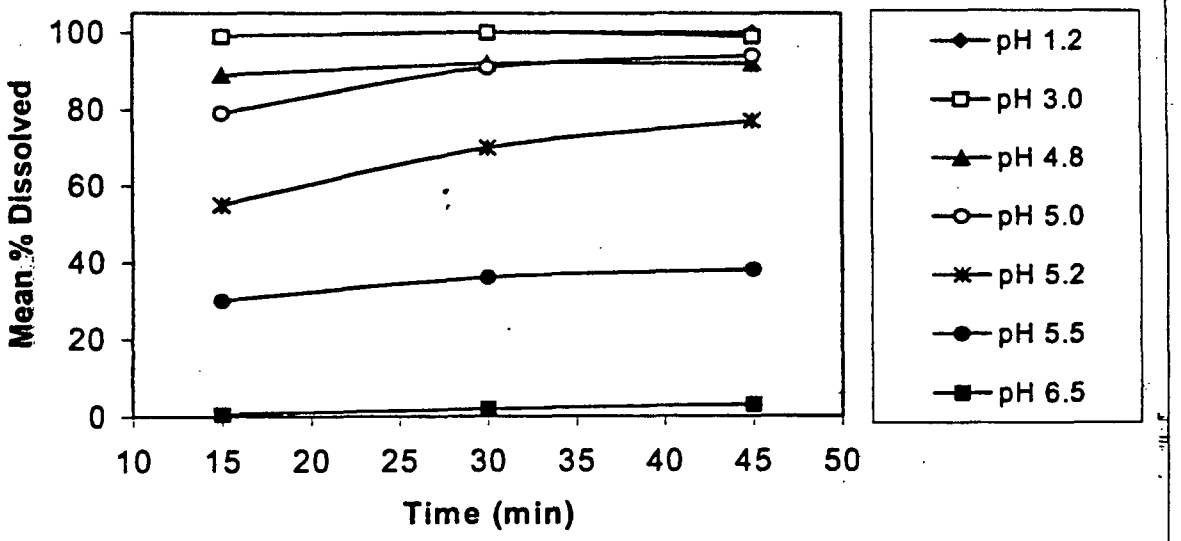
[b] pH of resulting solution.

ZD1839 was only soluble below pH 4.0, but not above pH 4.0 due to the marked reduction in solubility as pH increases. Based on the above permeability and solubility data, the Applicant indicates that ZD1839 can be categorized as a "Low Solubility-High Permeability" (Class 3) drug.

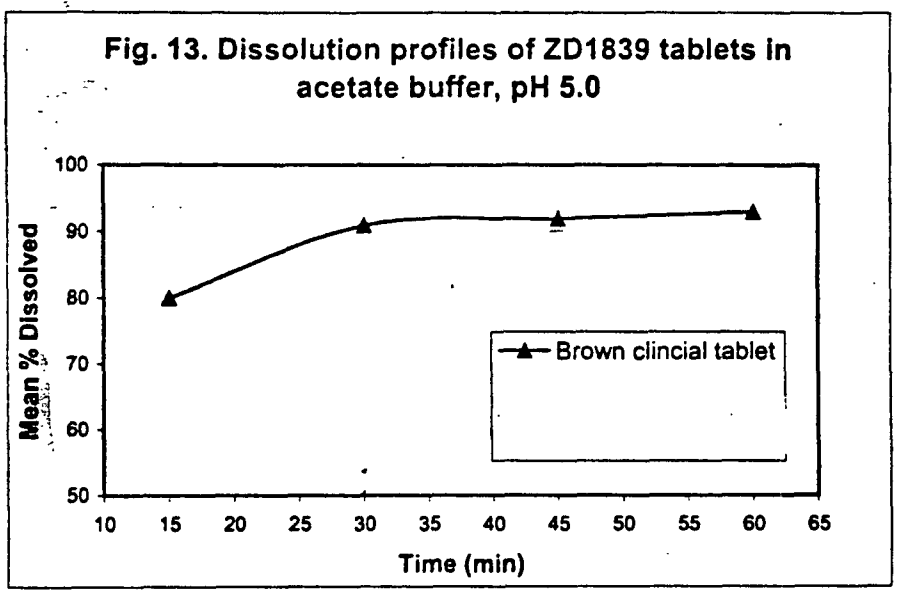
Dissolution

The Applicant attempted different pH's media to characterize the dissolution of ZD1839 250 mg tablets (Batch P/1427/33, 6 units/test) (Fig. 12).

Fig.12. Dissolution Profiles of ZD1839 250 mg brown clinical tablets



Dissolution testing was performed using USP Paddle at 50 rpm in 900 ml of dissolution medium at 37°C.



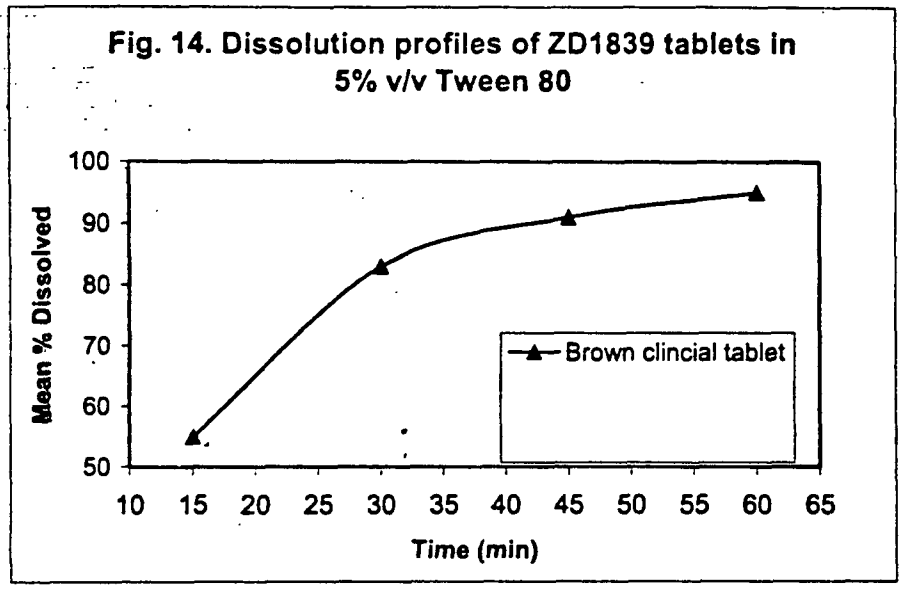
The Applicant used this testing medium (5% v/v aqueous Tween 80) to evaluate the effect of scale on dissolution of the 250 mg Phase 2/3 clinical tablets at batch sizes of [redacted]. All batches were manufactured by the same process and at the same site (Macclesfield). Comparable dissolution profiles were obtained.

[Applicant's Table]

Dissolution data on batches of IRESSA 250 mg Phase 2/3 clinical tablets manufactured at 3 different scales[a]

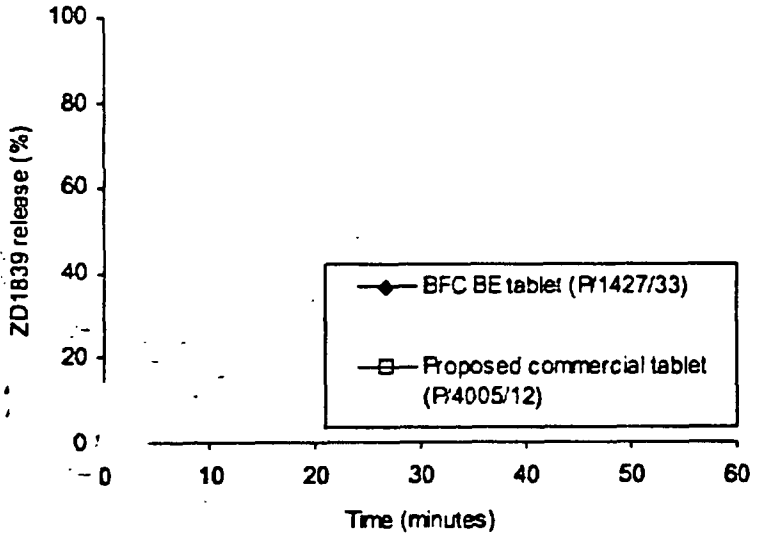
	P/1520/21 (n=6)		P/1607/45 (n=6)		P/1427/33 (n=18)	
Time	Batch size [redacted]		Batch size [redacted]		Batch size [redacted]	
(minutes)	Mean	Range	Mean	Range	Mean	Range
15	52		62		53	
30	84		86		83	
45	92		91		91	
60	96		94		94	

[a]Tween 80 (5% v/v), USP apparatus 2



Dissolution profiles were provided for the Phase 2/3 clinical brown tablet (Batch P/1427/33) and the commercial brown tablet (Batch P/4005/12).

[Applicant's Figure]



These data demonstrate that 5% v/v aqueous Tween 80 is the most discriminating dissolution test medium and can be suitable for routine quality control. Thus, the Applicant proposes the following dissolution method for IRESSA 250 mg commercial brown tablets:

Apparatus	USP Apparatus 2 (Paddle)
Paddle Speed	50 rpm
Medium	1000 ml of Tween 80 (5% v/v) in water
Temperature	37 °C
Analytical	

The Applicant proposes dissolution specifications of [redacted] % dissolved in 45 minutes, based on the following data:

[Applicant's Table]

Dissolution data for batches of IRESSA 250 mg Phase II/III clinical tablets (% ZD1839 released in 45 minutes)[a]

Batch	Mean	Range	Batch	Mean	Range
P/1520/21	92		P/1427/48	89	
P/1427/17	90		P/1427/49	91	
P/1427/18	88		P/1607/32	89	
P/1427/19	88		P/1607/45	93	
P/1427/25	89		P/1607/46	91	
P/1427/28	92		P/1607/47	91	
P/1427/32	92				
P/1427/33	88				

[a]Tween 80 (5% v/v), USP apparatus 2, n=6.

[Applicant's Table]

Dissolution data for batches of IRESSA 250 mg proposed commercial tablets (% ZD1839 released in 45 minutes)[a]

Batch	Mean	Range
P/4005/12	90	
P/4005/13	90	
P/4005/14	91	

[a]Tween 80 (5% v/v), USP apparatus 2, n=6.

Based on the data from the three commercial batches, we recommend specifications of [redacted] % dissolved in 45 minutes for IRESSA 250 mg commercial brown tablets.

What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Component	Phase 2/3 Tablet (Round, Brown)	Initial Commercial Tablet (Oval, Yellow)
Core	mg/tablet	m/tablet
ZD 1839	250	250
Lactose		
Microcrystalline cellulose		
Croscaremllose Sodium		
Povidone		
Sodium lauryl sulfate		
Magnesium stearate		
Total		
Film-Coat		
Hydroxypropyl methyl-Cellulose		
Polythylene glycol 300		
Titanium dioxide		
Yellow ferric oxide		
Red ferric oxide		
Total	511.45	512.16

with respect to AUC (Submission of August 8, 2001, IND [redacted] SN-389).

In the meeting of April 23, 2002, the sponsor made the decision to market a brown, round, film-coated tablet formulation [redacted] IRESSA 250 mg proposed commercial brown tablet is qualitatively and quantitatively identical to the 250 mg Phase 2/3 clinical tablet, except that the name 'IRESSA' and tablet strength marking '250' are impressed on one side of the tablet.

What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effects of food and increased gastric pH on the absorption of ZD1839 from the 250 mg brown clinical tablets were assessed in healthy male volunteers following a single 250 mg oral dose (Trial 36). Increased gastric pH was achieved by concomitant administration of ranitidine (450 mg) and oral sodium bicarbonate to maintain the gastric pH above 5 for 8 hours; this causes a decrease in ZD1839 solubility in the gastric fluid.

Table XIV. Effect of a high-fat breakfast on the pharmacokinetic parameters of a single oral 250 mg dose of ZD1839 in 25 healthy male volunteers

Parameter	Fasted	Fed	Ratio of glsmeans	90% CI* for the ratio
C_{max} (ng/ml)	111±38 (34%)	143±40 (28%)	–	–
*glsmean C_{max} (ng/ml)	104	137	1.32	116-149%
T_{max} (h)	5.0 2.0-24	5.0 (2.0-8.0)	–	–
AUC (ng.h/ml)	2658±1453 (55%)	3551±1671 (40%)	–	–
*glsmean AUC (ng.h/ml)	3118	2281	1.37	124-151%
t½ (h)	25.0±12.8 (48%)	26.8±14.9 (54%)	–	–

gls (geometric least squares mean) * two 1-sided confidence interval

Table XV. Effect of an increased gastric pH on the pharmacokinetic parameters of a single oral 250 mg dose of ZD1839 in 24 healthy male volunteers

Parameter	ZD1839 alone	ZD1839+Ranitidine	Ratio of glsmeans	90% CI* for the ratio
C_{max} (ng/ml)	132±48 (36%)	38±13 (34%)	–	–
*glsmean C_{max} (ng/ml)	122	36	0.293	25.7-33.4%
T_{max} (h)	4.9 (2.0-7.0)	5.9 (4.9-47.5)	–	–
AUC (ng.h/ml)	3252±1556 (48%)	1806±1226 (68%)	–	–
*glsmean AUC (ng.h/ml)	2739	1444	0.527	46.6-59.6%
t½ (h)	26.6±12.9 (48%)	29.4±18.5 (63%)	–	–

gls (geometric least squares mean) * two 1-sided confidence interval

Food increased AUC by 33% and C_{max} by 29% in 25 healthy male volunteers. Increased gastric pH reduced AUC by 44% and C_{max} by 70% in 24 healthy male volunteers.

The increase in exposure to ZD1839 in the presence of food by about 30% may not be clinically significant. The Applicant proposed in the package insert that patients could be administered IRESSA with or without a meal although patients during clinical trials took ZD1839 tablets on the morning on an empty stomach. The Applicant also included a precaution statement in IRESSA labeling that drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of IRESSA and therefore potentially may reduce efficacy.

F. Analytical Section

In all trials, the Applicant measured ZD1839 concentrations in plasma samples using a high-performance liquid chromatography assay with tandem mass spectrometric detection (HPLC-MS/MS). ZD1839 is the only drug-related entity measured in plasma. A detailed assay method and summary performance of quality control samples are presented in Appendix 2. The limit of quantification (LOQ) of the assay is 0.5 ng/ml. Calibration curves are linear over the concentration range of 0.5-100 ng/ml. The assay validation is acceptable with respect to precision, accuracy, specificity, and stability. Plasma samples with concentrations above 100 ng/ml were either diluted in control plasma or in ultra pure water to achieve concentrations within the linear range of the calibration curve (Submission of October 7, 2002).

VI. OCPB'S Labeling Recommendations

DRAFT

Absorption:

4 pages redacted from this section of the approval package consisted of draft labeling

APPENDICES

1. Pharmacometrics Review

NDA 21-399 IRESSA (Gefitinib; ZD1839)

Dosage:	250 mg oral tablets
Indication:	Advanced Non-Small Cell Lung Cancer
Submission Type:	NDA
Applicant:	Astra-Zeneca Pharmaceuticals
Submission Date:	March 21, 2002.
OCPB Division:	DPE-1 (HFD-860)
OND Division:	DODP (HFD-150)
Primary Reviewer:	Sophia Abraham, Ph.D.
Team Leader:	Atiqur Rahman, Ph.D.
Pharmacometrics Reviewer:	Brian Booth, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.

Executive Summary

The applicant requested accelerated approval for IRESSA because there is no effective therapy available for patients with third-line non-small cell lung cancer (NSCLC). FDA approval is conditionally based on demonstrated improvement in a surrogate endpoint. In this case, an improvement in the objective response (Lung Cancer Score (LCS)) and response rate are the basis for approval. The LCS score assigned to the patient based on the presence and severity of symptoms (shortness of breath, cough, chest tightness, ease of breathing, weight loss, clarity of thinking and poor appetite: scored 0-4 per symptom, with 0 = severe and 4 = asympotomatic). Response rate is assessed by bidimensional measurement of the tumor. This analysis performed by the applicant did not show any significant correlation between exposure and tumor response, LCS response or AEs. The FDA review of this analysis confirms the applicant's conclusions.

Objectives of the Analysis

- Estimate mean and variability of steady-state trough concentrations following 250 or 500 mg doses of ZD1839
- Identify covariates that affect the steady-state trough concentrations of ZD1839.
- Determine if any relationship exists between steady-state trough concentrations and adverse events (AE).
- Determine if any relationship exists between steady-state trough concentrations and clinical effectiveness endpoints (tumor response and lung cancer score (LCS) response).
- Compare the variability in steady-state trough concentrations between studies.

Background

ZD1839 possesses dose-proportional, multi-compartmental kinetics in healthy volunteers over doses of 50 to 500 mg. ZD1839 is metabolized by cytochrome P-450 (CYP) isozymes, especially CYP 3A4, and generates a number of active metabolites. There is very little renal excretion (~4%). The AUC and Cmax are approximately 2-fold higher in cancer patients than volunteers. The terminal elimination half-life is 30 hours in healthy volunteers and approximately 40 hours in cancer patients. The inter-patient variability in AUC is 55% in both volunteers and patients. In the pivotal study (39) and supportive trials (16), ZD1839 was administered to third-line lung cancer patients in either 250 or 500 mg daily doses.

METHODS

Design

Study #1: Trial 1839L/039 (39)-USA

This study was a randomized, double-blind, parallel group, Phase 2 study. Patients were randomized to receive either 250 or 500 mg of ZD1839 daily. Two hundred and twenty patients with confirmed, locally advanced or metastatic NSCLC were enrolled. Patients had received at least 2 previous courses of chemotherapy that contained platinum and docetaxel were enrolled.

Study #2: Trial 1839L/0016 (16)-Japan

This study was a randomized, double-blind, parallel group, Phase 2 study. Patients were randomized to receive either 250 or 500 mg of ZD1839 daily. Two hundred patients with confirmed, locally advanced or metastatic NSCLC were enrolled. Enrollment was limited to patients who had received 1 or 2 previous courses of chemotherapy; at least one course must have contained platinum. Enrollment was to include 100 Japanese and 100 non-Japanese patients.

Data

Study 39-Pharmacokinetics

Samples were taken at the steady-state trough prior to the next dose. Patients were scheduled to be sampled once every 28 days. Four hundred and fifty four of 491 samples from 187 patients were available for analysis. The excluded samples were not analyzed because of missing sampling times or dates, dose times, dose interruptions, or dose reductions.

Study 16-Pharmacokinetics

Samples were taken at the steady-state trough prior to the next dose. Patients were scheduled to be sampled once every 28 days. Five hundred and twenty of 598 samples from 176 patients were available for analysis. The excluded samples were not analyzed because of missing sampling times or dates, dose times, dose interruptions, or dose reductions.

The demographic characteristics of the patients in studies 16 and 39 are listed in Table 1 below.

Table 1. Patient Demographics from ZD 1839 Studies 16 and 39.

Demographic Characteristic	Study 1839IL/0016	Study 1839IL/0039	Combined
Total number of subjects	176	177	353
Age (years) (Mean ± SD)	59.7 ± 9.61	60.3 ± 10.6	60.0 ± 10.2
Weight (kg) (Mean ±SD)	64.2 ± 15.36	75.1 ± 16.6	69.6 ± 16.9
Height (cm) (Mean ± SD)	165.6 ± 9.53	169.3 ± 10.7	167.4 ± 10.3
Body Mass Index	23.3 ± 4.32	26.2 ± 5.0	24.7 ± 4.9
Creatinine Clearance ($ml.min^{-1}$) (Mean ± SD)	73.5 ± 23.56	98.9 ± 36.2	84.8 ± 32.4
Hepatic function			
1 = Normal (Grade 0-2)	166	133	299
2 = Moderate (Grade 3 –5)	2	4	6
3 = Severe (Grade 6 – 12)	8	0	8
Dose			
250 mg daily	92	84	176
500 mg daily	84	93	177
Gender			
0= Male Patients	125	97	222
1= Female Patients	51	80	131
Death			
0 = Patient has not died	122	108	230
1 = Patient has died	54	69	123
Race			
0 =Black	1	7	8
1 = White	96	144	240
2 =Japanese	79	26	105
Overall Response			
0=Non responder	140	147	287
1=Responder	36	23	59

Data Checking

Data checking was accomplished by examining different plots of the data and is discussed further in the Results/Discussion section.

Models

Structural Models

The basic structural model described the trough concentration as a function of the population mean steady state trough concentration and the variability

$$\theta_i = \theta_p * e^{\eta i}$$

θ_i = Individual predicted steady-state trough concentration
θ_p = population predicted steady-state trough concentration
η^i = inter-individual variance

The applicant also evaluated the effect of adding additional parameters to estimate steady state trough concentration , namely

- Adding two parameters to estimate steady state trough concentration for the two doses,
- Using FOCE and FOCE with interaction instead of FO.
- Using separate inter-individual variance parameters for the 250 and 500 mg doses
- Using separate structural model as well as the residual variance estimates for the 2 studies

Covariate Model

The covariate models to be evaluated were not described. The covariates to be tested were age, race, weight, height, gender, body mass index, hepatic function, creatinine clearance, total serum protein, serum albumin, and serum alpha1-acid glycoprotein.

Pharmacodynamics

The pharmacodynamic models to be tested were not described. Logistic regression seems to have been used for all pharmacodynamic analyses. Overall patient response, LCS and incidence of patient death were the pharmacodynamic endpoints tested.

Model Selection

The final model was to be chosen based on a visual inspection of the plots of predicted concentrations, the parameter estimates, their standard error and minimum objective function (MOF). No criteria acceptance for any of these descriptors was defined.

Software

The applicant manipulated and graphed data using Microsoft Excel. NONMEM (Ver. V1.1) was used for PK/PD modeling, using a Digital Visual fortran compiler (FORTRAN 90, Ver 9.0) on a Compaq Deskpro PC using Windows 95 with 255 MB RAM.

RESULTS AND DISCUSSION

Data Checking

Data was checked by visual examination of plotted data. The sampling times of the steady state trough concentrations ranged from 14 to 34 hours, with a mean of 24.6 hours (95%C.I. of 20 to 34.2 hours). Figure 1 shows that the concentrations of ZD 1839 overlap extensively, regardless of the ZD1839 dose.

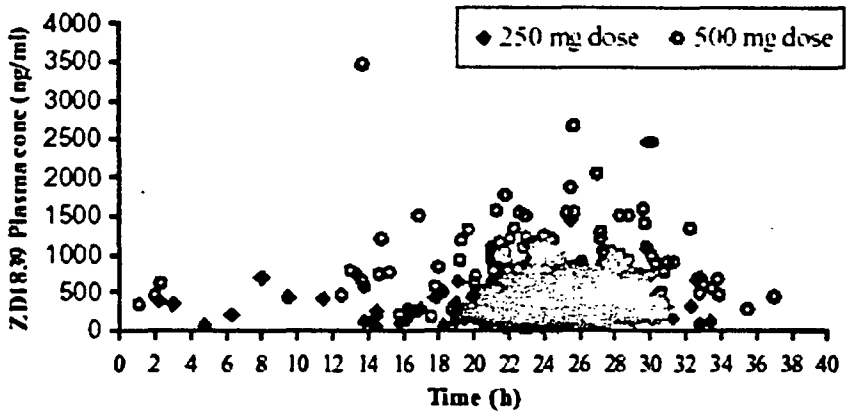


Figure 1. Distribution of steady state trough concentrations of ZD1839 over time for 250 and 500 mg doses from the combined studies.

Model Selection

The base pharmacokinetic model described the steady state trough concentration as function of the mean population steady state concentration and inter-individual variability.

The final basic model estimated steady-state trough concentration as a function of dose and with separate estimates of inter-patient variability for the 250 and 500 mg doses, using FOCE with interaction. The function is described as

$$\theta_i = (\theta_{p250}\ ((1\text{-code}) + (\theta_2 \text{code}))^* e^{\eta i250^*1\text{-code} + \eta i500^* \text{code}}$$

θ_i = Individual predicted steady-state trough concentration
θ_{p250} = population predicted steady-state trough concentration for the 250 mg dose
θ_2 = scale parameter that multiplies the 250 mg trough to the 500 mg trough
code: indicator variable for the 250 or 500 mg trough (code =0 for 250 mg; 1 for 500 mg)
$\eta i250$ = inter-individual variance for the 250 mg dose
$\eta i500$ = inter-individual variance for the 500 mg dose

This model (#7) was chosen because the MOF was reduced compared to the base model (#1) and the other models. The intra-subject variability incorporated a variance term for study. Table 2 summarizes the changes in MOF for each model assessed.

Table 2. MOF values for the population pharmacokinetic models

Model number	Structural model	Intra-individual error model	Inter-individual error model	Objective function	Comment
1	Θ_1 (FO method)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val})}$	11478.1	Minimisation successful
2	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FO method)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val})}$	11185.3	Minimisation successful
3	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FOCE method)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val})}$	11047.0	Minimisation successful
4	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FOCE method + interaction)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val})}$	10700.9	Minimisation successful
5	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FOCE method + interaction)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val\ 250\ mg}\ \eta_{val\ 500\ mg})}$	10700.6	Minimisation successful
6	$\Theta_{1\,(250\ mg\ STUDY\ 16)}$ $\Theta_{2\,(250\ mg\ STUDY\ 39)}$ $\Theta_{3\,(500\ mg\ STUDY\ 16)}$ $\Theta_{4\,(500\ mg\ STUDY\ 39)}$ (FOCE method + interaction)	F + (F * Eps(1))	$\theta_i = \theta p * \exp^{(\eta_{val\ 250\ mg}\ \eta_{val\ 500\ mg})}$	10700.6	Minimisation successful
7	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FOCE method + interaction)	F + (F * Eps(1)$_{250\ mg}$ + Eps(2)$_{500\ mg}$)	$\theta_i = \theta p * \exp^{(\eta_{val\ 250\ mg}\ \eta_{val\ 500\ mg})}$	10673.8	Minimisation successful
	Basic Pharmacokinetic Model				
7	$\Theta_{1\,(250\ mg)}$ $\Theta_{2\,(500\ mg)}$ (FOCE method + interaction)	F + (F * Eps(1)$_{250\ mg}$ + Eps(2)$_{500\ mg}$)	$\theta_i = \theta p * \exp^{(\eta_{val\ 250\ mg}\ \eta_{val\ 500\ mg})}$	10673.8	Minimisation successful

F = Predicted plasma concentration

The parameter estimates using this model are shown in Table 3.

Table 3. Parameter estimates for steady state trough concentrations of ZD 1839

Parameter	Mean	Standard error (%)
Mean population parameter for 250 mg trough concentration ($ng.ml^{-1}$)	261	4.4
Scale of 250 mg dose to 500 mg	1.96	6.4
Inter-individual variance for 250 mg trough concentration (%)	55.5	13.5
Inter-individual variance for 500 mg trough concentration (%)	59.0	13.6
Proportional residual error study 1839IL/0016 (%)	21.9	10.0
Proportional residual error study 1839IL/0039 (%)	29.6	13.5

The plot of the individual predicted concentrations versus the observed concentrations using this model is shown in Figure 2.

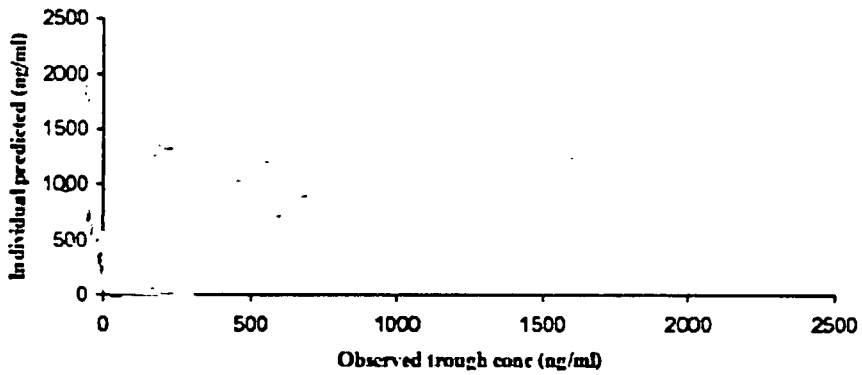


Figure 2. ZD1839 individual predicted concentrations versus the observed concentrations.

This plot, as well as the parameter estimates and their errors (Table 3) suggest that the model is relatively well modeled. There is a slight under-prediction at higher concentrations (> 1000 ng/mL), but this appears small and is not likely important because most of the data is at the lower end of the curve.

Covariate Model

The influence of covariates on the estimation of steady-state trough concentration was assessed by visual examination of graphical plots of demographic characteristics versus the estimated concentration (using the final base model). No clear relationship was observed for age, race, gender, height, hepatic function, creatinine clearance, serum albumin, alpha1 glycoprotein, total protein, body mass index or weight. Therefore, no covariates were fit to the basic model.

Pharmacodynamics

Individually predicted steady-state trough concentrations were plotted versus overall patient response, LCS and incidence of patient death. No relationships were visually discerned.

Individually predicted steady-state trough concentrations were plotted versus AEs. Nausea, vomiting, pruritis and changes in AST or ALT levels did not reveal any relationship. A probability analysis indicated that the probability of acne/rash and diarrhea increased with increased steady-state trough concentrations. A similar analysis indicated no significant relationship between exposure and adverse events.

Individually predicted trough concentrations were plotted against the co-administration of CYP 3A4 inhibitors, inducers or antacids. Again no clear effect could be discerned visually.

The applicant made the following conclusions

- Mean trough concentration of the 250 mg dose of ZD 1839 was 261 ng/ml (95% C.I. from 74 to 774 ng/ml)
- The trough concentrations of the 500 mg dose of ZD 1839 approximately two-fold higher than those of the 250 mg dose. (1.71 to 2.2)
- Inter patient variability was 55.5% for the 250 mg dose, and 59% for the 500 mg dose. ($p>0.1$)
- Residual variability was 22% for study 16 and 30% for study 39 ($p<0.05$). The applicant suggested that this difference may have resulted from differences in compliance with sampling.
- Bias was 26.7 ng/ml and precision was 80 ng/ml, which suggests a small under-prediction of the trough concentrations.
- There was no clear effect of patient demography or pathophysiology on the steady state trough concentrations
- CYP 3A4 inhibitors, inducers and antacids did not affect trough ZD1839 concentrations.
- There was no clear relationship between trough concentrations and effectiveness endpoints.
- Only diarrhea and acne/rash showed correlations with trough concentrations of ZD 1839.

- The predicted steady state trough concentrations of the 250 and 500 mg doses overlapped, and suggest the same adverse event profile. The AEs were not found to be exposure dependent.

Significance

These results essentially confirm the medical review that no difference between the 250 and 500 mg doses can be determined with respect to safety and efficacy. The PPK model used here appears to model the data reasonably well. The use of trough concentrations instead of Cmax or AUC to explore PK/PD may be reasonable because of the proportional kinetics of ZD 1839 (up to 500 mg). Additionally, given the rather long t1/2 of about 40 hours and a dosing interval of 24 hours, the peak to trough ratio at steady-state is close to one.

The wide range (poor compliance) in the timing of the samples may confound the results to some degree. In the visual inspection of plots of covariates versus concentration, the concentration data were lumped together. This variability in the timing of the samples contributed (to a small extent) to the variability in the concentration data.

The effect of sex on the trough concentration of ZD 1839 was investigated beyond a visual inspection because of the suggested sex difference observed in study 35. The data from study 16 was used for this analysis. There were 183 subjects with 553 samples. Fifty-four were female and 129 were male. The mean plasma ZD1839 concentrations (not corrected for body size) in females and males was 316.5 ± 169.5 and 276.3 ± 146.8 ng/ml, respectively, following the 250 mg dose. Following the 500 mg dose, these concentrations (not corrected for body size) were 591.6 ± 303.6 and 516.6 ± 336 ng/ml, respectively. Concentrations greater than three standard deviations from the mean were deemed outliers and were not included in the analysis. This resulted in the elimination of 11 samples, from 7 patients. The apparent clearance of ZD 1839 was determined from the steady-state concentrations and was adjusted for body weight. Figure 3 shows that apparent clearances of males (1) and females (0) are overlapping. The mean apparent clearance is about 19 L/day/kg or 0.8 L/hr/kg. Further, mixed effects testing indicated no significant difference in clearances for males and females (p=0.1576). Given the exploratory nature of the population analysis, in general, a sample size of 54 females versus 124 males is reasonable to identify important differences, if any. The results from the statistical analysis are in congruence with the graphical display.

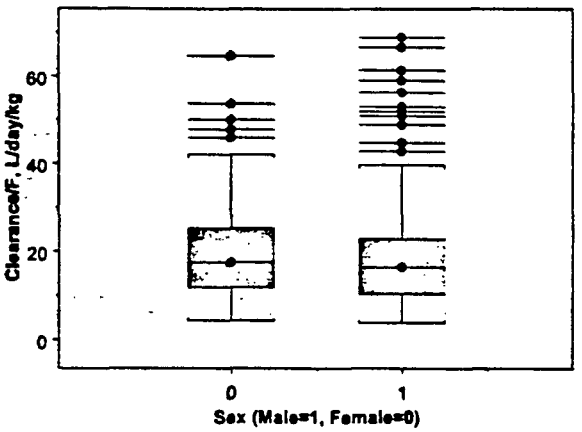


Figure 3. Boxplot showing the median, 25th and 75th percentiles of the clearance in females (0) and males (1).

The analysis was conducted in SAS ver 8 using mixed effect modeling.

The applicant concluded that no CYP 3A4 inducers or inhibitors affected the concentrations of ZD 1839. This result is in direct contrast with the specific in vivo drug-drug interaction studies performed by the applicant, with itraconazole (study 51), metoprolol (Study 38) and rifampicin (Study 30) which demonstrated significant effects on the pharmacokinetics of ZD 1839. The reason for this discrepancy may be due, in large part, to the approach taken to assess an interaction. In the current study, the applicant compared ZD 1839 concentrations between groups of patients that had either received on not received treatment with an inhibitor. However, the applicant did not distinguish between which specific inhibitor was administered, the timing of its dose in relation to the ZD1839 trough sample, the presence of other co-medications (e.g. inducers) etc. These issues could be expected to have a significant impact on whether a co-medication may have affected the ZD 1839 trough concentrations. Therefore, the approach used by the applicant is useful as a first step, but further investigation may have yielded results that were more consistent with the in vivo drug-drug interaction studies for itraconazole, metoprolol and rifampicin. Furthermore, the use of visual examination as the basis for concluding the presence or absence of a covariate effect is likely not ideal. In the case of inducers, the applicant did assess graphically whether phenytoin or glucocorticoids separately had an effect on ZD1839 concentrations, and concluded no effect. However, the phenytoin assessment (see uppermost figure in Appendix, page 17) suggests and interaction may have resulted, and further analysis may have useful in detecting such an interaction. Therefore, it may be more appropriate to have made conclusions based on a statistical comparison. In summary, the results of the population PK/PD study should be viewed with caution.

Points for consideration

- It is not clear why metabolite concentrations were ignored in these analyses.
- The applicant should have defined the criteria for accepting models.
- The applicant should have prospectively planned to study the effect of covariates on trough concentrations.
- The applicant did not describe how the probability analysis was performed for rash/acne and diarrhea with the trough ZD 1839 concentrations.

- The applicant did not validate the model, other than provide plots of the data.
- In future, the applicant should consider prospectively designing trials which would enable adequate testing of covariate effects.

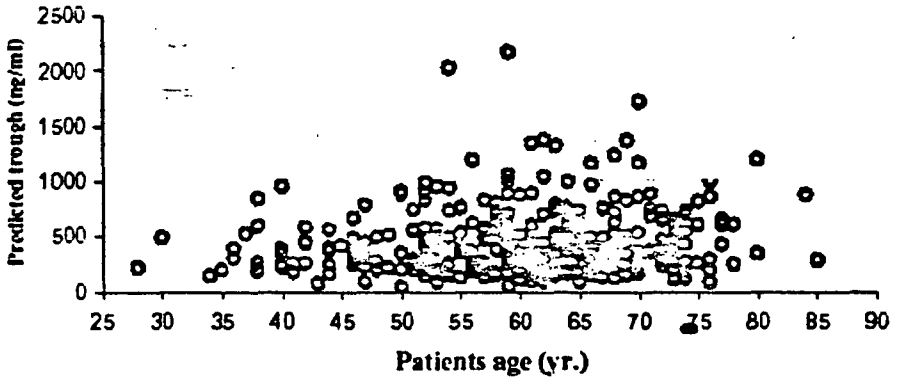
Appendix 1

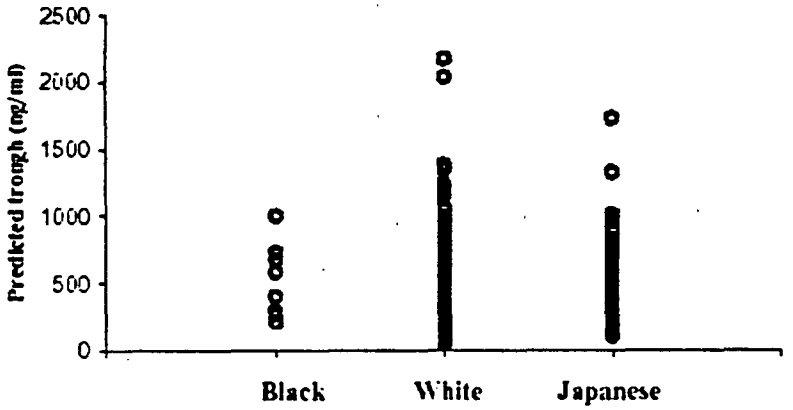
NONMEM Basic Pharmacokinetic Model,

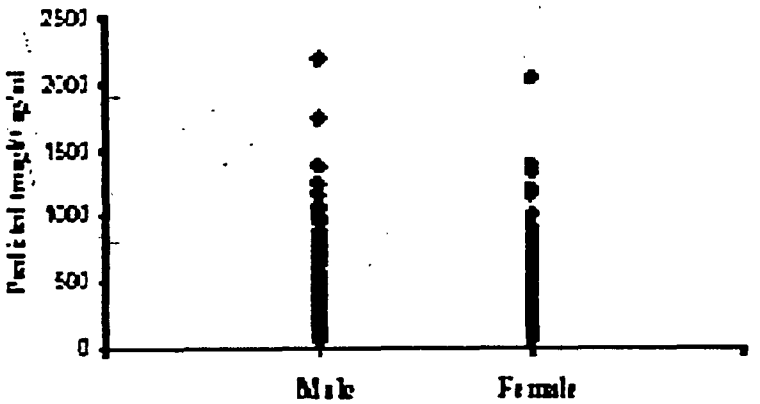
```
$PROB  ZD 1839 STUDY 16
$INPUT  ID CENT PAT DOSS DV STU
$DATA  1639.PRN
$PRED
 AA=0
 BB=0
 CC=0
 DD=0
 IF (DOSS.EQ.250)  AA=1
 IF (DOSS.EQ.500)  BB=1
 IF (STU.EQ.16)    CC=1
 IF (STU.EQ.39)    DD=1
  CONC = THETA(1)  * ((1-BB)+(THETA(2)*BB))
      AB = CONC        *  EXP(ETA(1)*AA + ETA(2)*BB)
      AA = AB + (AB    * (EPS(1)*CC + EPS(2)*DD))
       Y = AB + (AB    * (EPS(1)*CC + EPS(2)*DD))
$THETA  (10,600,800) (1,2,5)
$OMEGA  0.20 0.20
$SIGMA  0.50 0.50
$EST    METHOD=1 INTERACTION MAXEVAL=9000 SIGDIG=3 PRINT=5 POSTHOC
NOABORT
$COV
$TABLE  ID DOSS AB
      NOPRINT FILE=1639.TAB ONEHEADER
$SCAT   (RES WRES) VS DOSS
```

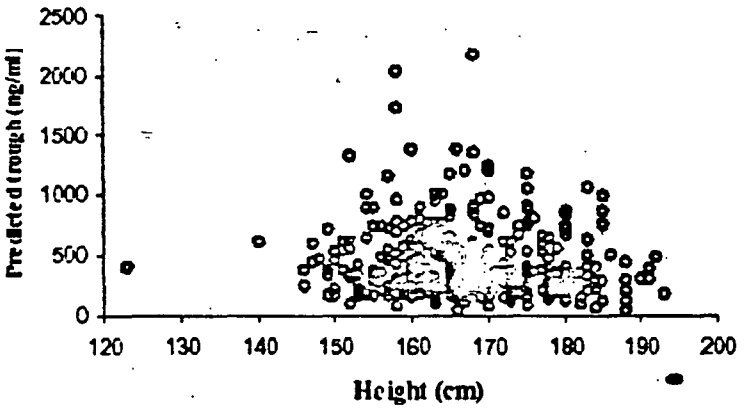
Model for the analysis of the categorical variables (AE's)

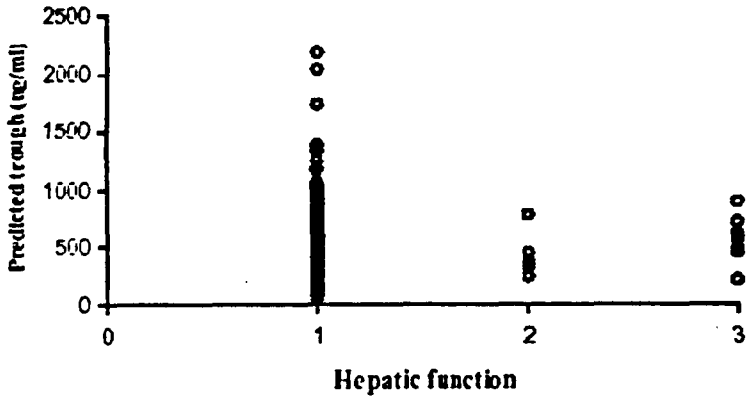
```
$PROBLEM  ZD 1839 STUDY 16
$INPUT    ID CON LCON DV SKI1 SKI3
$DATA     1639AE.PRN
$PRED
   VAL = (THETA(1) + (THETA(2)*LCON))+ ETA(1)
 LOGIT = EXP(VAL)
  PROB = LOGIT/(1 + LOGIT)
    F = PROB
   AA  = F
   IF (DV.EQ.1) THEN
    Y = PROB
   ELSE
    Y = 1-PROB
   ENDIF
$THETA  (-10,0.2,100) (0.000001,0.004,100)
$OMEGA  1.00
$EST    MET=COND MAXEVAL=999 SIGDIG=4 PRINT=2 LAPLACE LIKE
$TABLE  ID LCON CON AA
      NOPRINT FILE=1639AE.TAB ONEHEADER
$SCAT   (RES WRES) VS PRED
$SCAT   PRED VS DV UNIT
```

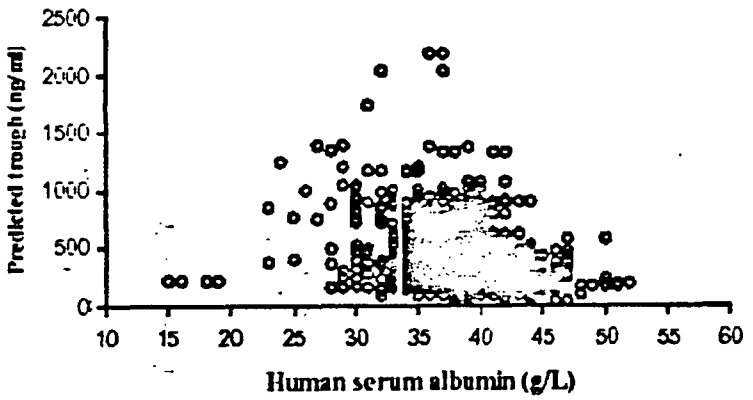

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
25 30 35 40 45 50 55 60 65 70 75 80 85 90
Patients age (yr.)

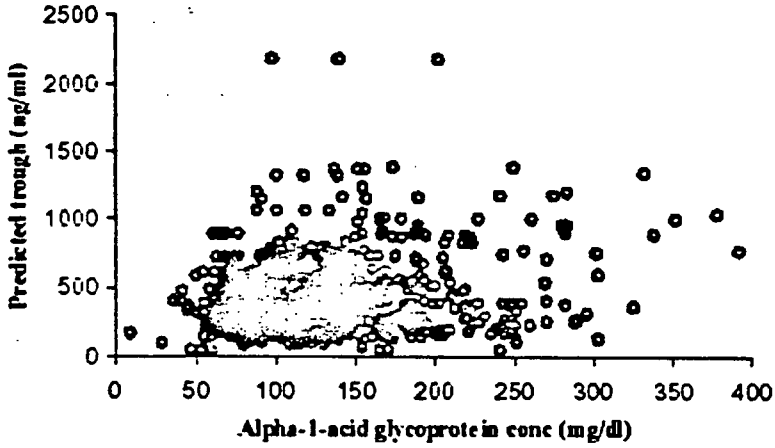

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
Black
White
Japanese

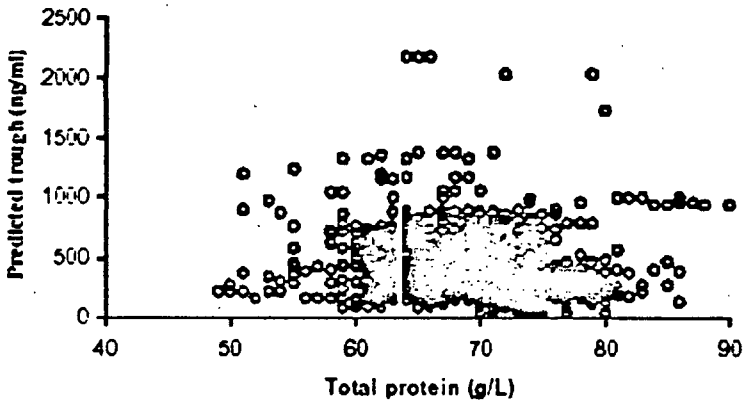

2500
2000
1500
1000
500
0
Male
Female

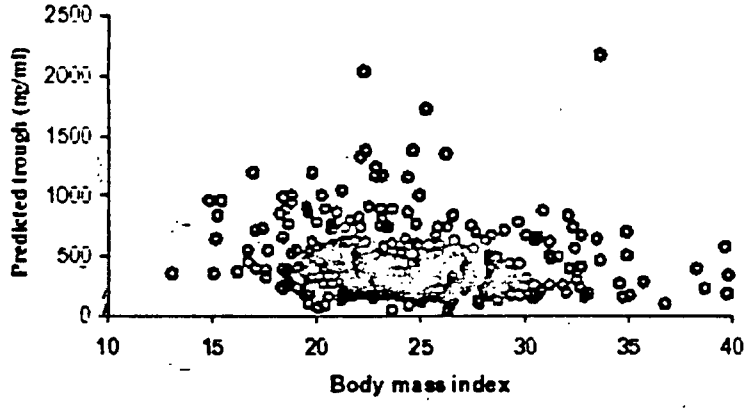

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
120
130
140
150
160
170
180
190
200
Height (cm)

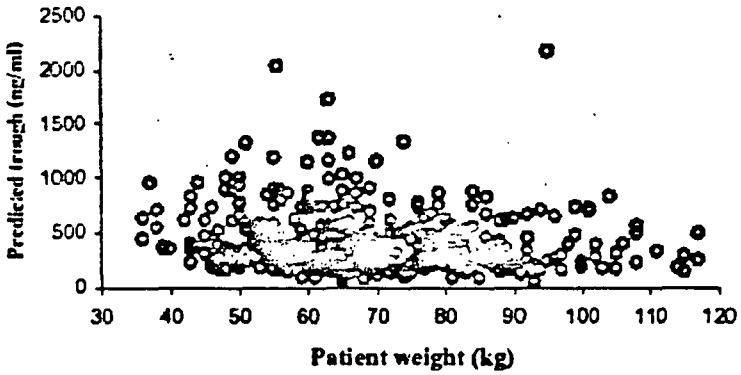

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
0
1
2
3
Hepatic function

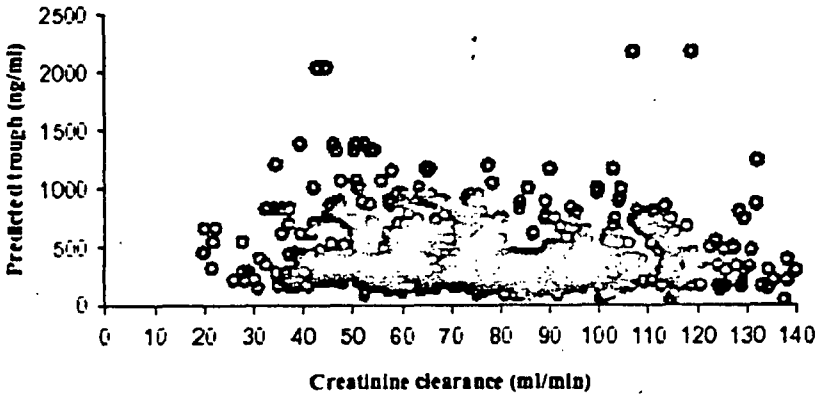

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
10
15
20
25
30
35
40
45
50
55
60
Human serum albumin (g/L)

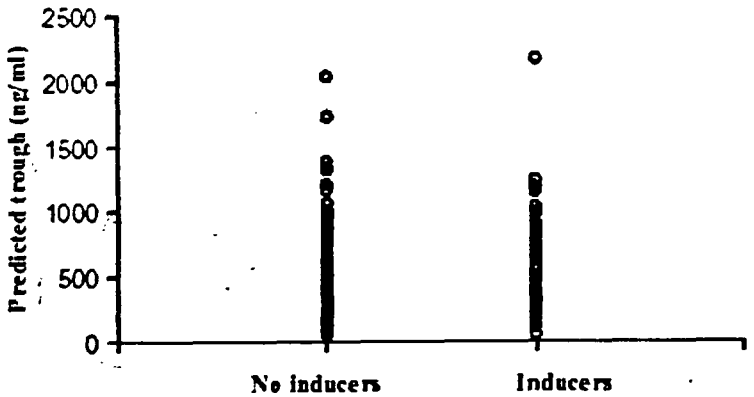

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
0
50
100
150
200
250
300
350
400
Alpha-1-acid glycoprotein conc (mg/dl)

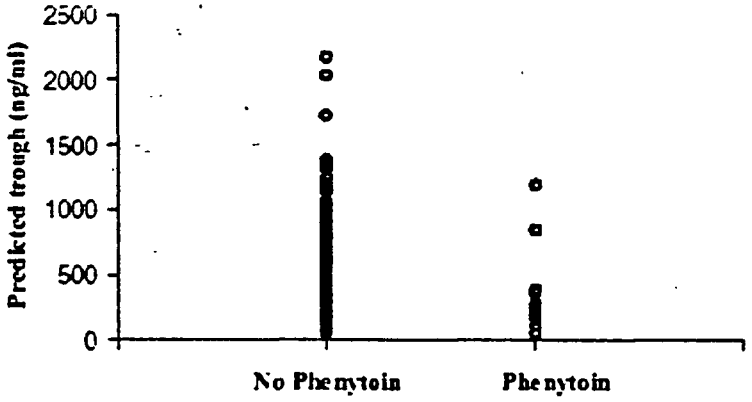

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
40
50
60
70
80
90
Total protein (g/L)


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
10
15
20
25
30
35
40
Body mass index


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
30 40 50 60 70 80 90 100 110 120
Patient weight (kg)

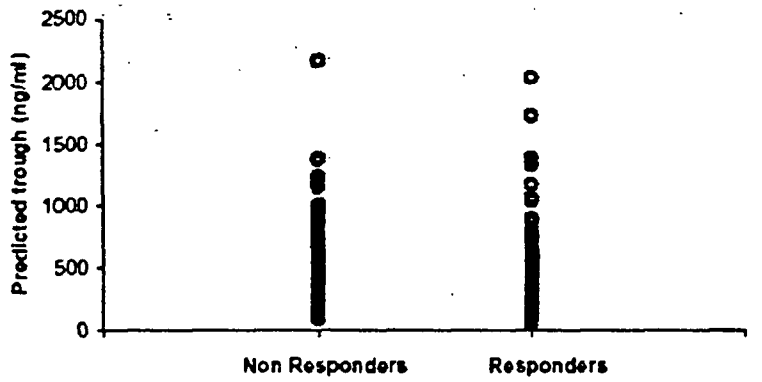

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Creatinine clearance (ml/min)

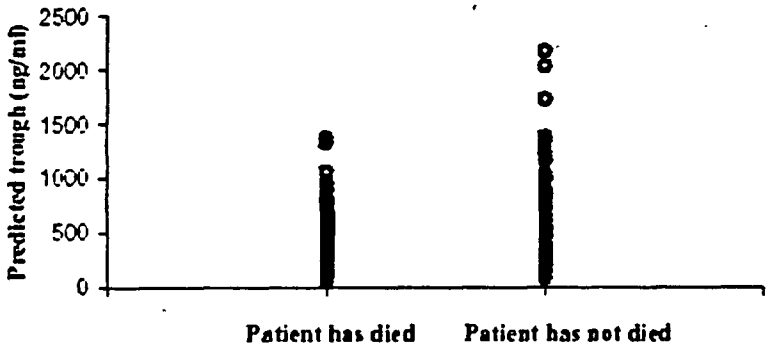

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
No inducers
Inducers

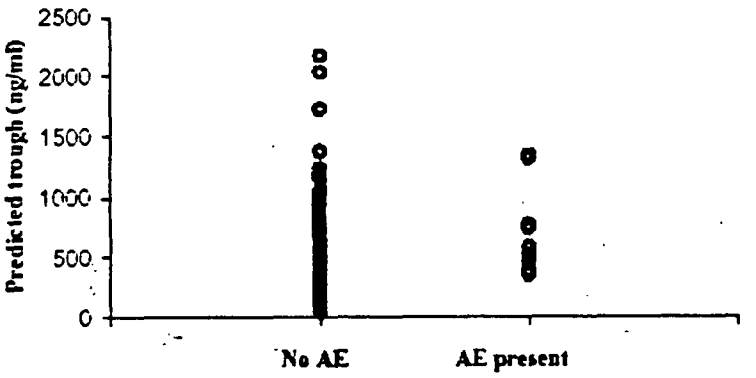

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
No Phenytoin
Phenytoin

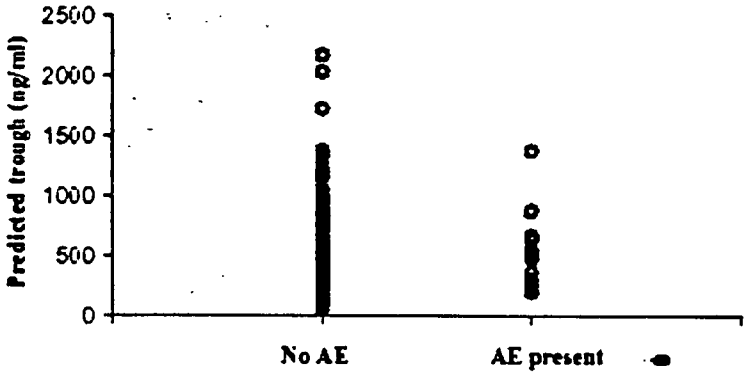

Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
No Antacids
Antacids


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
No inhibitors
Inhibitors


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
Non Responders
Responders


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
Patient has died
Patient has not died


Predicted trough (ng/ml)
2500
2000
1500
1000
500
0
No AE
AE present



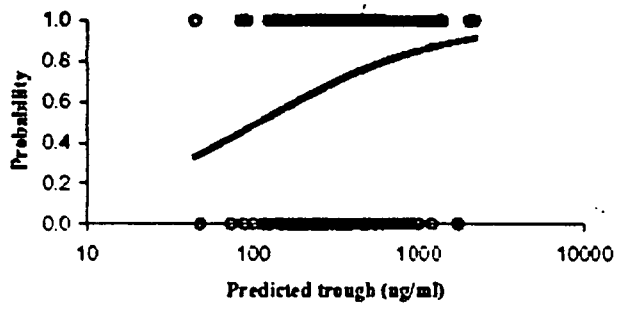


Figure 38.0
Relationship between the probability of acne and or a rash and the predicted steady state trough concentration.

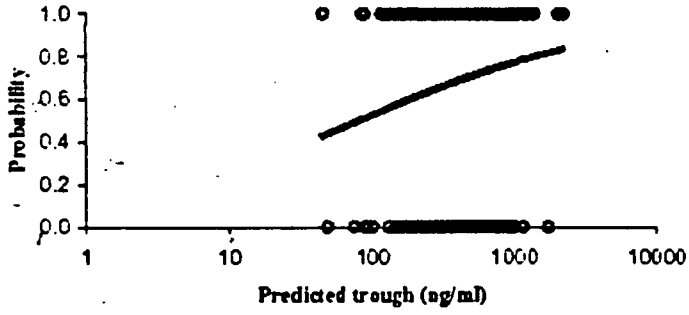
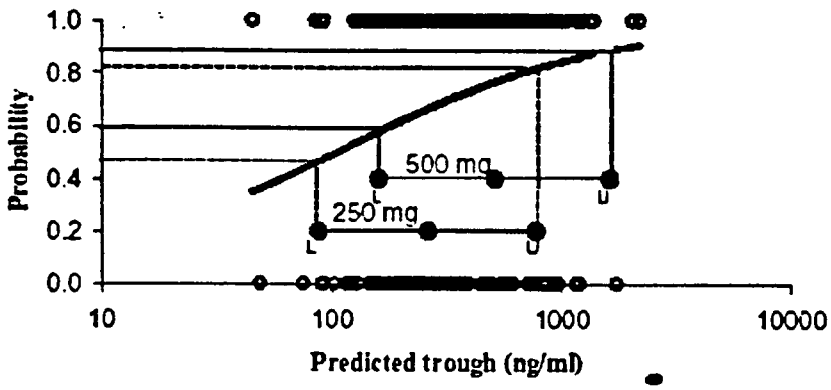


Figure 39.0
Relationship between the probability of diarrhoea and the predicted steady state trough concentration.



L = Lower 95 % confidence limit
U = Upper 95 % confidence limit

Figure 40.0
Relationship between the variability of the predicted steady state trough concentration for the 250 mg and 500 mg dose and the probability of acne and or rash.

12 pages redacted from this section of the approval package consisted of draft labeling

9 PAGE(S) COPYRIGHT MATERIAL - REMOVED FROM THIS SECTION

A Sensitive Assay for ZD1839 (Iressa) in Human Plasma By Liquid-liquid Extraction And High Performance Liquid Chromatography With Mass Spectrometric Detection: Validation And Use in Phase I Clinical Trials

Journal of Pharmaceutical and Biomedical Analysis, Vol. 29, Issue1-2, (June 2002), 221-228

APPENDIX 4

Filing MEMO

Office of Clinical Pharmacology and Biopharmaceutics			
New Drug Application Filing and Review Form			
V. General Information About the Submission			
	Information		Information
NDA Number	21-399	Brand Name	IRESSA
OCPB Division (I, II, III)	DPE 1	Generic Name	Gefitinib
Medical Division	DODP (HFD-150)	Drug Class	anilinoquinazoline
OCPB Reviewer	Sophia Abraham	Indication(s)	NSCLC
OCPB Team Leader	Atiqu Rahman	Dosage Form	250 mg tablets
		Dosing Regimen	One tablet daily
Date of Submission	Aug. 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	Aug. 15, 2002	Sponsor	AstraZeneca
PDUFA Due Date		Priority Classification	1p
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	X			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:				
Plasma protein binding:	X	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	x	1	1	
Patients-				
single dose:	X	2		
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2	2	
In-vivo effects of primary drug:	X	1	1	
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	1	1	
II. Biopharmaceutics				
Absolute bioavailability:	x	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:	x	1	1	Single-dose
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
Dissolution:	x	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
		16	16	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	
Comments sent to firm ?	x	
QBR questions (key issues to be considered)	Clinical pharmacology of the major active O-desmethy metabolite	
Other comments or information not included above		
Primary reviewer Signature and Date	Sophia Abraham 8/12/02	
Secondary reviewer Signature and Date		

CC: NDA , HFD-870 (Lee), HFD-150(Baird), HFD-860(Mehta, Marroum, Rahman, Abraham), CDR (Biopharm)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sophia Abraham
10/15/02 02:00:56 PM
BIOPHARMACEUTICS

Jogarao Gobburu
10/15/02 05:55:35 PM
BIOPHARMACEUTICS

Brian Booth
10/16/02 08:51:35 AM
BIOPHARMACEUTICS

Atiqur Rahman
10/16/02 11:34:25 AM
BIOPHARMACEUTICS