CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-743

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics NDA Review
MEMO

Brand name: TARCEVA™

Generic name: Erlotinib hydrochloride

Type of dosage form and strength(s): 25, 100 and 150 mg tablets

Indication(s): Patients with advanced or metastatic non-small cell lung cancer (NSCLC) (Stage IIIB/IV) who have failed at least one [ ] prior regimen.[ ]

NDA number, type: NDA 21-743, 1P, CMA Pilot 1

Applicant: OSI Pharmaceuticals

Submission date (letter date):	12-May-04	RRZ	003	
	29-Jul-04	N	000	
	3-Aug-04	N	000	BB
	6-Aug-04	N	000	BZ
	20-Aug-04	N	000	BZ
	13-Sept-04	N	000	BB

OCPB Division: Division of Pharmaceutical Evaluation I

OND Division: Division of Oncologic Drug Products

OCPB Team Leader: Brian P. Booth, Ph.D.

The applicant has demonstrated with an in vivo study that rifampicin induces cytochrome P-450 and that this induction leads to 2/3 reduction in the AUC of Tarceva. This finding is important, because a reduction in the AUC of Tarceva would be expected to have an impact on the effectiveness of the drug, which in this case may impact on a patient's overall survival. In my opinion, there is sufficient information available from the rifampicin-Tarceva drug-drug interaction study to provide a dose adjustment (450 mg) to avoid the large reduction in Tarceva AUC for patients who will be treated with both drugs. Similar specific dose adjustments have been made to compensate for reduced drug AUC for Iressa, Gleevec and Exemestane.

This labeling recommendation was rejected by the medical division based on concerns that there is no clinical experience with the 450 mg dose of Tarceva. Another confounding issue is the pharmacokinetic variability in the population. Some patients on who are treated with the increased dose of Tarceva may experience significant toxicity in if the rifampicin effect is less than the median 67 % reduction.

Nevertheless, the clinical division believes this is an important issue that requires redress. In consultation with the clinical division, Dr. Williams has proposed a phase 4 study to address dosing of Tarceva in patients treated with rifampicin. This study is expected to provide additional information about the AUC and tolerability of Tarceva doses specifically chosen to compensate for rifampicin-induced reduction in concentrations. Given the concern about adjusting the Tarceva dose based on the current information, this phase 4 study is the next best option for addressing the issue.

/S/

Brian Booth, Acting Team Leader
Division of Pharmaceutical Evaluation 1.

CC NDA 21-743
PZimmerman, MCohen,JJohnson, Grant Williams
MMehta, NAMRahman, GWilliams, JDuan, JGobburu
CDR Biopharm

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/s/

Brian Booth
10/1/04 06:35:24 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-743	Brand Name	Tarceva
OCPB Division (I, II, III)	I	Generic Name	erlotinib hydrochloride
Medical Division	Oncology (DODP)	Drug Class	EGFR antagonist
OCPB Reviewer	Gene Williams	Indication(s)	stage IIIB or IV non-small cell lung cancer (NSCLC) in patients who have received prior chemotherapy.
OCPB Team Leader	Brian Booth	Dosage Form	25 and 150 mg tablets
		Dosing Regimen	
Date of Submission	29-Jul-04	Route of Administration	oral
Estimated Due Date of OCPB Review	31-Aug-04	Sponsor	OSI Pharmaceuticals
PDUFA Due Date	29-Jan-05	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				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	[redacted]		
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:	X	14		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:	X	3		
multiple dose:	X	3		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:				
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: TARCEVA™

Generic name: Erlotinib hydrochloride

Type of dosage form and strength(s): 25, 100 and 150 mg tablets

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OCPB Division name: Division of Pharmaceutical Evaluation I

OND: Division name: Division of Oncologic Drug Products

OCPB Reviewer name: Gene M. Williams, Ph.D.

OCPB Team Leader name: Brian P. Booth, Ph.D.

OCPB Pharmacometrics Reviewer Name: John Z. Duan, Ph.D.

OCPB Pharmacometrics Team Leader: Jogarao Gobburu, Ph.D.

Table of Contents

Page

1 Executive Summary

1.1 Recommendations *3*

1.2 Phase 4 Commitments *3*

1.3 Summary of Important Clinical Pharmacology and

Biopharmaceutics Findings 3

2 *Question Based Review*

2.1 *General Attributes of the Drug* 7

2.2 *General Clinical Pharmacology* 8

2.3 *Intrinsic Factors* 36

2.4 *Extrinsic Factors* 40

2.5 *General Biopharmaceutics* 49

2.6 *Analytical Section* 54

3 *Detailed Labeling Recommendations* 60

4 *Appendices*

4.1 *Proposed Package Insert (Original and Annotated)*

4.2 *Individual Study Review*

4.3 *Consult Review (Including Pharmacometric Reviews)*

4.4 *Cover Sheet and OCPB Filing/Review Form*

1. *Executive Summary*

1.1. Recommendations

The application is acceptable provided that satisfactory agreement is reached between the Applicant and the Agency regarding (1) language in the package insert, (2) a change in the dissolution specification from Q = [redacted] to Q = [redacted]%, (3) the need to perform a study in hepatically-impaired subjects, (4) the need to complete the ongoing midazolam drug interaction study, and (5) the need to perform in vitro studies of the ability of erlotinib to be metabolized via non-CYP routes.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

1. We recommend that a study be performed to determine the pharmacokinetics of erlotinib in hepatically-impaired cancer patients. The study will have two phases. For both phases the primary objective is pharmacokinetics. In the first phase, an assessment of whether pharmacokinetic changes occur due to hepatic impairment will be made. Assuming that significant pharmacokinetic changes occur, the results will be population modeled and simulations will be used to choose a dose adjustment strategy. FDA will review the chosen strategy prior to initiation of the second phase of the study. The second phase of the study will verify the dose adjustment strategy by using it in a cohort of hepatically-impaired patients and measuring their pharmacokinetics.

2. We recommend that a study be conducted to assess the ability of dose adjustment to compensate for the large decrease in erlotinib AUC seen when TARCEVA is co-administered with a strong enzyme inducer. The primary objective of the study is to determine a dose of TARCEVA that, when administered to subjects receiving rifampicin, will produce plasma concentrations approximating those seen in patients receiving 150 mg QD TARCEVA without rifampicin. Study design will be driven by population pharmacokinetic modeling and simulation using the current data on the interaction of rifampicin and erlotinib. FDA will review the chosen strategy prior to initiation of the study.

3. We recommend that the Applicant agree to complete the ongoing midazolam drug interaction study. The results of this study will determine the need to accomplish additional in vivo and in vitro drug interaction studies.

4. We recommend a dissolution specification of Q = [redacted] @ 45 minutes, [redacted] Apparatus 2 (Paddle) @ [redacted] RPM, [redacted]

5. We recommend that the Applicant explore the contribution of non-CYP routes to the metabolism of erlotinib.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3 pages)

CLINICAL PHARMACOLOGY

Rationale for Dose Selection and Dose Interval

The Phase I Study 248-004 identified 200 mg daily as the dose-level leading to dose-limiting toxicities (diarrhea). Subsequently, 150 mg daily (one level below the DLT) was confirmed to be the recommended dose in cancer patients. The average trough concentration on Day 24 – 29 was 918 ng/mL, which is well above the concentration required for erlotinib activity in various nonclinical assays, even when erlotinib's in vitro protein binding value of 95% is considered. Based on these considerations, it was concluded that the 150 mg/day dose would be sufficient to provide a high anti-neoplastic effect with a tolerable and manageable safety profile.

In Vitro Studies and Metabolism

Erlotinib is metabolized in human liver primarily by the cytochrome P450 isoform CYP3A4, but also by CYP1A2 and, to a minor extent, by CYP2C8. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumor tissue may contribute to the metabolic clearance of erlotinib. Studies with human liver microsomes identified a strong inhibition of the formation of erlotinib metabolites by ketoconazole, a potent CYP3A4 inhibitor. The predominant metabolism via CYP3A4 also raised the question of the role of enzyme inducing agents such as rifampicin. Clinical studies to address interaction with ketoconazole and rifampicin have been conducted.

In vitro studies examining erlotinib's activity as a CYP inhibitor revealed some potential for erlotinib to inhibit CYP 2C8 (I:Ki = 0.3) and 2C9 (I:Ki = 0.1). The I:Ki of erlotinib for CYP3A4 ranged from 0.3 – 0.55. The Applicant has a clinical study in progress to determine the effect of erlotinib on the pharmacokinetics of the CYP3A4 substrate midazolam. We recommend a commitment to complete this study.

Effect of Intrinsic Factors on Erlotinib Pharmacokinetics

Erlotinib's putative mechanism of action is inhibition of the Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase. However, EGFR-positive status was not an entry criteria in the safety and efficacy studies. A non-pre-specified analysis of EGFR status and plasma AAG concentrations as predictors for survival benefit in TARCEVA-treated patients showed that plasma AAG is a strong predictor ($p = <.0001$), while EGFR receptor status is a lesser predictor ($p = 0.11$). EGFR status did not predict the incidence of rash or diarrhea.

The effect of age on erlotinib pharmacokinetics was evaluated in Study BR.21, comparing subgroups aged < 65 years with those ≥ 65 years. The sum of the median plasma concentrations of erlotinib plus OSI-420 was increased by 17% in the patients who were ≥ 65 years old, compared to younger patients. The small difference in exposure due to age is considered to have little clinical significance.

In a population pharmacokinetic analysis performed using data from 708 patients (62% female) in 6 studies, the effect of gender had only borderline statistical significance on clearance (CL) of erlotinib. In the final model, typical CL was 4.29 L/h for females and 4.70 L/h for male patients. This difference in CL between genders is considered to have little clinical significance.

The majority of volunteers and patients included in the clinical program were Caucasian, with only small numbers of other races participating in individual studies. In the population pharmacokinetics analyses, race was not found to be a significant variable. Ultimately, we cannot assess if there are differences due to race because of the small numbers of non-Caucasians studied.

No data are currently available in patients with either renal or hepatic impairment. A Phase IV commitment to study subjects with hepatic impairment is recommended.

Effect of Extrinsic Factors on Erlotinib Pharmacokinetics

The effect of smoking history on erlotinib pharmacokinetics was explored in Study BR.21. Current smokers had a 24% greater clearance than patients who were not current smokers. The mechanistic reason for the change due could be an increase in erlotinib metabolism by CYP1A in smokers.

Because erlotinib is predominantly metabolized by cytochrome P450 3A4, specific interaction studies have been conducted to evaluate the clinical consequences Co-administration of erlotinib with ketoconazole, a potent inhibitor of CYP3A4, resulted in a significant (67%) increase in erlotinib exposure (Study NP16612). Due to the high inter-subject variability of the available data and the differential inhibitory potency of various CYP3A4 inhibitors, specific recommendations for dose reduction are judged inappropriate. The package insert advises that dose modifications, for whatever reason they may be deemed appropriate, should be considered in 50 mg steps and the level of dose adjustments should be directed by the individual patient tolerability based on clinical evaluations.

The CYP3A4 inducer rifampicin has been demonstrated to impact the exposure to erlotinib; in Study NP16638 co-administration led to a 64% reduction in erlotinib AUC. These data suggest that for patients taking potent CYP3A4 inducers, erlotinib exposure could be sub-optimal or ineffective for the period of co-administration. The proposed labeling suggests that alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible. We recommend that the dose of erlotinib be increased in patients receiving enzyme inducers.

Pharmacodynamic Effects

Erlotinib blocked K^+ currents through recombinant hERG channels expressed in Chinese Hamster Ovary (CHO) cells at very high concentrations with an IC_{20} of 3 μM (1,170 ng/mL). In contrast, erlotinib had no effect at 3 μM concentration on action potential duration, amplitude, maximum upstroke velocity, or resting membrane potential in rabbit Purkinje fibers. The potential cardiovascular effect of erlotinib was also evaluated in

conscious dogs with no observed effects on cardiac conduction times at doses up to 100 mg/kg and plasma levels ranging from 600 to 8,400 ng/mL. The median population C_{max} in NSCLC cancer patients receiving 150 mg oral daily dose of erlotinib was estimated to be 1703.6 (SD: 519.3) ng/mL. Based on the positive hERG results (IC20: 3 μM =1,170 ng/mL) and current regulatory guidelines, further investigation of the potential effect of erlotinib on ECG (in particular, QTc) in humans was considered necessary.

A study to investigate the effect of erlotinib on QT-intervals was initiated (Study NP16793), but had to be prematurely discontinued as a consequence of the poor tolerability of healthy volunteers to the 150 mg daily dose, all 6 of whom developed rash (4 of mild intensity, 2 of moderate intensity). A retrospective review of all previously-collected ECG data was then initiated, in which all ECGs from 152 subjects across 7 studies were reanalyzed centrally at an outside laboratory specializing in the high resolution manual analysis of ECG data and morphological interpretation. This analysis found no evidence for any effect of erlotinib on QT-intervals or other ECG parameters. Similarly, ECGs collected during the conduct of therapeutic studies have provided no evidence for an adverse effect of erlotinib on any ECG parameter.

The effects of erlotinib exposure on key safety outcomes were investigated in NSCLC patients in each of the 2 Phase III studies where erlotinib was administered concomitantly with chemotherapy (Studies OSI2298g and BO16411) and also in the Phase III study with erlotinib monotherapy (Study BR.21). The focus of these analyses was to explore relationships between exposure to erlotinib (and OSI-420) and the 2 most frequently occurring drug-related adverse effects – rash and diarrhea – and between exposure and changes in laboratory parameters.

The exposure-effects analyses demonstrated that increased erlotinib exposure correlated with the incidence of Grade 3 rash in one trial (OSI2298g) but did not reach statistical significance in the 2 other trials (BO16411 and BR.21). This lack of consistency across studies may arise from the low incidence (< 10%) of Grade 3 (and 4) events recorded in the analysis population. There was a common trend for Day 1 (acute) exposure to have a correlation with time to onset of rash or diarrhea in Studies OSI2298g and BO16411.

BIOPHARMACEUTICS

The formulation and manufacturing process for the three tablet strengths (25, 100, and 150 mg) have remained unchanged throughout clinical development, with the exception that before the Phase III trials the 25 mg tablet was not film coated.

Biopharmaceutical studies have demonstrated that Tarceva is a Biopharmaceutics Classification System Class 2 drug with good oral bioavailability A study to address the absolute bioavailability (Study OSI2716g) compared the pharmacokinetics of 25 mg erlotinib given by intravenous infusion with a single 150 mg oral tablet. The results of this study were difficult to interpret as they revealed a mean oral bioavailability of 106%. A secondary analysis was undertaken in which the erlotinib plasma concentration versus time data from both treatments were modeled simultaneously with a nonlinear

elimination function and therefore took into account the faster clearance of erlotinib observed at the lower IV dose. This additional analysis resulted in an oral bioavailability of 59%, which is considered to be a more accurate reflection of the true oral bioavailability or erlotinib from TARCEVA.

A bioequivalence study [OSI2716g] demonstrated that the smallest tablet strength, 25 mg (x 6), was bioequivalent to the largest tablet, 150 mg.

Two studies in healthy volunteers [NP16584 and NP16787] demonstrated a significant increase in the AUC of erlotinib when the tablets were taken together with food. Administration of erlotinib without food is recommended in the proposed labeling, and this is consistent with the method of administration throughout the clinical program, where patients/subjects were advised to take the tablets 1 hour before or 2 hours after food.

2. *Question-Based Review (QBR)*

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The FDA has recently approved gefitinib (IRESSA®), an "... antagonist of the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK) ...", "... as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies." Quotes in the preceding sentence are from the current IRESSA package insert.

Recent literature reports (**Lynch TJ,** N Engl J Med. 2004 May 20;350(21):2129-39. Epub 2004 Apr 29. **Paez JG, et al.,** Science. 2004 Jun 4;304(5676):1497-500. Epub 2004 Apr 29.) suggest that mutations in the EGFR receptor may predict for clinical response to IRESSA.

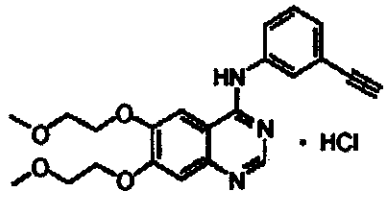
Erlotinib's (TARCEVA's) putative mechanism of action is "... inhibition of the Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase." The indication sought for TARCEVA is "... for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen." Quotes in the preceding sentence are from the proposed TARCEVA package insert.

Because of the similarities of putative mechanisms of action and indications between TARCEVA and IRESSA, and the literature that supports that EGFR status may predict for response to IRESSA, there is interest in whether EGFR status may predict for response to TARCEVA.

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? (*Do not include full details of formulation here. Details go in Biopharmaceutics section.)*

The below (indented) is reproduced from the proposed package insert. The conclusions are those of the Applicant, not the FDA Chemist.

"Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4.HCl$ and a molecular mass of 429.90. The molecule has a pKa of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane. Aqueous solubility of erlotinib hydrochloride is dependent on pH with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2."



2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The below (indented) are reproduced from the proposed package insert.

"TARCEVA (erlotinib hydrochloride) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor.

"TARCEVA is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen."

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended daily dose of TARCEVA is 150 mg taken orally at least one hour before or two hours after the ingestion of food.

2.2. General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Applicant's ***"2.5.3.2 Rationale for Dose Selection and Dose Interval"*** appears on page 10 of the clinical overview and is reproduced below (indented).

> "The Phase I Study 248-004 identified 200 mg daily as the dose-level leading to dose limiting toxicities (diarrhea) (see Section 2.7.2.3.2.1). Subsequently, 150 mg daily (one level below the DLT) was confirmed to be the recommended dose in cancer patients. The average trough concentration on Day 24 – 29 was 918 ng/mL, which is well above the concentration required for erlotinib activity in various nonclinical assays, even when the 95% protein binding of erlotinib is considered. Based on these considerations, it was concluded that the 150 mg/day dose would be sufficient to provide a high anti-neoplastic effect with a tolerable and manageable safety profile."

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The endpoints used were either clinical benefit or toxicity endpoints or measures of tumor shrinkage. Study BR.21 is the primary study supporting efficacy and safety. The primary endpoint for study BR.21 was overall survival. Secondary endpoints were

A. quality of life (QoL) as measured by the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaires QLQ-C30 and the lung cancer module QLQ-LC13,
B. response rates (RR),
C. response duration,
D. progression-free survival (PFS), and
E. nature, severity, and frequency of toxicities.

Study BR.21 also had the objective of correlating the expression of tissue EGFR levels (at diagnosis) with outcomes and response to treatment, and correlating trough levels of erlotinib with clinical responses and/or adverse events.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes – see **2.6 Analytical Section**

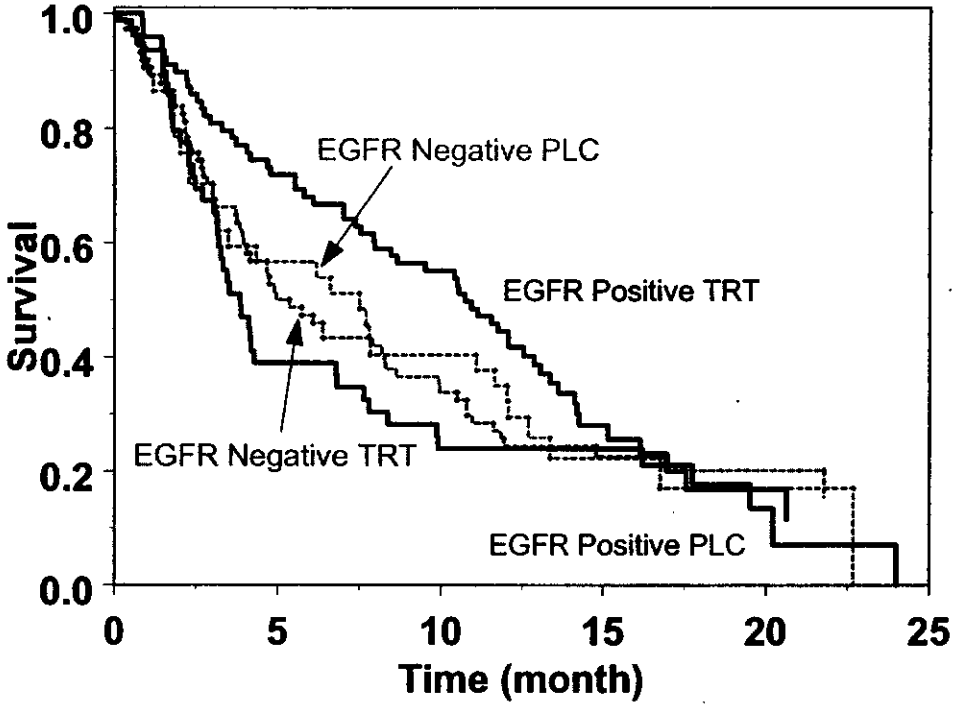
2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The below is adapted from the Pharmacometrics Review which is included in this review as **Appendix 4.3**.

For the reasons stated in **Section 2.1** of this review, the effect of EGFR receptor status on the treatment effect of erlotinib is of special interest. A plot of survival rate in EGFR positive and negative patients shows trends toward differences, as shown below (**FDA Figure 1.**). In those receiving erlotinib, it appears that receptor positive patients may have increased survival. In the placebo group differences are not as marked, but there is a trend toward receptor positive patients having decreased survival time.

FDA Figure 1. Fraction Surviving Versus Time by Treatment and EGFR Status



In order to investigate the observed trend in the treatment group, a Cox Proportional Hazards Model was used. The results are summarized below in **Table 1.** While not statistically significant at the 0.05 level, the Hazard ratio is reduced in patients with EGFR-positive status.

Table 1. Cox Model of the Effect of EGFR Status on Survival in Erlotinib-Treated Patients

Variable	Parameter Estimate	Std Error	Chi-Square	Pr>ChiSq	Hazard Ratio	Lower 95%Cl	Upper 95%Cl
EGFR	-0.29604	0.18623	2.5269	0.1119	0.744	0.516	1.071

Three covariates were found to be significant ($p < 0.05$) predictors for survival. These covariates are Treatment, Baseline AAG concentration and Baseline ECOG Performance Status (**FDA Table 2.**).

Table 2. Cox Model of the Effect of Significant Covariates on Survival in

Erlotinib-Treated Patients						
Variable	Estimate	StdErr	P-value	Hazard Ratio	HR Lower CI	HR Upper CI
Treatment	-0.346	0.09213	0.0002	0.708	0.591	0.848
Baseline AAG	0.676	0.07962	<.0001	1.966	1.682	2.298
Baseline ECOG	0.404	0.05686	<.0001	1.498	1.34	1.675
Treatment: 1= Tarceva 0=Placebo; Baseline ECOG Performance Status (0, 1, 2, 3)						

The conclusion from these analyses is that there is a strong trend for EGFR receptor status to have greater survival benefit. There are statistically significant increases in survival due to Treatment, Baseline AAG concentration and Baseline ECOG Performance Status.

These results are from non-pre-specified analyses in studies not designed to search for prognostic factors. We have brought our results to the attention of the Medical Officer and the Statistician. They are investigating our results and considering if the results should impact the package insert.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The below is adapted from the Pharmacometrics Review which is Appendix 4.3 of this review.

The occurrence of adverse events in study BR21 is summarized in the following table **(FDA Table 3. Applicant's Table 2-1.)**.

FDA Table 3. Applicant's Table 2-1.

	BR.21 Placebo (N=242)						BR.21 Erlotinib (N=485)					
	Any		3		4		Any		3		4	
MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total patients with any AE	233	(96)	87	(36)	54	(22)	481	(99)	195	(40)	107	(22)
RASH	42	(17)	0	(0)	0	(0)	366	(75)	40	(8)	3	(<1)
Diarrhoea	44	(18)	2	(<1)	0	(0)	261	(54)	28	(6)	1	(<1)
Anorexia	93	(38)	11	(5)	1	(<1)	250	(52)	38	(8)	5	(1)
Fatigue	108	(45)	39	(16)	10	(4)	250	(52)	67	(14)	19	(4)
Dyspnoea	84	(35)	36	(15)	27	(11)	198	(41)	82	(17)	52	(11)
Cough	70	(29)	6	(2)	0	(0)	159	(33)	18	(4)	0	(0)
Nausea	59	(24)	4	(2)	0	(0)	158	(33)	14	(3)	0	(0)
Infection	37	(15)	5	(2)	0	(0)	116	(24)	20	(4)	0	(0)
Vomiting	47	(19)	4	(2)	0	(0)	113	(23)	9	(2)	2	(<1)

The most common AEs in erlotinib treatment group compared to placebo are rash (75% vs 17%) and diarrhea (54% vs. 18%). Logistic regression models were used to explore the relationship between exposure and these two adverse events. Since most of these AEs are Grade 1 or 2 in severity as shown in the following table (**FDA Table 4.**), the AEs are treated as 3 categories: 0 = no AEs, 1=Grade 1, 2 = Grade 2 and above.

FDA Table 4. Rash and Diarrhea by Treatment and Grade												
Treatment Group	Erlotinib (N=485)						Placebo (N=242)					
Grade	Any		1-2		3-4		Any		1-2		3-4	
	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Rash	363	(75)	321	(66)	42	(9)	40	(17)	40	(17)	0	(0)
Diarrhea	261	(54)	232	(48)	29	(6)	44	(18)	42	(17)	2	(<1)

The covariates tested were treatment, AUC of erlotinib, baseline weight, age at registration, BSA, height, gender, median AAG concentration, baseline AAG concentration, median albumin concentration, baseline ECOG Performance Status, disease stage at entry, smoking status, EGFR status (+ or -), best response to prior therapy, prior platinum regimens and prior regimens.

For rash, treatment, AUC of erlotinib, AAG concentration, best response to prior therapy, body weight, and smoking status were significant predictors. For diarrhea, treatment, AUC of erlotinib, AAG concentrations, gender, age, and prior platinum use were significant. Details of these analyses can be found in **Appendix 4.3** (Pharmacometrics Review).

When a univarite analysis using EGFR status as an explanatory variable is performed, the incidence of either rash or diarrhea is not related to EGFR status, as shown in the following tables. Below (**FDA Table 5.**) are the results for diarrhea.

FDA Table 5. Cox Model of the Effect of EGFR Status on Incidence of Diarrhea in Erlotinib-Treated Patients

Variable	Estimate	Std Err	WaldChiSq	ProbChiSq
Intercept	-1.7112	0.1658	106.4942	<.0001
Intercept	-0.3145	0.15	4.3966	0.036
Egfr	-0.0192	0.1272	0.0228	0.8799

Below are the results for rash.

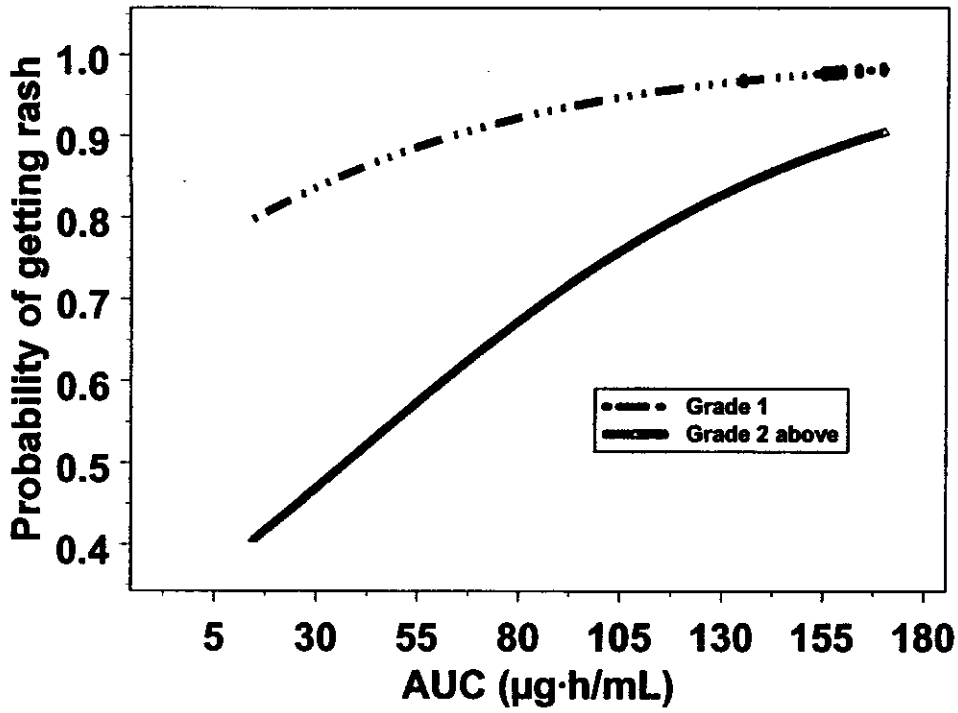
FDA Table 6. Cox Model of the Effect of EGFR Status on Incidence of Rash in Erlotinib-Treated Patients

Variable	Estimate	Std Err	WaldChiSq	ProbChiSq
Intercept	-0.9106	0.1482	37.7495	<.0001
Intercept	0.0689	0.1442	0.2282	0.6328
Egfr	0.1362	0.1210	1.2675	0.2602

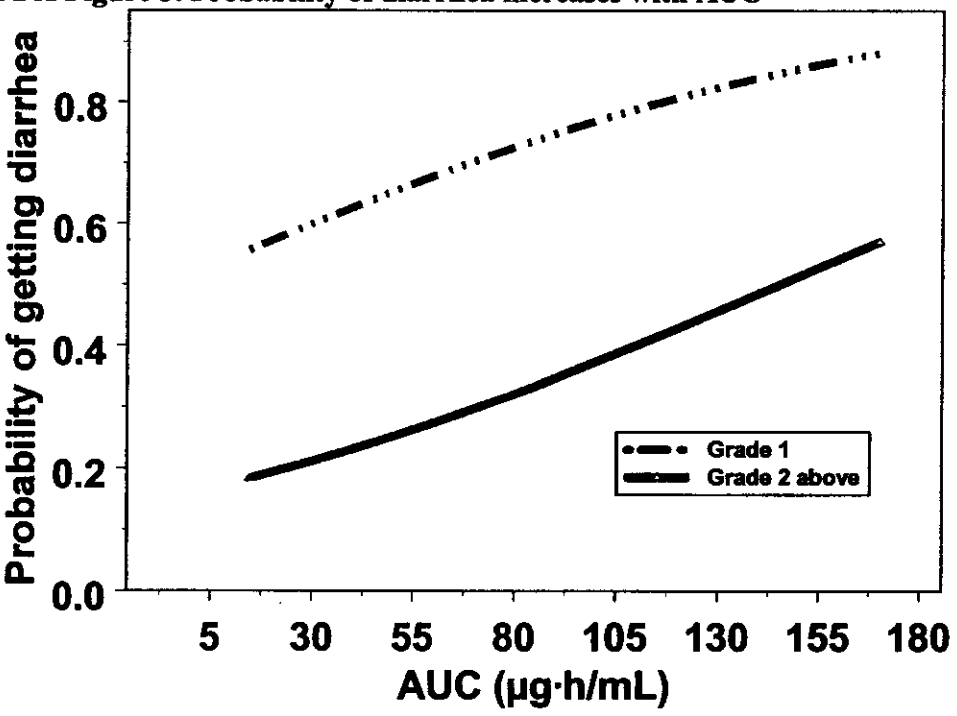
When treatment, AUC and other variables are added in the model, EGFR status continues to not have a significant effect. Thus, there is no evidence that EGFR status has effects on the incidence of rash or diarrhea based on the current available data. Details of these analyses can be found in **Appendix 4.3** (Pharmacometrics Review).

AUC is a stable predictor for rash but is a less strong and less stable predictor for diarrhea. From the 5th percentile to the 95th percentile (70 μg·h/L difference), the hazard for rash is tripled (hazard ratio=3.27) whereas the hazard for diarrhea is doubled (hazard ratio=2.23).

FDA Figure 2. Probability of rash increases with AUC



FDA Figure 3. Probability of diarrhea increases with AUC



AAG concentration is a predictor for both rash and diarrhea. For both AEs, when the concentrations of AAG increase, the odds to get these AEs decrease. The distribution of AAG (g/L). The following table (**FDA Table 7.**) lists several values of differences for AAG concentrations and hazard ratios for survival. The corresponding odds ratios for

rash and diarrhea are also listed. Futrther details regarding this analysis appear in **Appendix 4.3** (Pharmacometrics Review).

Table 7. Cox Model of the Effect of AAG on Survival and the Incidence of Rash and Diarrhea				
AAG difference	g/L	Survival HR	Rash OR	Diarrhea OR
Interquartile	0.65	1.68507	0.49466	0.503942
90%-10%	1.4	3.076806	0.219575	0.228545
95%-5%	1.75	4.074977	0.150307	0.158021
Range	3	11.11549	0.038825	0.042303

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

Study to Determine Effect on ECG Parameters

Erlotinib blocked K+ currents through recombinant hERG channels expressed in Chinese Hamster Ovary (CHO) cells at very high concentrations with IC_{20} of 3 μM (1,170 ng/mL) [Study V2001141]. In contrast, erlotinib had no effect at the 1,170 ng/mL concentration on action potential duration, amplitude, maximum upstroke velocity, or resting membrane potential in rabbit Purkinje fibers [study V2001151]. The potential cardiovascular effect of erlotinib was also evaluated in conscious dogs with no observed effects on cardiac conduction times at doses up to 100 mg/kg and plasma levels ranging from [redacted] ng/mL [Study D2001142]. The mean C_{max} in NSCLC cancer patients receiving 150 mg oral daily dose of erlotinib is estimated to be 1703.6 ng/mL. Based on the positive hERG results a further investigation of the potential effect of erlotinib on ECG (in particular, QTc) in humans was planned.

An ECG study conducted in healthy volunteers measured QTc intervals in subjects receiving multiple daily oral doses of erlotinib (Study NP 16793). The study was initially conducted in healthy volunteers because of the difficulty in obtaining stable ECG data in late stage cancer patients on multiple therapies. If clinically significant changes in ECG were observed in healthy subjects, further monitoring of ECG changes in patients during clinical trials would be performed.

As detailed below, Study NP16793 was prematurely terminated after completion of the initial open-label safety cohort (Part A) because of poor tolerability in healthy volunteers. A report was prepared summarizing ECG data in 6 healthy subjects after 7 daily oral doses of 150 mg erlotinib.

A follow up meta-analysis (Report #1009305) was subsequently compiled, assessing available ECG data across 7 healthy volunteer studies with a total of 152 subjects. The outcomes of that analysis are presented below (see **ECG Meta-analysis: Report No. 1009305, below**).

NP 16793 Evaluation of the effect of single and multiple doses of Tarceva™ (erlotinib) on ECG parameters in healthy adult male and female subjects

The primary objective of this study was to investigate the effect of single and multiple daily doses of orally administered erlotinib on QTcF (QT interval with Fridericia's correction). The study was designed to be performed in 2 parts. In Part A (an open-label safety cohort), 6 healthy subjects (5M/1F) were tested at the highest clinical dose of 150 mg per day for 7 days to determine the safety and tolerability of the highest dose regimen before opening the study to a larger group of subjects. Part B was to be a randomized, double-blind, placebo-controlled, parallel-group study in 144 healthy volunteers divided into 3 groups: 36 subjects receiving placebo once daily for 7 days, 36 subjects receiving 75 mg erlotinib once daily for 7 days, and 72 subjects receiving 150 mg erlotinib once daily for 7 days.

All 6 subjects participating in Part A of the study experienced facial/upper body rash of mild (4 subjects) or moderate (2 subjects) intensity. The rash generally appeared after approximately 4 days of dosing but persisted significantly beyond the end of dosing, in one case lasting over 100 days. Four of the subjects received treatment for the rash, which was declined by the other subjects. Despite the rash, all subjects completed the scheduled 7 consecutive daily 150 mg doses. Three of the subjects experienced gastrointestinal events, with 1 requiring loperamide for treatment of diarrhea. Two of the subjects experienced mild eye disorders (dry eyes). Clinical laboratory observations were unremarkable and no effects on vital signs were observed.

It was concluded from the initial cohort of 6 subjects that consecutive 150 mg daily doses of erlotinib are not well tolerated by healthy volunteers. On this basis the planned parallel group phase of the study (Part B) was not conducted.

During Part A, there was no effect of the 150 mg erlotinib dose on mean QTc-intervals, which were marginally reduced on Day 1 and Day 7 relative to the baseline taken on Day -1. All QTcF-intervals recorded during the study were classified as normal, and no subject exhibited any increase in QTcF-interval of $\geq$ 30 msec (**FDA Table 8., Applicant's Table 2-29**).

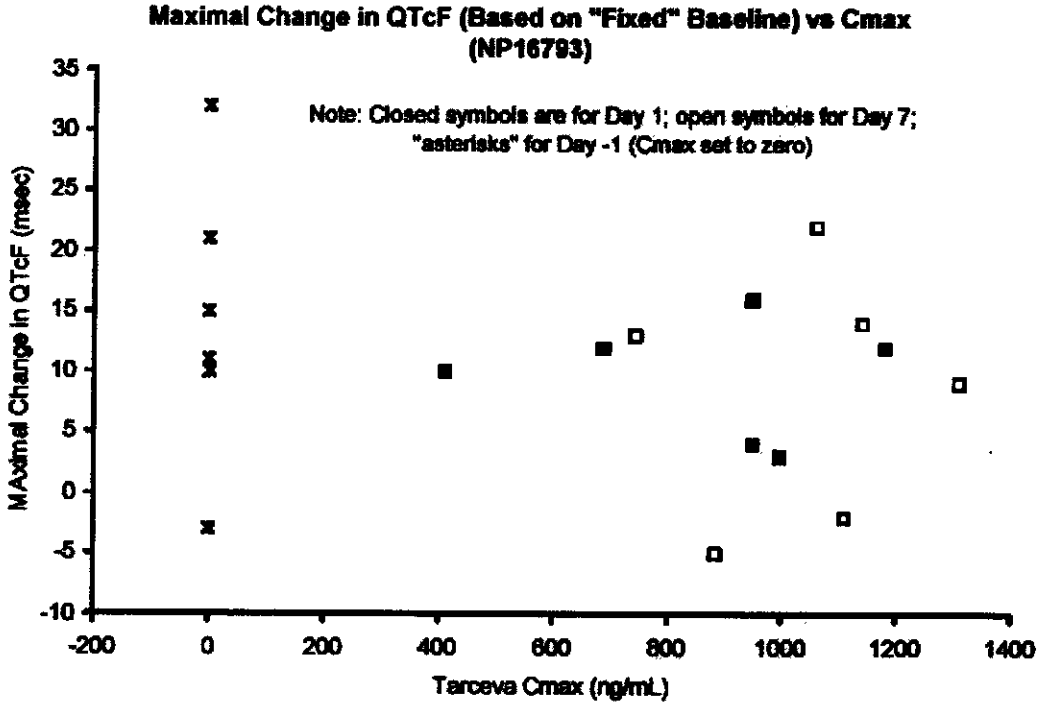
FDA Table 8. Applicant's Table 2-29

Table 2-29: Study NP16793 – Effects of Erlotinib on QTc-Intervals
Maximal Changes from Baseline in QTcF- and QTcB-intervals on Day 7, by Subject

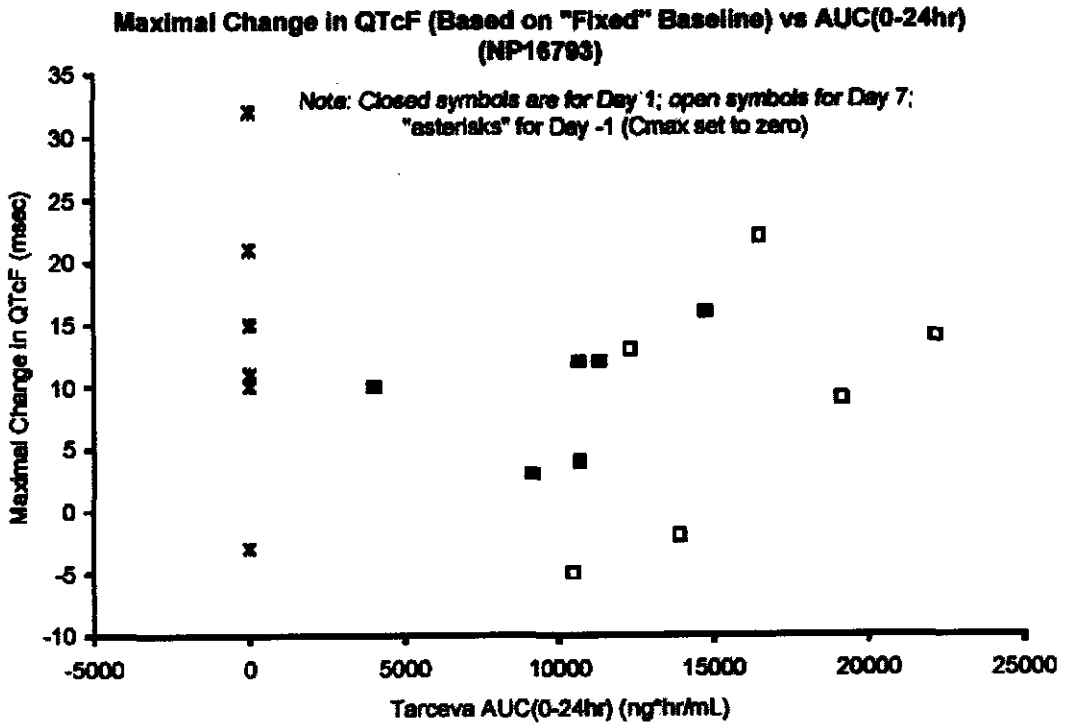
Subject	QTcF			QTcB		
	Max Change	% Change	T_{max}	Max Change	% Change	T_{max} (h)
32971/0001	-2	-1	6	19	5	6
32971/0002	9	2	10	30	8	8
32971/0003	13	3	8	31	8	8
32971/0004	-5	-1	16	2	0	16
32971/0005	22	6	8	31	8	12
32971/0006	14	4	8	21	5	24

Individual Maximal Change in QTcF-Interval vs C_{max}

NOTE: "MAximal" in y-axis label. Should be "Maximal"



Individual Maximal Change in QTcF-Interval vs AUC of Erlotinib



There appeared to be no relationship between maximal change in QTcF-interval versus maximum plasma concentration (C_{max}) or against AUC of erlotinib on either Day 1 or Day 7 of dosing (**FDA Table 8., Applicant's Table 2-29**). All ECGs were assessed as normal with respect to both T- and U-waves.

ECG Meta-analysis: Report No. 1009305

This report summarized ECG data collected from 7 healthy volunteer studies with a total of 152 subjects. All ECG data were reanalyzed centrally at an outside laboratory specializing in the high-resolution manual analysis of ECG data and morphological interpretation. Although several of these studies did not have a placebo arm, QTc interval changes from baseline and maximum QTc-interval changes were evaluated with respect to time after dose, peak plasma drug (and active metabolite, OSI-420) concentrations and AUC to determine the potential relationship of any changes in QTc intervals with systemic drug exposure. Limited placebo data was, however, available in single dose Study 248-001 where 17 out of 51 subjects received placebo and in multiple dose Study 248-002 where 2 subjects out of 8 received multiple oral placebo doses. In Study NP16793, all 6 subjects receiving active erlotinib at 150 mg daily for 7 days had serial baseline ECG measurements on Day -1 similar to Days 1 and 7 of active treatment.

An integrated meta-analysis was performed of placebo and the 100 mg, 150 mg, and 200 mg erlotinib doses using Day 1 data from 7 studies (**FDA Figure 9., Applicant's Table 2-27**). Serial measurements of QTc-intervals over 24 hours after dosing were available in

a minimum of 12 subjects at each dose. No effect of erlotinib was seen on mean QTc (F or B)-intervals at any of these doses. An analogous meta-analysis was performed for day 7 multiple dose (steady state) data from 2 studies (Studies NP16793 and NP16787) where subjects received therapeutic doses of 100 or 150 mg erlotinib per day. There was no increase in QTc (F or B)-intervals relative to baseline (pretreatment on Day 1) despite having 7 consecutive days of dosing.

FDA Table 9. Applicant's Table 2-27

Table 2-27: Overview of Studies included in ECG Meta Analysis

Study No.	Title	Dosing regimen
248-001 N = 51 total (34 active and 17 placebo)	A Phase 1 Double-Blind, Placebo-Controlled, Evaluation of the Safety, Toleration, and Pharmacokinetics of OSI-774 Following Escalating Single Oral Doses in Healthy Male Subjects	Single oral doses of erlotinib or placebo (2:1 ratio) Solution/suspensions from 1 – 1000 mg 200 mg tablets
248-002 N = 8 total (6 active and 2 placebo)	A Phase 1 Double-Blind, Placebo-Controlled, Evaluation of the Clinical Pharmacology of Multiple Doses of OSI-774 in Healthy Male Subjects	200 mg QD on day 1 & 8 and 200 mg BID on days 4-7*
NP16584 (Completed) N =21	Effect of food on the pharmacokinetics of Tarceva (erlotinib), an orally active epidermal grown factor receptor (EGFR) tyrosine kinase inhibitor, in healthy male volunteers	Single oral doses of 150 mg erlotinib in the presence and absence of food
NP16612 (Cohort A N = 6) (Cohort B, N = 14 at data cut-off)	Comparison of the single dose pharmacokinetics of Tarceva (erlotinib) administered alone or concomitantly with ketoconazole in healthy male volunteers.	Single 25 mg (Cohort A) or 100 mg (Cohort B) oral doses of erlotinib in the presence or absence of 200 mg ketoconazole
NP16638 N = 24	Effect of rifampicin on the pharmacokinetics of Tarceva (erlotinib), an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in healthy male volunteers	Single 150 mg oral doses of erlotinib in the presence and absence of 600 mg rifampicin
NP16787 N = 22	Evaluation of the effect of food on the multiple dose pharmacokinetics of Tarceva (erlotinib) in healthy male volunteers	100 mg oral doses of erlotinib daily for 8 days in presence or absence of food.
NP16793 N =6	Evaluation of the Effect of Single and Multiple Doses of Tarceva (erlotinib) on ECG Parameters in Healthy Adult Male and Female Subjects	150 mg oral doses of erlotinib for 7 days

*modified from protocol due to adverse events.

The effect of erlotinib on ECG parameters was also assessed in each of the 7 individual studies, independent of the meta-analysis. QTc-interval changes were evaluated after multiple dose administration of erlotinib in 3 separate studies with doses ranging from 100 mg to 400 mg/day for 3 to 8 days. Mean QTcF-interval did not increase after last dose compared with that on Day 1 in any of these studies. Similarly, at the highest single dose of 1000 mg erlotinib (Study 248-001), no apparent increase in QTcF-interval was

observed. There was no observed relationship between maximal changes in QTc (F or B) interval and peak erlotinib concentrations (or AUC) of up to 7,000 ng/mL after a single dose or 1,990 ng/mL after multiple doses for up to 8 days. Peak plasma concentrations or AUC of active metabolite (OSI-420) also did not demonstrate any relationship with maximal changes in QTc (F or B)-interval. In the presence of a very potent CYP3A4 inhibitor, ketoconazole, erlotinib had no effect on QTcF-interval despite increases in peak plasma concentration and AUC by 37% and 83%, respectively. The coadministration of a CYP3A4 inducer, rifampicin, also had no effect on QTc-intervals.

Throughout these 7 studies, 2 subjects exhibited abnormal U-waves: 1 followed erlotinib administration on Days 7 and 8 after dosing and the other occurred before study drug administration on Day -1. Six erlotinib-treated subjects and 1 placebo-treated subject exhibited abnormal T-waves following treatment. Expert review of these abnormalities indicated them to be nonspecific and not clinically relevant.

In conclusion, administration of erlotinib to healthy volunteers at single doses of up to 1000 mg or at multiple doses of up to 400 mg per day for 3 days or at 100 to 150 mg/day for 7 to 8 days did not result in any prolongation of QTc (F or B)-intervals nor any other effect on ECG parameters.

The data accumulated has the limitations that positive controls were not utilized and that modeling was not performed to estimate if small QTc changes might be occurring. The power of the current approach to detect small changes in QTc (i.e., a 5 - 10 msec change) is unknown. However, given the lack of a noticeable signal that erlotinib administration alters QTc, and the ability of the drug to produce a survival benefit in patients with locally advanced or metastatic non-small cell lung cancer, the current evidence supports that QT-prolongation, if it is occurring at all, is not sufficient to outweigh the benefit of the therapy.

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

The dose and dosing regimen were selected based upon tolerability (see **Section 2.2.1** of this review); the Applicant believes that a higher dose cannot be used. As the relationship between dose and efficacy is not understood, use of lower doses cannot be recommended. The relationship between dose and response is an unresolved issue.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? *(Provide tables to refer to in subsequent questions in this section.)*

Single Dose Pharmacokinetics

Model independent PK parameters of erlotinib are presented in **FDA Table 10., Applicant's Table 2-19** after administration of a single dose in various studies in healthy volunteers.

Plasma concentrations of erlotinib appear rapidly after oral administration with median T_{max} ranging from 0.5 to 1.0 hours from solution in doses ranging from 3 to 30 mg. In higher doses of 100 mg to 1000 mg given as suspension (Study 248-001), median T_{max} at various doses ranged from 1.5 to 4.0 hours. Absorption from formulated tablet at doses of 100 to 200 mg was comparable with oral suspension with median T_{max} ranging from 2 to 4 hours (**FDA Figure 10., Applicant's Table 2-19**). In Study 248-001, where dose was increased from 1 to 1000 mg, peak plasma concentration increased with dose from 0.0149 µg/mL to 5.93 µg/mL (because the 1 mg dose was too low to generate data, the lowest value comes from the 3 mg dose). The AUC also increased with dose from 0.496 µg•h/mL at 10 mg to 126 µg•h/mL at 1000 mg.

FDA Table 10. Applicant's Table 2-19

Table 2-19: Erlotinib Single Dose Plasma PK Parameters in Healthy Volunteers, Median (min-max)

Study	Dose mg (Fed/fasted)	Formulation No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg*h/mL)	$t_{½\lambda}$ (h)
248-001	3 (fasted)	Solution 4	0.0149	0.8	NC	NC
	10 (fasted)	Solution 4	0.0885	1.0	0.496	3.43
	30 (fasted)	Solution 4	0.460	0.5	2.22	5.83
	100 (fasted)	Suspension 4	0.971	1.5	10.0	6.21
	300 (fasted)	Suspension 4	2.40	2.5	37.6	9.04
	1000 (fasted)	Suspension 4	5.93	4.0	126	7.70
	200 (fasted)	Tablet 3	1.54	2.0	22.9	9.04
	200 (fed)	Tablet 3	1.58	2.0	23.6	6.32
248-002	200 (fasted)	Tablet 3	0.963	2.5	21.1	8.8
NP16584	150 (fed)	Tablet 9 (Period 1 only)	1.34	3.0	20.3	9.0
NP16584	150 (fasted)	Tablet 9 (Period 1 only)	0.704	3.0	10.3	7.0

Table 2-19: Erlotinib Single Dose Plasma PK Parameters in Healthy Volunteers, Median (min-max)

Study	Dose mg (Fed/fasted)	Formulation No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg*h/mL)	$t_{1/2z}$ (h)
NP16638	150 mg (fasted)	Tablet 24 (Group 1 and 2 combined)	1.31	1.5	17.6	8.49
NP16612	100 mg (fasted)	Tablet 24 (Group 1 and 2)	0.628	2.0	11.1	8.49
OSI2716g	150 mg	Capsule 37 (Arm A)	1.39	2.12	25.87	14.39
	150 mg	Capsule 18 (Arm B)	1.335	2.015	33.51	18.96

NC = not calculated

Multiple Dose Pharmacokinetics

The PK parameters derived from multiple dose studies in healthy volunteers are summarized in **FDA Table 11., Applicant's Table 2-21**. Steady state erlotinib concentrations were reached within a week following once daily drug administration (**FDA Figure 4., Applicant's Figure 2-4**). The average accumulation factor of erlotinib taken at 100 – 150 mg daily varied from 1.5 to 2.1 in 2 healthy volunteer studies (Studies NP16793 and NP16787) (**FDA Figure 5., Applicant's Figure 2-5**). The expected accumulation ratio from once daily dosing of a drug with a half-life of 15 - 24 hours is 1.5 - 2.0. The observed plasma terminal half-life for erlotinib ranged from 7 to 22.5 hours (**FDA Table 12., Applicant's Table 2-22**) and is consistent with the observed accumulation.

In Study 248-002, where erlotinib was given at a 200 mg every 12 hours to healthy subjects (400 mg/day), the accumulation factor based on trough plasma levels was estimated to be much higher (5.4). An extent of accumulation of 5.0 would be expected from an effective half-life of 37 hours given twice daily. The accumulation was, therefore, somewhat higher in this study. The cause is not known. The PK data after multiple doses were limited in this study because only a few trough samples were collected before premature termination of the study.

FDA Table 11., Applicant's Table 2-21

Table 2-21: Erlotinib Multiple Dose Plasma PK Parameters in Healthy Volunteers, Median (min-max)

Study	Tablet Dose mg (Fed/fasted)	No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	Css/F L/h	AUC $_{0-tau}$ (µg*h/mL)	Rac (h)
248-002[A]	200 mg BID	5	NC	NC		NC	5.4
NP16787	100 mg QD (fasted)	8 (Day 7)	1.10	3.5	7.9	12.7	2.1
NP16787	100 mg QD (fed)	6 (Day 7)	1.45	4.0	6.9	14.56	2.0
NP16793	150 mg (fasted)	6 (Day 7)	1.09	4.0	10	15.2	1.5

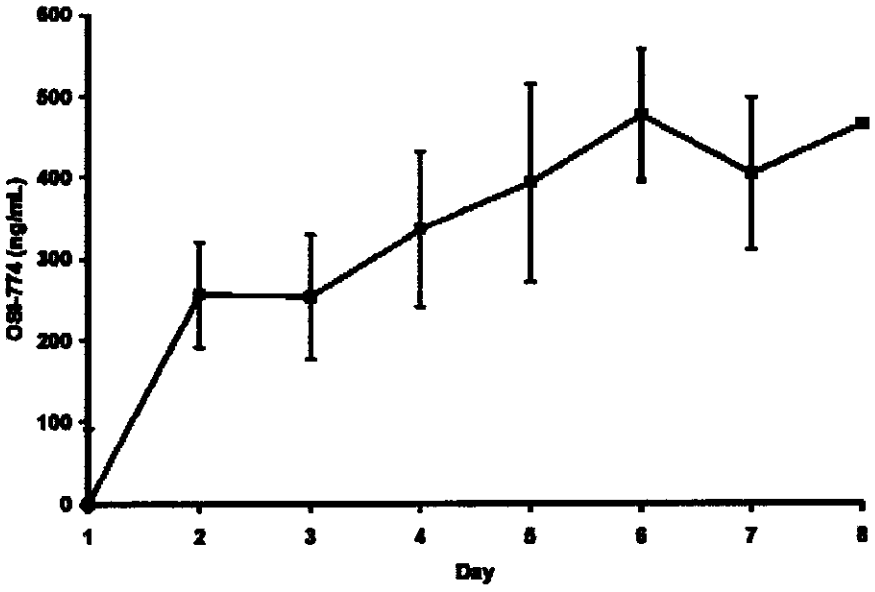
NC = Insufficient data for calculation.

Rac = accumulation index.

[A] Trough samples only were collected for the multiple dose portion of the study.

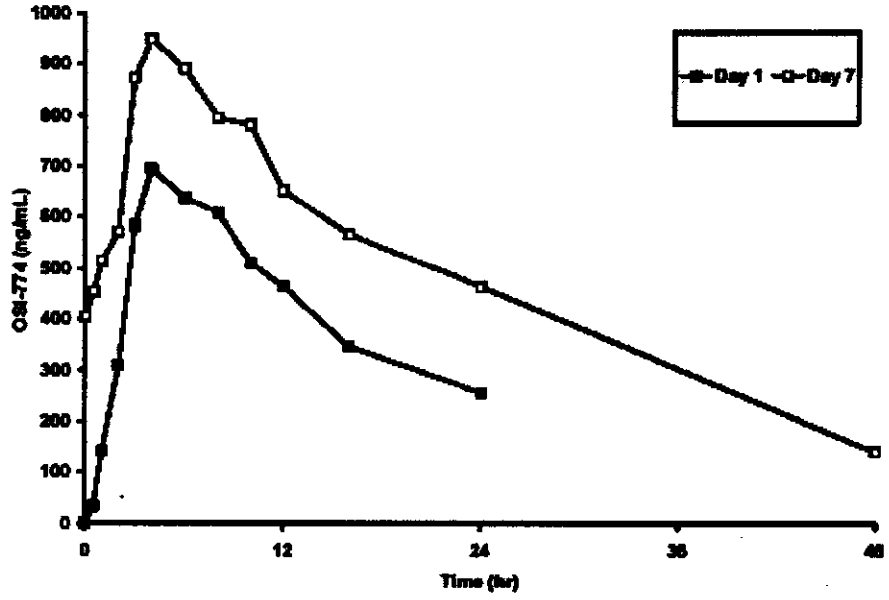
FDA Figure 4., Applicant's Figure 2-4

Figure 2-4: Study NP16793: Mean (± SEM) Trough (C_{min}) of Erlotinib vs Treatment Day



FDA Figure 5., Applicant's Figure 2-5

Figure 2-5: Mean Erlotinib Concentrations vs Time On Day 1 and Day 7 after 150 mg given once daily (NP16793)



2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Pharmacokinetics in Patients Versus Healthy Volunteers

Erlotinib pharmacokinetics were evaluated in healthy subjects and cancer patients. In cancer patients, pharmacokinetics were studied with erlotinib both as monotherapy and in combination with standard chemotherapies. Data comparing healthy volunteers with cancer patients after a single dose are summarized in **FDA Table 12., Applicant's Table 2-22** and after multiple doses administered at the therapeutic dose range of 100 to 150 mg a day in **FDA Table 13., Applicant's Table 2-23.** In general, cancer patients appear to have higher $AUC_{0-\infty}$ and longer plasma terminal half-life than healthy subjects after a single dose. There is, however, large variability in the PK parameters, and the number of patients in each study is small. The median values of AUC_{0-24} are also higher for cancer patients compared with healthy volunteers, suggesting lower oral clearance of erlotinib in cancer patients.

FDA Figure 12., Applicant's Table 2-22

Table 2-22: Erlotinib Single Dose Plasma PK Parameters at Therapeutic Dose Levels, Median (min-max)

Dose	Study	Population	No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg*h/mL)	$t_{½k}$ (h)
100 mg	248-004	Patients	3	0.428	2.0	6.98	18.7
	248-005	Patients	3	1.36	2.3	22.2[a]	NC
	NP16612	HV	24	0.628	2.0	11.1	8.49
	NP16787	HV	11	0.676	2.0	6.21[a]	NC
150 mg	248-004	Patients	3	1.24	2.0	50.3	22.5
	NP16638	HV	24	1.31	1.5	17.6	8.49
	NP16584	HV	9 (Period 1 only)	0.704	3.0	10.3	7.0
	NP16793[a]	HV	6	0.950	4.0	10.6[a]	NC
	OSI2716g	HV	37 Arm A	1.39	2.12	25.87	14.39
			18 Arm B	1.335	2.015	33.51	18.96

NC = Insufficient data for calculation

[a] AUC_{0-24}

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FDA Table 13., Applicant's Table 2-23

Table 2-23: Erlotinib Multiple Dose Plasma PK Parameters at Therapeutic Dose Levels, Median (min-max)

Dose	Study	Population	No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	AUC_{0-tau} (µg*h/mL)	Rac (h)
100 mg QD	248-004	Various cancer Patients	3	1.16	4.0	19.0	2.7
	BO16411	NSCLC Patients	11	1.59	3.0	20.6	NC
	BO16450	Metastatic breast cancer Patients	16	1.59	3.0	24.2	NC
	NP16787	HV	8	1.10	3.5	12.7	2.1
150 mg	248-004	Patients	19-22	1.67	2.0	24.9	1.5
	NP16793	HV	6	1.09	4.0	15.2	1.5

NC = Insufficient data for calculation.
Rac = accumulation index.

2.2.5.3 What are the characteristics of drug absorption?

Oral Absorption

Erlotinib appears in human plasma rapidly after oral administration, with time for peak plasma concentrations appearing between 1.5 and 3 hours. In humans, oral bioavailability of the formulated tablet was determined in 20 healthy volunteers (16 female and 4 male, Study OSI2716g) using the 150 mg tablet compared with a 25 mg dose given as a short intravenous infusion. The bioavailability based on dose-normalized area under the plasma concentration time curve was 106% with a 95% confidence interval of 99% to 114%. Therefore, model independent analysis assuming dose-linearity between 25 mg and 150 mg erroneously suggests > 100% oral bioavailability of the formulated tablet. Pharmacokinetic analysis of both IV and oral profiles gave different terminal half-lives of 13 hours and 21 hours, respectively. These findings suggest a faster rate of elimination of erlotinib at low plasma concentrations arising from 25 mg IV dose compared with that from a higher dose given as a 150 mg oral tablet. Potential nonlinear PK behavior between 25 and 150 mg may have led to the overestimation of absolute oral bioavailability of erlotinib.

Therefore, a secondary PK analysis was performed to estimate oral bioavailability using a method in which erlotinib plasma concentration-time data following oral and IV administration were fit simultaneously to a compartmental structural model with a nonlinear elimination function (Study OSI2716g). This could account for faster clearance of erlotinib at the lower intravenous dose. A 2-compartment model with nonlinear

elimination and first order absorption was found to best fit the plasma concentration-time data. Using this approach, the average population bioavailability was estimated to be 59% (95% CI 55% to 63%). While studying the effect of food on pharmacokinetics of erlotinib in male volunteers (Study NP 16787), both AUC and C_{max} increased in the presence of food compared with fasted state. The estimated mean AUC ratio between fed and fasted states on Day 1 (first dose) and Day 7 (after 7 doses) were 1.66 and 1.34, respectively, suggesting that absolute bioavailability of erlotinib in the fasted state is < 100%.

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

Volume of distribution

In Study OSI2716g, where erlotinib was administered to healthy volunteers (4 males, 16 females) as a 25 mg short IV infusion, the steady state volume of distribution (V_{ss}) was 83.84 ± 17.56 L; n = 18.

Drug distribution in tumor

Tumor-to-plasma erlotinib ratio was measured in 4 patients with aerodigestive cancers (Study DMS-D0003). Erlotinib was administered 150 mg once daily for 9 days prior to surgical resection or biopsy. Plasma samples were measured on Day 1 and 8, while tumor samples were collected at 0.5 to 1 hour after drug administration on Day 9. Erlotinib concentrations in tumors ranged from 5% to 161% of the observed steady-state C_{max}. The active metabolite OSI-420 was present in tumor in concentrations similar to the observed steady-state C_{max} in plasma. Therefore, these tissues are rational target tissues for antitumor effects.

Plasma protein binding

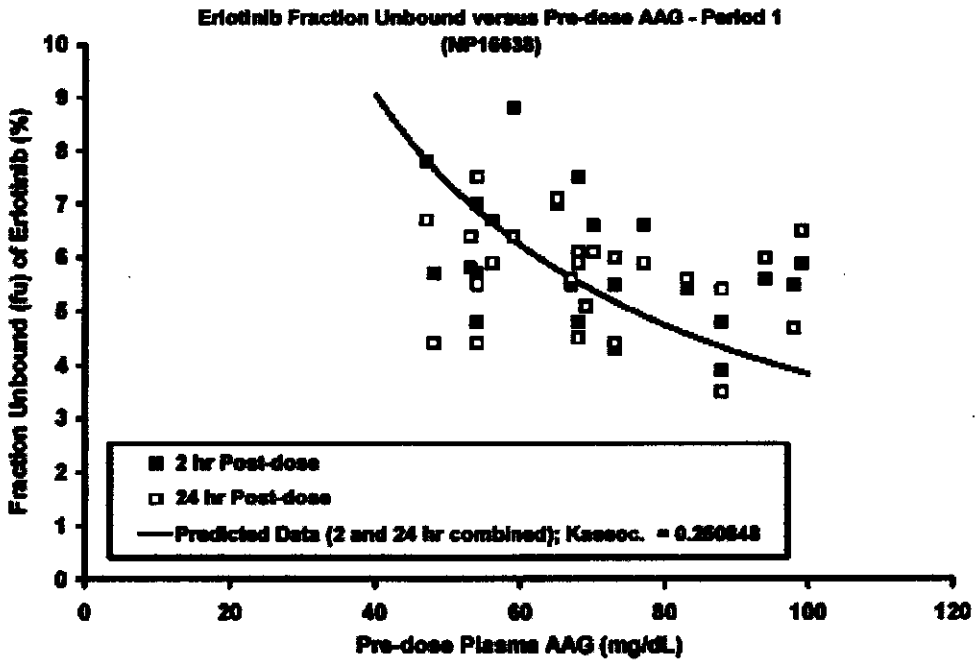
Plasma protein binding of erlotinib was evaluated by equilibrium dialysis (Studies I2001125, I960015, V2001130). Total plasma protein binding of erlotinib ranged from 92% to 95%. Erlotinib is highly bound in blood (96.5%) with contributions of about 34% in blood cells and 62% in plasma (Study V2001130). Human serum albumin and AAG are 2 major proteins contributing to erlotinib binding in plasma. Binding was found to be sensitive to concentrations of fatty acids. In vitro protein binding interactions were tested using [^{14}C]-erlotinib at 3.8 µg/mL in the presence of warfarin that binds primarily to serum albumin (Study U2000139). Concentrations of warfarin ranging from 0 to 74 µg/mL did not have a significant affect on erlotinib plasma protein binding. Similarly, propranolol, which binds primarily on α1-acid glycoprotein, did not have an affect on erlotinib binding at propranolol concentrations ranging from 0 to 500 ng/mL. The effects of erlotinib on the binding of [^{3}H]-propranolol and [^{14}C]-warfarin was investigated. Plasma protein binding of warfarin or propranolol in human plasma was not affected by erlotinib.

Binding of erlotinib was also evaluated at varying concentrations of human serum albumin and AAG. Human serum albumin protein in concentrations of 30, 40, and 50 mg/mL had only marginal increase in erlotinib binding (89.8%, 91.6%, and 93.4%, respectively). In contrast, changes in AAG concentrations had more pronounced effect on binding of erlotinib. Mean percent binding of erlotinib at 3.8 μg/mL increased from 52.3% to 78.5% and 96.3% in the presence of AAG concentrations of 0.38, 1.0 and 5.0 mg/mL, respectively, in isotonic phosphate buffer.

The effect of AAG on the pharmacokinetics of erlotinib, in particular the fraction unbound in plasma, was evaluated in several clinical pharmacology studies in healthy volunteers as well as in some patient studies. In the erlotinib-rifampicin drug-drug interaction study (NP16638), the data show erlotinib binding increases (fu decreases) as plasma level of AAG increases when data from both subject groups were combined in Period 1 (erlotinib alone) at either 2 hour or 24 hour post erlotinib dose (**FDA Figure 6., Applicant's Figure 2-2**).

FDA Figure 6., Applicant's Figure 2-2

Figure 2-2: Erlotinib Fraction Unbound versus Predose AAG



A similar observation was made in the erlotinib-ketoconazole drug-drug interaction study (Study NP16612) with respect to changes in AAG concentration and the fraction of unbound erlotinib in plasma -- erlotinib binding increased (f_u decreases) as plasma level of AAG increased.

The decrease in fraction of unbound erlotinib in plasma with increased AAG concentration can theoretically decrease erlotinib clearance (CL) and hence increase AUC (exposure). The effect of AAG on AUC was, however, variable among different clinical pharmacology studies. A trend for linear relationship was observed in the rifampicin study (Study NP16638) and in patients with metastatic breast cancer (Study BO16450) but was unclear in the ketoconazole study (Study NP16612). The pharmacokinetics of erlotinib have high inter- and intra-subject variability. AUC (hence, CL/F) is dependent on multiple factors and the effect of a single factor such as changes in AAG may not be easily detected in studies with small numbers of subjects.

The effect of AAG on the pharmacokinetics of erlotinib has, therefore, been evaluated using a population PK approach combining several Phase II and III trials. AAG, in addition to total bilirubin, were the two most important covariates explaining inter-individual variability for CL. High AAG was associated with a slower rate of CL (-15.9% for AAG = 2.3 g/L, the 95th percentile). The decrease in CL associated with increased AAG level is consistent with the extensive protein binding of erlotinib. Increased AAG level results in lower erlotinib free fraction and therefore decreased CL.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study suggests that metabolism is the primary route of elimination. Excretion is primarily via feces.

Following oral dosing of 100 mg of ^{14}C-erlotinib to 4 healthy male volunteers, 91% of the ^{14}C dose was recovered in excreta: approximately 83% in feces and 8% in urine. Approximately 88% of the recovered ^{14}C (approximately 80% of the original dose) could be identified. The relative amounts of the moieities identified in excreta is shown in **FDA Table 14.** below.

FDA Table 14. Excretion and 2 hour plasma concentrations after oral dosing of 100 mg of ^{14}C erlotinib

	Excreted in Urine	Excreted in Feces	Total excretion	Plasma @ 2h post-dose
	% dose			% total ^{14}C present @ 2h
Acids of OSI-413/420 (M11b,a) (OSIP629019AB, 20AB1)	2.2	27.2	29.4	4.2
OSI-493 (M6)	0.45	20.6	21	1.6
OSI-356 (M16)	0.01	9.6	9.6	0.7

O-demethyl OSI-493 (M2)	0.13	4.7	4.8	not detected
OSI-420 (M14)	0.18	3	3.2	5.4 (M13 + M14)
O-demethyl OSI-356 (M17)	not detected	3.2	3.2	not detected
Different glucuronides	1.1	1.1	2.2	not detected
OSI-413 (M13)	0.01	1.7	1.7	5.4 (M13 + M14)
Erlotinib	0.29	1	1.2	82.8
OSI-943 (M12)	0.11	1	1.1	not detected
Sulfate of OSI-356 (M10)	0.6	not detected	0.6	not detected
Total (sum of column)	**5.08**	**73.1**	**78**	**not applicable**

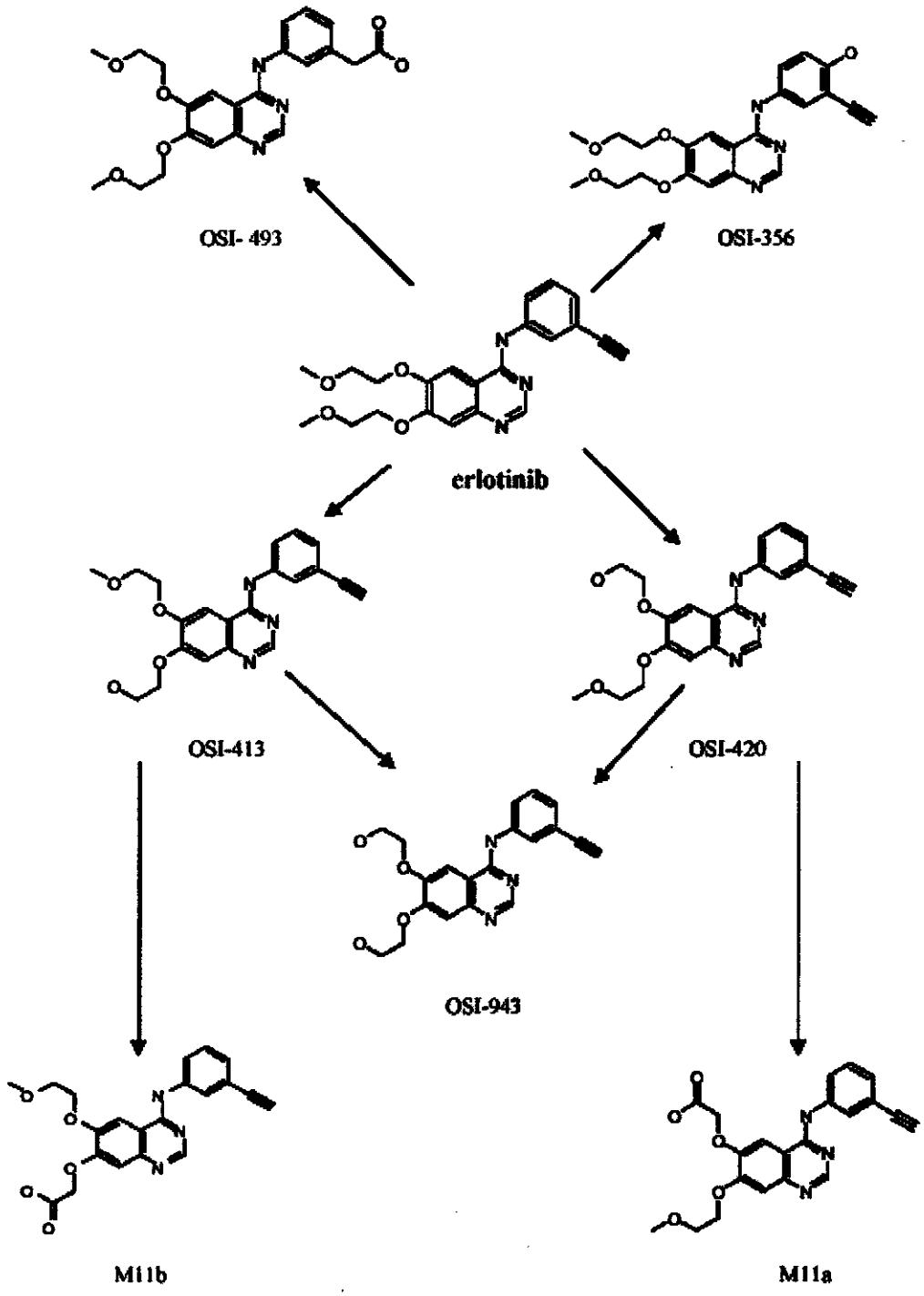
Table derived from Applicant's Table 2-28, Summary of Clinical Pharmacology Studies, p. 88.

2.2.5.6 What are the characteristics of drug metabolism?

Erlotinib metabolism followed 3 major pathways (**FDA Figure 7., Applicant's Figure 2-8**):
1) O-demethylation of either side chain (formation of OSI-413 or OSI-420 or both (OSI-943), or followed by oxidation of OSI-413 or OSI-420 to the respective carboxylic acids (M11a and b).
2) Oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid (OSI-493) which can be followed by de-methylation of a side chain.
3) Aromatic hydroxylation of the phenyl-acetylene moiety (OSI-356), which can also be followed by demethylation of a side chain.

FDA Figure 7., Applicant's Figure 2-8

Figure 2-8: Main Pathways of Erlotinib Metabolism in Humans, Dogs and Rats



The hepatic enzymes involved in the formation of the major metabolites in humans were identified as cytochrome P450 isoenzymes CYP3A4 and CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumor tissue might also occur. Potential drug-drug interactions might arise from co-administration of inhibitors or inducers of these enzymes. Accordingly, clinical drug-drug interaction studies were performed with concomitant administration of the CYP3A4 inhibitor ketoconazole (Study NP16612) and the CYP3A4 inducer rifampin (Study NP16638). In vitro incubations of erlotinib with human liver microsomes revealed a slow turnover with an apparent K_m value of 7 – 10 µM (Studies V990216, 1008627). Structures of metabolites were identified by [redacted] The most prominent metabolites obtained were OSI-356 (20%), OSI-420 (8.5%), and OSI-493 (~ 12%), and only minor formation of OSI-413 (2.2%) and OSI-943 (~ 2%) [Study 1008627].

In vitro studies using human liver microsomes and several inhibitors of cytochrome P450 isoenzymes revealed a strong inhibition of the formation of the different erlotinib metabolites (OSI-413/420, OSI-356, and OSI-493) by ketoconazole (80% to 95%, inhibitor of CYP3A4), and a weak inhibition by furafylline (6% to 20%, inhibitor of CYP1A2) (Study V990216). Using human liver microsomes and recombinant human CYP3A4, a similar metabolite pattern was obtained [Study 1008627] and apparent K_m values were calculated as 10.1 and 5.9 µM, respectively (Study V990216), which indicated a predominant role of CYP3A4 in erlotinib metabolism. Maximal inhibition of erlotinib metabolism by 10 µM ketoconazole was 80% in spite of an approximate K_i value of 0.032 µM (Study 1008627), which corresponds to literature data for midazolam as substrate [von Moltke, 1996]. The data would suggest a much stronger inhibition *in vitro* and a stronger drug-drug interaction following co-administration of ketoconazole as observed *in vivo* (increase of AUC less than 2-fold in Study NP16612). Similarly, since erlotinib is predominantly metabolized by CYP3A4, induction of this isoenzyme by co-administered compounds such as rifampin could drastically reduce the overall exposure to erlotinib. However, C_{max} was decreased by only 32% and AUC by approximately 64% in Study NP16638.

With human recombinant CYP1A2, erlotinib was metabolized to OSI-420 following Michaelis-Menten kinetics with an apparent K_m value of 24 µM (Study V2001129). This low affinity in comparison with the clearance by CYP3A4 suggested a minor contribution of CYP1A2 to the overall elimination (and therefore, a minimal potential for inhibitory interactions involving this enzyme in vivo), but might be favored under conditions of CYP3A4 inhibition. The metabolite pattern with CYP1A2 was slightly different from CYP3A4 with respect to predominant formation of O-demethylated OSI-356 (Study 1008627), which was detected in human feces. The metabolism of erlotinib by human recombinant CYP1A1 did not follow Michaelis-Menten kinetics but revealed linearity for less than 1 minute, most likely due to a strong mechanism-based inhibition of the enzyme (Study V2001129). Without induction, only a small amount of CYP1A1 is expressed in human tissues.

In addition, erlotinib was metabolized by human recombinant CYP1B1 (an isoenzyme related to CYP1A1 that is expressed in tumor tissues), but only to a minor extent by CYP2C8 (Study 1008627) and not by CYP2C9, CYP2C19, and CYP2D6 (Study V990216). As a consequence, metabolism by CYP1B1 with predominant formation of the pharmacologically active metabolite OSI-356 inside the tumor tissue might contribute to the antitumor activity of erlotinib.

In summary, erlotinib is metabolized in human liver primarily by the cytochrome P450 isoform CYP3A4 but also by CYP1A2 and, to a minor extent, by CYP2C8. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumor tissue might contribute to the metabolic clearance of erlotinib.

Since Phase II metabolites were detected in vivo, glucuronidation of OSI-420 was investigated in vitro using liver microsomes from different species as well as several recombinant human UDP-glucuronosyltransferase isoenzymes. Low but comparable rates of glucuronidation were obtained only with human and dog liver microsomes, containing more than 1 UGT isoenzyme (Study V2001133). Since glucuronidation of erlotinib metabolites is only a minor pathway of elimination, clinical interactions with potent inhibitors of human UGTs appear unlikely.

2.2.5.7 What are the characteristics of drug excretion?

248-006 An Open Study to Examine the Metabolism and Excretion of [^{14}C]-OSI-774 (formerly CP-358,774) in Healthy Male Volunteers

This open label study was performed to examine the metabolic profile and routes of excretion of [^{14}C]-erlotinib in healthy male volunteers. A single 100 mg oral dose of [^{14}C]-erlotinib (100 μCi) was administered as a suspension to four healthy male subjects. Radioactivity in urine, feces, blood, and plasma was measured by liquid scintillation counting.

Approximately 91% of the administered dose was recovered from the urine and feces with the majority of the total administered radioactivity in the feces (83% ± 6.8%) and the urine accounting for only 8.1% ± 2.8%. Erlotinib was extensively metabolized, as demonstrated by < 2% of the administered dose excreted as unchanged drug in urine and feces. In addition to a minor amount of unchanged drug, 13 metabolites in urine, 10 metabolites in feces, and 4 metabolites in plasma were identified (see **Section 2.2.5.6** of this review: **FDA Table 14.**).

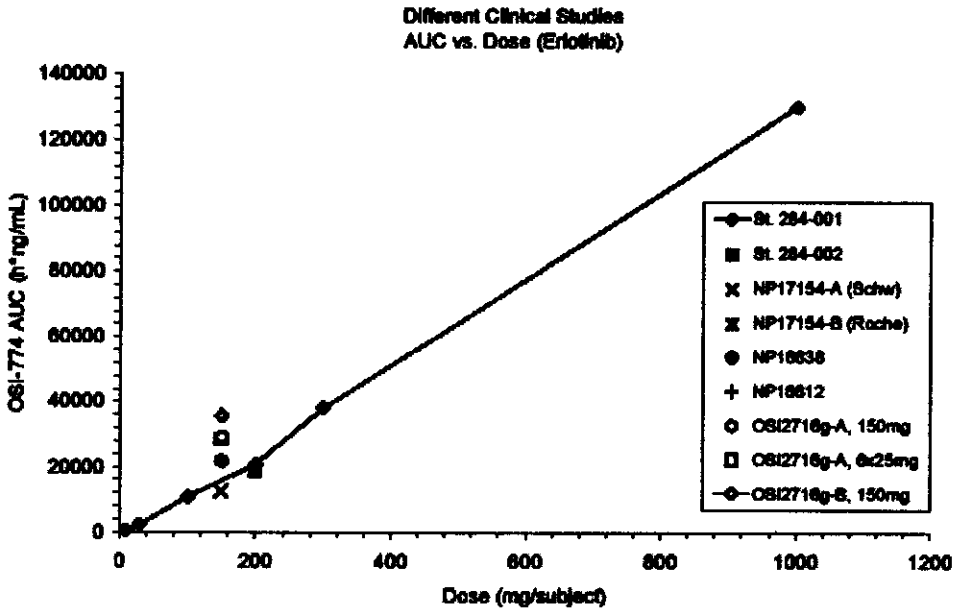
2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose proportionality

Overall, AUC increased with dose when erlotinib was given as a single dose up to 1000 mg with the formulation changing from solution (3 to 30 mg) to suspension or tablet **(FDA Figure 8., Applicant's Figure 2-3)**.

FDA Figure 8., Applicant's Figure 2-3

Figure 2-3: AUC vs Dose of Erlotinib in Different Healthy Volunteer Studies

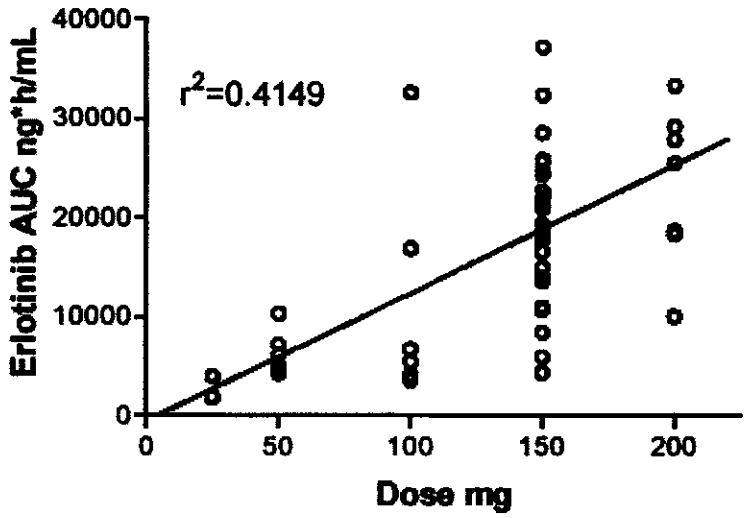


There was large variability in erlotinib AUC between studies, as shown for the 150 mg dose. A similar dose-proportionality for erlotinib AUC was also observed in cancer patients (Study 248-004) in spite of large inter-patient variability at a given dose **(FDA Figure 9., Applicant's Figure 2-16)**.

FDA Figure 9., Applicant's Figure 2-16

Figure 2-16: Study 248-004 – Correlation between Erlotinib Plasma AUC, C_{max} and Dose

Results of a weighted ($1/x^2$) linear regression of erlotinib plasma AUC_{0-24} vs dose following the first dose of Erlotinib



As AUC decreases with reduction in dose, the line appears to have an x-intercept, suggesting the slope for linearity may change from very low doses (< 50 mg) to higher dose ranges (100 to 1000 mg), although data at low doses are limited. This is consistent, however, with the longer half-life observed after the 150 mg oral dose compared with 25 mg IV dose in the same subjects in crossover study OSI2716g. Mean (± SD) terminal half-life at 25 mg IV and 150 mg oral doses were 13 (± 6) and 21 (± 10) hours, respectively. The exact mechanism or specific pathway that may be saturated at the low dose range is not known. At doses ranging from 100 mg to 1000 mg, AUC increases linearly with no observable saturation in its elimination. There is high variability in estimates of AUC across studies, suggesting high inter-subject variability of erlotinib pharmacokinetics.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Steady state erlotinib concentrations were reached within a week following once daily drug administration. The average accumulation factor of erlotinib taken at 100 – 150 mg daily varied from 1.5 to 2.1 in 2 healthy volunteer studies (Studies NP16793 and NP16787). An extent of accumulation of 1.5 and 2.0 would be expected from once daily dosing for a drug with an approximate effective half-life of 15 and 24 hour, respectively. The observed plasma terminal half-life for erlotinib ranged from 7 to 22.5 hour and is consistent with the observed accumulation.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There is high inter-subject and inter-study variability in clearance and plasma terminal half-life of erlotinib estimated across several healthy volunteer studies. Median clearance ranged from 5.22 to 15.0 L/h and half-life ranged from 7.0 to 19.1 hours among 6 studies in a total of 110 subjects at doses ranging from 100 to 200 mg **(FDA Table 14., Applicant's Table 2-18)**.

FDA Table 14., Applicant's Table 2-18

Table 2-18: Median (range) Erlotinib Oral Clearance and Half-Life after Single Dose Administration in Healthy Volunteers Studies

Study	Dose (mg) (fed/fasted)	Number of Subjects	Cl/F (L/h)	$T_{1/2\lambda}$ (h)
248-001	200 (fasted)	3M	8.7 (6.5 – 17.3)	9.0 (5.3 – 9.5)
NP16584	150 (fed)	9M	7.4 (6.1 – 8.1)	9.0 (6.0 – 11)
NP16584	150 (fasted)	9M	15 (8.5 – 30)	7.0 (4.1 – 11)
NP16612	100 (fasted)	24M	9.0 (4.7 – 28)	8.49 (4.8 – 15.3)
NP16638	150 (fasted)	24M	8.5 (4.5 – 23)	8.49 (4.1 – 17.8)
OSI2716g (Arm A)	150 (fasted)	22F	5.27 (2.79 – 7.93)	16.3 (9.89 – 36.8)
		19M	6.62 (3.70 – 13.24)	12.3 (6.67 – 27.6)
(Arm B)	150 (fasted)	16F/4M	5.22 (2.06-7.33)	19.1 (7.63 – 49.1)

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population Pharmacokinetic Model

The population PK analysis with single agent erlotinib demonstrated that the covariates affecting erlotinib disposition were similar to those observed with chemotherapy combination studies. For erlotinib given as monotherapy in NSCLC patients, the mean population PK parameter was 3.95 L/hr for CL/F and 233 L for V_c/F. Similar estimates

for erlotinib given in combination with chemotherapies for the apparent clearance (CL/F) and apparent volume of distribution (Vc/F) of erlotinib were 4.4 L/hr and 213 L, respectively. Considering the magnitude of effect and the plausible biologic reasoning, total bilirubin and AAG were considered to be the most important covariates for erlotinib CL in both population analyses. The effects of these covariates are considered to be modest and not clinically important, in comparison with the large inter-patient variability of CL of approximately 50%. The effects of other covariates such as gender, albumin, and creatinine clearance were found to be similar in both analyses. These effects were statistically significant ($p < 0.05$), but given the large estimated CV of the parameters, and the small magnitude of their effects, those covariates are believed to have a minimal effect on CL.

In conclusion, the disposition and covariates effect of erlotinib in patients receiving erlotinib as a single agent was consistent with the results in the population PK analysis performed in chemotherapy combination. Although several covariates were found to be associated with erlotinib clearance, their effects were modest and are considered to not be clinically important.

Pharmacokinetics in Special Populations
Effect of Gender

A population PK analysis was performed using data from 708 patients (62% female) in 6 studies. The effect of gender had borderline statistical significance on clearance in this analysis. In the final model, typical CL was 4.29 L/h for females and 4.70 L/h for male patients. This difference in CL between males and females was small considering the inter-individual variability (CV) of 40.5% for CL in the model used to describe these population PK data. The small difference in CL between genders was considered to have little clinical significance (Report 04-0142-1219).

Effect of Race
The single dose pharmacokinetics for erlotinib were compared using data from 2 comparable Phase I trials; one in Japanese NSCLC patients (Study JO16564) and the other in western cancer patients (Study 248-004), in which 50/56 patients were Caucasian, 3 were Hispanic, 1 was Black, and 1 was Asian (**FDA Table 15., Applicant's Table 2-26**). There was no apparent difference in PK characteristics of erlotinib between Japanese and western patients. The race effects of Caucasian compared with other races were tested in the population PK analysis (Studies BO16411 and OSI2298g) and were not significant. While no differences due to race are observed, the non-Caucasian dataset is too limited to conclude that pharmacokinetics are unaffected by race.

FDA Table 15., Applicant's Table 2-26

Table 2-26: Single Dose Erlotinib PK Parameters in Japanese vs Western Cancer Patients, Median (min-max)

Study	Dose (mg) No. of Subjects	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg*h/mL)	$t_{1/2z}$ (h)
248-004 Leg 2 Dose 1	50 3	0.400	4.0	9.50	15.3
	100 3	0.428	2.0	6.98	18.7
	150 3	1.24	2.0	50.3	22.5
	200 7	1.60	4.0	54.2	33.3
JO16564[a]	50 3	0.194 (0.084)	5.0 (3.6)	3.27[b] (1.78)	14.8 (10.5)
	100 6	0.571	6.0	7.70	18.0
	150 6	0.958	6.0	12.8	25.9

[a] mean (SD) values.
[b] AUC_{0-24} values.

Effect of Age

The effect of age on erlotinib pharmacokinetics was evaluated in Study BR.21, comparing subgroups aged < 65 years with those ≥ 65 years. Trough concentrations (the sum of erlotinib plus OSI-420) were increased by 17% in the patients who were ≥ 65 years old, compared to younger patients. This slight elevation in exposure is judged clinically insignificant.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

No dose adjustment is recommended.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

Data from pediatric subjects is not included in the NDA. There are no plans for pediatric studies. No package insert language is recommended.

2.3.2.3 Gender

No dose adjustment is recommended.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

No dose adjustment is recommended.

2.3.2.5 Renal impairment

Renal impairment has not been studied. However, less than 1% of the administered dose is excreted as parent in urine (see **Section 2.2.5.5** of this review).

No dose adjustment is recommended.

2.3.2.6 Hepatic impairment

Hepatic impairment has not been studied. Based upon excretion pattern (see **Section 2.2.5.5** of this review) and in vitro metabolic studies (see **Section 2.2.5.6** of this review), the primary route of elimination is metabolism and the liver is likely the primary organ responsible for elimination. Because data are not available, specific data-derived dosage adjustment recommendations cannot be made. We recommend a Phase 4 commitment to study subjects with hepatic impairment be made.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

There is no pharmacogenetics information in the application. However, as detailed in **Section 2.1**, there are pharmacogenetic issues related to literature information on differences in response with the approved EGFR antagonist IRESSA.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation use information in the application.

2.3.2.9 Are there other human factors that are important to understanding the drug's efficacy and safety?

There are no apparent "other human factors" that are important to understanding the drug's efficacy and safety.

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

In Study BR.21 patients who smoked had a 24% greater clearance in erlotinib than did former smokers or patients who had never smoked. The change due to smoking could be explained by smoking inducing CYP1A.

Due to the high inter-subject variability in erlotinib pharmacokinetics, specific recommendations for dose adjustment are judged inappropriate. The proposed package insert states that dose modifications should be considered in 50 mg steps and the level of dose adjustments should be directed by the individual patient tolerability based on clinical evaluations. As this method of dose modification is consistent with the conduct of the efficacy and safety study (Study BR.21), and the exposure-efficacy relationship for erlotinib is unknown (see **Section 2.2.4.4),** the method seems appropriate.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes – see **Sections 2.4.2.2, 2.4.2.3** and **2.4.2.4**, below.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, erlotinib is a CYP substrate. There is no evidence that metabolism is influenced by genetics.

V960013 In Vitro Metabolic Stability of CP-358,774 in Human and Rat Liver Microsomes – Correlation with CYP1A Activity

V990216 Identification of CYP Isoform(s) Responsible for the Metabolism of CP-358,774

These studies were undertaken to determine the nature of the cytochrome P450 isoenzymes involved in the in vitro formation of erlotinib metabolites with liver microsomes. Initial studies correlated the microsomal metabolic rate with the expression levels of CYPs 1A1 and 1A2 and revealed predominant involvement of CYP1A1 and, to a lesser extent, CYP1A2. Further studies using human liver microsomes and specific CYP inhibitors, as well as recombinantly expressed human CYPs 1A1, 1A2, 2C9, 2C19,

2D6, 3A4, and 3A5, confirmed CYP1A1 as metabolizing enzyme but also revealed the predominant role of CYP3A4/5 in erlotinib metabolism. All other isoenzymes appeared not to be involved. CYPs 1A1, 3A4, and 3A5 catalyzed the formation of OSI-413, OSI 420, OSI-356, and OSI-493, with OSI-356 being the most prominent form produced by CYP3A4 and CYP1A1, but a more pronounced formation of OSI-420 by CYP3A5. Apparent K_m values for erlotinib metabolism were 10.1 and 5.9 μM in human liver microsomes and cDNA expressed human CYP3A4, respectively. Inhibition of microsomal metabolism by 10 μM ketoconazole (a not fully specific inhibitor of CYP3A4) revealed 80% to 95% inhibition of the formation of the different metabolites, which was indicative of CYP3A4 being the most important, but not exclusive, metabolizing enzyme.

V2001129 Comparison of the Activity of Human CYP1A1 and CYP1A2 in the Metabolism of OSI-774 to OSI-420

The objective of this study was to compare the activity of CYP1A1 and CYP1A2 in the metabolism of erlotinib to OSI-420. This was not possible, however, due to inhibition of CYP1A1 by erlotinib. Metabolism of erlotinib by CYP1A2 obeyed classic Michaelis-Menten kinetics. The affinity constant (K_m) was 24 μM, confirming a moderately high affinity of CYP1A2 for erlotinib. When compared with the clearance by CYP3A4 or by hepatic microsomes determined in previous studies, however, it is anticipated that the contribution of CYP1A2 to the overall elimination of erlotinib in vivo would be minor. This suggests that, at the concentrations of the drug achieved, there is a minimal potential for inhibitory interactions involving this enzyme in vivo.

1008627 In Vitro Studies on the Interaction Potential of Tarceva (erlotinib HCl; OSI-774) with Other Drugs at Human Cytochrome P450 Isoenzymes

The objective of this study was to evaluate the hepatic cytochrome P450 enzymes responsible for metabolizing erlotinib. Erlotinib showed slow oxidation rates during incubation with human liver microsomes and human hepatocytes. In human liver microsomes, biphasic kinetics was observed with linearity for no longer than 10 minutes of incubation. Within this short time interval, erlotinib turnover in human liver microsomes followed Michaelis-Menten kinetics with an apparent K_m of 7.2 μM. Previous studies revealed the involvement of CYPs 1A2 and 3A4 in its biotransformation. This study demonstrated erlotinib is also metabolized, to a small degree, by CYP2C8. In addition, significant metabolism by CYP1B1 was observed with a very low K_m value for the recombinant human isoenzyme (~ 1 μM). CYP1B1 is expressed in tumor tissues and may contribute to the anti-tumor effect of erlotinib by formation of the pharmacologically active metabolite OSI-356 inside the tumor tissue. However, the activity of CYP1B1 in tumor tissue could also lead to resistance to the effect of erlotinib by metabolism, as it is not clearly known what role the OSI-356 metabolite plays in the overall anti-tumor activity of erlotinib.

In conclusion, in vitro experiments support that erlotinib is metabolized primarily by CYP 3A4/5. CYPs 1A1, 1A2 and 1B1 can be demonstrated to metabolize erlotinib in vitro, but likely have little role in metabolizing erlotinib in vivo.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Erlotinib is an inhibitor of CYP enzymes. It's activity as an inducer is slight.

Inhibition

FDA Table 16., below, summarizes the in vitro studies performed to evaluate the ability of erlotinib and OSI-420 to inhibit cytochrome P450 isozymes.

FDA Table 16. In vitro inhibition of CYP isozymes by erlotinib or OSI-420

	Study 970160	Study 970161	Study1008627	Study 2001129	
CYP	I/Ki (erlotinib)[A]	I/Ki (erlotinib)[A]	I/Ki (erlotinib)[A]	I/Ki (erlotinib)[A]	Conclusion
1A1				Ki not determined, IC50 <0.1uM	In vivo relevance of 1A1 inhibition unknown -- no action indicated
1A2	< 0.088[B]				Potential for in vivo interaction remote -- no action indicated
1B1			< 0.088[B]		In vivo relevance of 1B1 inhibition unknown -- no action indicated
2C8			0.293		Await midazolam results to evaluate need for clinical study; large Efficacy-Safety study with paclitaxel has been completed -- no action currently indicated
2C9	0.100				Await midazolam results to evaluate need for clinical study -- no action currently indicated
2C19	< 0.107 – < 0.213[B,C]				Await midazolam results to evaluate need for clinical study -- no action currently indicated
2D6	< 0.088[B]				Potential for in vivo interaction remote -- no action indicated

3A4	0.293	0.550			Phase 4 commitment to complete in vivo study
CYP	**I/Ki (OSI-420)[D]**	**I/Ki (OSI-420)[D]**			**Conclusion**
1A2	0.012	0.012			Potential for in vivo interaction remote – no action indicated
2C9	0.004				Potential for in vivo interaction remote – no action indicated
2C19	< 0.006 – < 0.012[B,C]				Potential for in vivo interaction remote – no action indicated
2D6	0.007				Potential for in vivo interaction remote – no action indicated
3A4	0.016	0.010			Potential for in vivo interaction remote – no action indicated

[A]I = steady-state Cmax of erlotinib following 150 mg QD TARCEVA dose = 1.7 μg/mL = 4.4 μM

[B]IC50 not determined (IC50 > 100 uM); Ki assumes IC50 = 100 uM (the highest tested concentration)

[C]Km not reported; Ki calculated using literature values (FDA Guidance) for Km

[D]I = steady-state Cmax of OSI-420 with 150 mg QD TARCEVA dose = 0.096 μg/mL = 0.25 μM

V970161 Interactions of CP-358,774 and CP-373,420 with CYP1A2 and CYP3A4

Dixon plots revealed that the inhibition of CYP3A4 by erlotinib and the inhibition of CYPs 3A4 and 1A2 by OSI-420 were not clearly defined (mixed noncompetitive/uncompetitive inhibition).

V2001129 Comparison of the Activity of Human CYP1A1 and CYP1A2 in the Metabolism of OSI-774 to OSI-420

A strong inhibition of CYP1A1 by erlotinib was observed. The reaction rate for this enzyme was linear for less than 60 seconds, suggesting the possibility that the compound was acting as a mechanism-based inhibitor of CYP1A1. This was investigated further by pre-incubation of the enzyme with erlotinib in the presence of its essential cofactor, NADPH. This would enable metabolism and any CYP1A1 inactivation to proceed. A second substrate (ethoxyresorufin) was then added to assess residual enzyme activity. Erlotinib was a potent inhibitor of CYP1A1 with an IC_{50} value of < 0.1 μM. The mechanism of inhibition was not clearly established in these studies. The Km of ethoxyresorufin under these conditions was not determined, thus, a Ki for erlotinib and I/Ki cannot be determined. While mechanism based (or "suicide") inhibition by covalent binding to the enzyme due to formation of a reactive metabolite is a likely explanation for the results, it is possible that the parent or a metabolite forms a tight-binding complex with the enzyme, blocking activity but not destroying the enzyme. As CYP1A1

expression is very limited in human tissues, the physiological relevance of this inhibition is unknown.

1008627 In Vitro Studies on the Interaction Potential of Tarceva (erlotinib HCl; OSI-774) with Other Drugs at Human Cytochrome P450 Isoenzymes

The inhibition of CYP3A4 by erlotinib was complex -- inhibition of midazolam metabolism was pre-incubation time-dependent and had an inactivation rate constant k_{inact} of 0.009 min^{-1}. A clinical interaction study with midazolam to measure effects of erlotinib on CYP3A4 substrates is in progress [NP17536]. The mechanism-based interaction with CYP3A4 potentially alters the clearance of erlotinib itself.

Induction

FDA Table 17., below, summarizes the in vitro study of the ability of erlotinib to induce cytochrome P450 isozyme activity.

FDA Table 17. In vitro induction of CYP3A4 in primary human hepatocytes

	3A4 activity – fold induction*	
uM	erlotinib	rifampicin
0 (vehicle control)	0	0
1	1	3.8
3.2	0.6	4.7
10	1	5.7

*fold induction = (treated activity - vehicle activity) + vehcile activity

Results with human hepatocytes from different donors incubated with erlotinib and rifampicin showed some variability (up to 3.3-fold induction of enzyme activity for erlotinib within an individual) but were consistent with only a weak potential of erlotinib to modulate CYP3A4 activity (less than one-third of rifampicin).

Induction of cytochromes P450 other than 3A4 was not tested in assays measuring functional activity.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No data is presented on the ability of erlotinib to act as a substrate and/or an inhibitor of P-glycoprotein transport processes.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The ability of erlotinib to act as a substrate and/or an inhibitor of glucuronidation was studied.

V2001131 Results of OSI-774 Interactions With Bilirubin Glucuronidation In Vitro

The IC_{50} value for human liver microsomes was 0.92 μM and for expressed human UGT1A1 enzyme 0.93 μM.

V2001117 Inhibition Kinetics of OSI-774 with Bilirubin UGT and the Inhibitory Effect of OSI-774 on Other Human UGT Isoforms

V2001134 The Inhibition of Cynomolgus Monkey Liver Microsomal Glucuronidation of Bilirubin by OSI-774 (See Section 4.2.3.7.3 for details)

The potential of erlotinib to inhibit the glucuronidation of recombinantly expressed human UDPglucuronosyltransferase isoenzymes 1A6, 1A9, and 2B7 was evaluated with probe substrates for those isoforms (1-naphthol, propofol, and hyodeoxycholic acid, respectively). The inhibitory effect of erlotinib was also evaluated with respect to the same three substrates glucuronidated by human liver microsomes.

The type of inhibition of bilirubin glucuronidation could not be clearly established from the K_i determinations. K_i values were calculated by applying equations describing competitive and noncompetitive inhibition. Fitting the data to the noncompetitive equation gave 2- to 3.5-fold higher K_i values (1.1 to 4.8 μM) than the competitive situation (0.34 to 1.3 μM). All the values, however, were < 5 μM, which was lower than the reported K_m value for bilirubin glucuronidation of 24 μM [Senafi, 1994]. Among other human UGTs, only UGT1A9 was shown to be inhibited by erlotinib, although at higher concentrations than UGT1A1 (IC_{50} = 31 μM). Propofol glucuronidation in human liver microsomes was inhibited by erlotinib (IC_{50} = 24 μM) to a similar degree as propofol glucuronidation by the expressed UGT1A9. In contrast to bilirubin glucuronidation by UGT1A1, glucuronidation of octylgallate by UGT1A1 and of propofol by UGT1A9 was only partly inhibited, as 30% to 50% of activity was still remaining at erlotinib concentrations of 250 μM. This suggests erlotinib is not causing inhibition at the active site and, therefore, might not be capable of totally inhibiting glucuronidation activity.

V2001133 Preliminary Assessment of In Vitro Glucuronidation of OSI-420 and Inhibition of Bilirubin UDP-Glucuronosyltransferase by OSI-420

UGT screening assays were performed on OSI-420 using expressed human UDPglucuronosyltransferases 1A1, 1A6, 1A9, and 2B7. Positive control assays with a probe substrate were carried out in parallel with screening assays.

OSI-420 was glucuronidated at very low rates, and activity could be detected only in assays with microsomal preparations (not with the expressed glucuronyltransferases), but these sources of UGT enzymes represent a heterogeneous pool of enzymes. The activity observed in the microsomal preparations might be due to the contribution of more than one isoform at rates of glucuronidation lower than the limits of sensitivity for the standard radiochemical HPLC assay and so preclude the ability to detect glucuronidation in the expressed forms.

The extent of OSI-420 inhibition of bilirubin glucuronidation in liver microsomes was equivalent across the species used in the interaction experiments. The metabolite of erlotinib was a considerably less potent inhibitor of bilirubin glucuronidation than erlotinib itself as the IC_{50} values were considerably higher in the range of 6.8 to 8.7 μM compared with 0.5 to 1.2 μM for erlotinib.

V2001135 Preliminary Results of OSI-774 Metabolites Interactions with Bilirubin Glucuronidation in Human Liver Microsomes In Vitro

V2001137 The Effect of OSI-774 Metabolites Interactions with Bilirubin Glucuronidation in Human Liver Microsomes in Vitro

The objective of these 2 studies was to evaluate the ability of erlotinib metabolites M11a and M11b (the acids of OSI-420 and OSI-413, respectively) and OSI-493 to inhibit bilirubin glucuronidation by human liver microsomes. All tested metabolites appeared to be relatively poor inhibitors of human bilirubin UGT with IC_{50} values of 43 μM for OSI-493, 49 μM for M11a, and 71 μM for M11b. M11b was the best potential inhibitor, as up to 87% of the activity could be inhibited by 1 mM concentration of the metabolite. OSI-493 and M11a appeared to be effective inhibitors, but only inhibited up to 59% of the total enzyme activity, which may suggest different metabolite binding or noncompetitive inhibitory mechanisms in hepatic endoplasmic reticulum. plasma concentration of these metabolites are less than 1 μM, it is unlikely that they will inhibit hepatic bilirubin UGT activity in patients being treated with erlotinib.

V2002310 Kinetic Analysis of the Inhibition of Human Hepatic Microsomal Bilirubin UDP-Glucuronosyltransferase by OSI-774

V2002311 Report on Study of the Inhibition of Bilirubin UGT by OSI-774 in Human Hepatic Microsomal Preparations

The objective of these 2 studies was to evaluate the kinetics and the mechanism and reversibility of inhibition of bilirubin UGT by erlotinib in human liver microsomes. Kinetics of bilirubin glucuronidation was measured using different concentrations of substrate (30 to 122 μM bilirubin) in the presence of different concentrations of the

inhibitor (0 to 3 μM erlotinib). Kinetic analysis revealed a competitive mechanism of inhibition and reversibility of the inhibition.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify co-administration of another drug.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Patients with NSCLC are likely to receive medications to aid respiratory function, such as bronchodialators and steroids.

2.4.2.8 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?

Studies to Assess CYP3A4 Interactions
Two studies were performed in healthy volunteers to evaluate the effects of a CYP3A4 inhibitor (ketoconazole) and a CYP3A4 inducer (rifampicin) on the pharmacokinetics of erlotinib. Based on the observation in vitro of an inhibitory effect (K_i = 8 μM) of erlotinib on human CYP3A4 enzyme, a drug-drug interaction study of multiple doses of erlotinib on midazolam pharmacokinetics is in progress (Study NP17536). Because of poor tolerability of multiple doses of erlotinib in healthy volunteers, the study is being conducted in cancer patients. This clinical study is ongoing and no PK data are available.

NP16612 Comparison of the single dose pharmacokinetics of Tarceva™ (erlotinib) administered alone or concomitantly with ketoconazole in healthy male volunteers

The objective of this study was to assess the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of erlotinib. For patients in Cohort A (the relevant cohort), this was a single-center, open-label, one-sequence, two-period cross-over study. Six volunteers in Cohort A received 25 mg of erlotinib in the presence and absence of ketoconazole.

Ketoconazole had a clear effect on the $AUC_{0-\infty}$ and C_{max} of erlotinib. Erlotinib exposure ($AUC_{0-\infty}$) in the presence of ketoconazole increases by 64% compared with 100 mg erlotinib alone. When erlotinib was administered concomitantly with ketoconazole, C_{max} increased by 67% compared with erlotinib administered alone (**FDA Table 18., Applicant's Table 2-4**).

FDA Table 18., Applicant's Table 2-4

Table 2-4: Study NP16612: Mean Ratios (90% CI) of Erlotinib Exposure Parameters following its Administration ± Ketoconazole (based on 1-way ANOVA)

Exposure Parameter	No. subjects per Group	Mean Ratio per Group[a] (95% CI)	Mean Ratio[b] (90% CI)
AUC0-∞ (ng*h/mL)	12	Group 1: 1.64 (1.34, 2.00) Group 2: 0.88 (0.72, 1.07)	1.86 (1.48, 2.35)
C_{max} (ng/mL)	12	Group 1: 1.67 (1.22, 2.28) Group 2: 0.83 (0.60, 1.13)	2.02 (1.40, 2.91)

[a] 2nd versus 1st administration.

[b] Mean ratio in Group 1 (with ketoconazole) versus mean ratio in Group 2 (without ketoconazole).

Due to the high inter-subject variability in erlotinib pharmacokinetics and the differential inhibitory potency of various CYP3A4 inhibitors, specific recommendations for dose adjustment are judged inappropriate. The proposed package insert states that dose modifications should be considered in 50 mg steps and the level of dose adjustments should be directed by the individual patient tolerability based on clinical evaluations. As this method of dose modification is consistent with the conduct of the efficacy and safety study (Study BR.21), and the exposure-efficacy relationship for erlotinib is unknown (see **Section 2.2.4.4),** this method seems appropriate.

NP 16638 Effect of rifampicin on the pharmacokinetics of Tarceva™ (erlotinib), an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in healthy male volunteers

The primary objective of this study was to assess the effect of rifampicin, a potent inducer of CYP3A4, on the pharmacokinetics of erlotinib. In this study, 24 healthy volunteers participated in a randomized, open-label, parallel-group study with 2 periods. Subjects in both treatment groups received 150 mg erlotinib orally in treatment periods 1 and 2 separated by 2 weeks. In addition, subjects in Group A (n = 12) received rifampicin 600 mg orally once daily for 7 days starting 1 week following the first dose of erlotinib and ending 1 day prior to the second dose of erlotinib.

Subjects in Group A showed a mean decrease in C_{max} of 29 % and a mean decrease in $AUC_{0-\infty}$ of about 66% after rifampicin treatment **(FDA Table 19., Applicant's Table 2-5).** Induction of CYP3A4 following rifampicin administration was confirmed by the cortisol metabolic index measured in subjects from Group A. The mean cortisol metabolic induction ratio, ie, cortisol metabolic index after versus before rifampicin administration, was estimated to be 3.64. This suggested increased CYP3A4 activity through a rifampicin-mediated induction. The results of this study emphasize the importance of CYP3A4 activity on erlotinib pharmacokinetics.

The proposed labeling suggests that alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible. We have recommended a labeling change (see Section 3. of this review): "If an alternative treatment is unavailable, a dose greater than 150 mg should be considered."

FDA Table 19., Applicant's Table 2-5

Table 2-5: Study NP16638: Mean Ratios (90% CI) of Erlotinib Exposure Parameters Following Administration With Rifampicin versus Without Rifampicin (based on 1-way ANOVA)

Exposure Parameter	No. subjects per Group A/B	Mean Ratio per Group[a] (95% CI)	Mean Ratio[b] (90% CI)
$AUC_{0-\infty}$ (ng*h/mL)	11/12	Group A: 0.34 (0.28, 0.41) Group B: 1.04 (0.86, 1.24)	0.33 (0.26, 0.41)
C_{max} (ng/mL)	12/12	Group A: 0.71 (0.54, 1.09) Group B: 0.85 (0.65, 1.11)	0.83 (0.61, 1.13)

[a] 2nd versus 1st administration.

[b] Mean ratio in Group A (with rifampicin) versus mean ratio in Group B (without rifampicin).

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No pharmacodynamic drug-drug interactions have been predicted based on mechanisms.

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

Until the ongoing study of the ability of erlotinib administration to alter midazolam pharmacokinetics is completed, the ability of erlotinib to alter the pharmacokinetics of co-administered CYP3A4 substrate drugs is an unresolved issue.

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

The role of the EGFR receptor status as a predictor for survival benefit is an unresolved issue (see **Section 2.2.4.1**).

2.5. General Biopharmaceutics

This section should summarize the salient points about the attributes of the drug product.

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The highest tablet strength available is 150 mg. Using the FDA standard of 250 mL, solublility would be categorized as "High" if it exceeded 0.6 mg/mL (150 mg/250 mL; 600 ug/mL) across pHs 1 – 7.5. The solubility of Erlotinib HCl across the entire pH range is shown below (**FDA Table 20. Applicant's Table 2-1**). Erlotinib does not demonstrate "High" solubility at any pH.

FDA Figure 20. Applicant's Table 2-1

Table 2-1: The Effect of pH on Erlotinib HCl Solubility

pH	Solubility (µg/mL)*
9.60	
9.10	
8.55	
7.93	
7.29	
6.92	
6.39	
5.83	
5.28	
4.88	
4.44	
3.96	
3.69	
3.19	
2.65	
2.11	
1.40	

* Solubility determined at ambient temperature and expressed with respect to the free base concentration.

In vitro studies using monolayers of Caco-2 cells have shown that the inherent permeability of erlotinib is high (Study 01-GENT.P02). 10 µM erlotinib had a permability of 3.4 X 10-5 cm/s while the positive control propranolol had a value of 1.7 X 10.5 and the negative control atenolol had a value of 0.018 X 10-5 cm/s . Erlotinib HCl is therefore a Class 2 compound according to the Biopharmaceutics Classification System.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed to-be-marketed formulation is the formulation used in the pivotal clinical trial.

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?

- BCS classification system
- Formulation ingredient information
- Dissolution profiles

• Others

As the proposed to-be-marketed formulation was used in the pivotal clinical trial, bioequivalence data is not needed.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

As the proposed to-be-marketed formulation was used in the pivotal clinical trial, bioequivalence data is not needed.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

As the proposed to-be-marketed formulation was used in the pivotal clinical trial, bioequivalence data is not needed.

2.5.3 What is the effect of food on the bioavailability (BA) 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?

Food significantly increased both the erlotinib plasma C_{max} and AUC following oral administration. Two studies have been conducted in healthy subjects, one comparing single dose PK in fed and fasted individuals (Study NP16584) and another designed to elucidate the impact of food on the multiple dose PK (Study NP16787). In NP16584, the mean ratio of $AUC_{0-\infty}$ fed/fasted (n = 9 per treatment group) was 2.09 (90% CI 1.65 - 2.64). In study NP16787, the Day 1 mean ratio of AUC_{0-24h} fed/fasted (n = 11 per treatment group) was 1.66 (90% CI 1.20 – 2.32). Although some of the study goals were not met, i.e., NP16584 data was analyzed as a parallel group study due to a period effect, and only the single dose data from NP16787 were evaluable, both studies indicated a significant increase in erlotinib plasma exposure when administered with food. Therefore, administration of Tarceva without food is recommended, and this is consistent with the method of administration throughout the clinical development program where patients/subjects were advised to take the tablets 1 hour before or 2 hours after food.

2.5.4 When would a fed BE study be appropriate and was one conducted?

As the proposed to-be-marketed formulation was used in the pivotal clinical trial, bioequivalence data is not needed.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

In order to ensure that drug product dissolution rate is not limited by solubility during the course of dissolution testing the solubility of the drug substance in the media should be

well in excess of the final concentration achieved following complete dissolution of the drug product. A solubility in excess of 5-fold of the final concentration is generally accepted as affording such "sink" conditions. In order to have a common method for dissolution testing of 25mg, 100mg and 150mg Tarceva™ tablets a media was sought that supported a solubility of at least — ıg/ml since this is five times greater than the concentration of — ˈmg/ml achieved when a 150mg tablet dissolves in . — ˈml of dissolution media. Dissolution profiles using a media of — and pH 4.5 and pH 6.8 buffers are not available since these media were unable to support sufficiently high concentrations of erlotinib hydrochloride and were not, therefore, evaluated. Likewise, solubility at pH 6.8 and in — suggested that USP simulated intestinal and gastric fluids would also be unsuitable and dissolution profiles are not available in these media.

The Table below (**FDA Table 21.**) summarizes the data submitted using the Applicant's desired dissolution conditions.

FDA Table 21. Dissolution Using — and — , Apparatus 2 (Paddle) @ —RPM, —				
LOT ID	**TABLET STRENGTH**	**Q =**	**Q =**	**Notable Changes Due To Q =**
	(mg)	**Pass @**	**Pass @**	
1	25	S1 @ 30 min	S2 @ 20 min	S2 testing to pass
2	25	S2 @ 20 min	S2 @ 30 min	
3	25	S2 @ 20 min	S2 @ 30 min	
4	25	S1 @ 30 min	S1 @ 45 min	
5	25	S2 @ 20 min	S2 @ 30 min	
6	25	S1 @ 30 min	S1 @ 30 min	
7	25	S1 @ 30 min	S1 @ 30 min	
8	100	S1 @ 30 min	S2 @ 20 min	S2 testing to pass
9	100	S1 @ 45 min	S1 @ 45 min	
10	100	S1 @ 45 min	S1 @ 45 min	
11	100	S2 @ 30 min	S2 @ 45 min	
12	150	S1 fail, S2 & S3 not performed	S1 fail, S2 & S3 not performed	
13	150	S1 fail, S2 & S3 not performed	S1 fail, S2 & S3 not performed	
14	150	S1 @ 45 min	S1 fail, S2 & S3 not performed	Unknown
15	150	S1 fail, S2 & S3 not performed	S1 fail, S2 & S3 not performed	
16	150	S1 @ 45 min	S2 @ 30 min	S2 testing to pass
17	150	S2 @ 30 min	S2 @ 45 min	
18	150	S2 @ 20 min	S2 @ 30 min	
19	150	S2 @ 45 min	S2 @ 45 min	
20	150	S2 @ 45 min	S2 @ 45 min	
21	150	S2 @ 20 min	S2 @ 45 min	

The Reviewer concludes that Figure X. supports that Q = — , rather than the Applicant's desired Q = — , is appropriate. Thus, we recommend a specification of Q = — , @ 45 minutes, — and — Apparatus 2 (Paddle) @ —RPM, —

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Tarceva film-coated tablets are available in three dosage strengths containing erlotinib HCl equivalent to 25 mg, 100 mg, and 150 mg of erlotinib free base. The 100 mg and 150 mg tablets are strength-proportional while the 25 mg strength contains the same excipients but has a greater excipient: drug substance ratio due to the increased amounts of tablet that afford a product of suitable size **(FDA Table 22., Applicant's Table 2-2).**

FDA Table 22., Applicant's Table 2-2.

Table 2-2: Tablet Composition – Tablet Core and Film Coat

Tablet Core				
Component	Function	25 mg mg/tablet	100 mg mg/tablet	150 mg mg/tablet
Erlotinib HCl	Active Ingredient	27.32	109.29	163.93
Lactose monohydrate				
Microcrystalline Cellulose				
Sodium starch glycolate				
Magnesium stearate				
Total Weight		100.00	300.00	450.00

Film Coat				
Component	Function	25 mg mg/tablet	100 mg mg/tablet	150 mg mg/tablet
Tablet Core				
White				
Total Weight		105.00	315.00	472.50

Reference: Module 3 Section 3.2.P.1

A bioequivalence study was performed to compare the 25 and 150 mg tablet strengths.

OSI2716g, A Randomized, Open-Label Crossover Study of OSI-774 in Healthy Adult Volunteers to Evaluate the Absolute Oral Bioavailability of 150 mg Tablets and the Bioequivalence of 25 mg and 150 mg Tablets

This was a single center, open-label, randomized, crossover study. Healthy male and female adult subjects were randomized to 2 study arms, A and B, to test the relative bioavailability of the 25 and 150 mg Tarceva tablets (Arm A), and to determine the absolute oral bioavailability of the 150 mg Tarceva tablet (Arm B), respectively. All

treatments were administered after overnight fasting and with a 2-week washout period between treatments.

There were 37 evaluable subjects (16 male and 21 female) in Arm A of this study. The results, shown below in **FDA Table 23., Applicant's Table 2-4,** met the criteria for bioequivalence.

FDA Table 23, Applicant's Table 2-4

Table 2-4: Statistical Analysis of Bioequivalence Between Six 25-mg Tablets and One 150-mg Tablet of OSI-774 (Study Arm A)

	PK Parameters	Treatment	Ratio of the Geometric Least Squares Means (90% CI)
Erlotinib	C_{max}	6 x 25 mg	0.95 (0.88, 1.04)
	(ng/mL)	1 x 150 mg	
	$AUC_{0-\infty}$	6 x 25 mg	1.00 (0.96, 1.05)
	(ng * h/mL)	1 x 150 mg	

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

The NDA is not for a modified release formulation of an approved immediate product.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Unapproved products or altered approved products were not used as active controls,

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

There are no significant, unresolved issues related to in vitro dissolution or in vivo BA and BE.

2.6 Analytical section

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies.

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Review Section 2.6.4 will address the methods used to measure the moieties selected for analysis.

2.6.2 Which metabolites have been selected for analysis and why?

The NDA does not detail how the decision of what metabolites to measure was decided. The Reviewer speculates that the decision to measure only parent and OSI-420 was made based upon the results shown in **FDA Table 24., Applicant's Table 2-28**, which is reproduced below.

Study to Determine Metabolism/Excretion
248-006 An Open Study to Examine the Metabolism and Excretion of [14C]-OSI-774 (formerly CP-358,774) in Healthy Male Volunteers
This open label study was performed to examine the metabolic profile and routes of excretion of [14C]-erlotinib in healthy male volunteers. A single 100 mg oral dose of [14C]-erlotinib (100 μCi) was administered as a suspension to four healthy male subjects. Radioactivity in urine, feces, blood, and plasma was measured by liquid scintillation counting. Plasma concentrations of erlotinib and its major circulating metabolite, OSI 420, were quantified by a validated high performance liquid chromatography ultraviolet (HPLC-UV) assay.

FDA Table 24., Applicant's Table 2-28

Table 2-28: Metabolite Pattern in Human Plasma and Excreta

Sample	Plasma[1]	Urine[2]	Feces[2]	Total Excreta[3]
Erlotinib	82.8	0.29	1.0	1.2
OSI-413 (M13)	5.4 (both)*	0.01	1.7	1.7
OSI-420 (M14)		0.18	3.0	3.2
OSI-943 (M12)	nd	0.11	1.0	1.1
OSI-356 (M16)	0.7	0.01	9.6	9.6
OSI-493 (M6)	1.6	0.45	20.6	21.0
O-demethyl OSI-356 (M17)	nd	nd	3.2	3.2
O-demethyl OSI-493 (M2)	nd	0.13	4.7	4.8
sulfate of OSI-356 (M10)	nd	0.6	nd	0.6
Acids of OSI-413/420 (M11b,a) (OSIP629019AB, 20AB1)	4.2	2.2	27.2	29.4
Different glucuronides	nd	1.1	1.1	2.2
% of administered dose excreted[2]		5.3	75.1	80.4
Total recovery[3]		8.1	83.0	91.1

1) % of total radioactivity in plasma at 2 hours after single oral administration (100 mg)[248-006].
2) metabolites identified in excreta in % of dose [248-006].
3) mean cumulative excretion within 11 days after oral administration [248-006].
* OSI-420 and OSI-413 co-elute in the plasma bioanalytical method.
nd = not detected

The relative activity of erlotinib and selected metabolites is presented below as **FDA Table 25.**

FDA Table 25. *In vitro* activities of parent and metabolites		
	Inhibition of EGFR Tyrosine Kinase Activity: IC50 (nM)	Inhibition of Cellular EGFR Tyrosine Kinase Activity: IC50 (nM)
erlotinib	2	20
OSI-413	1.4	8
OSI-420	2.5	14
OSI-943	no data	24
	Table derived from Applicant's Tables 2.1 and 2.2, nonclinical summary, p 14	

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

"Total drug" was measured for all moieties. The basis for choosing to measure total drug was not presented in the submission.

At therapeutic concentrations of erlotinib, in vitro experiments show that binding proteins are not saturated (see **Section 2.2.5.4** of this review). This suggests that measurement of total drug is appropriate and may have been the basis of the Applicant's decision to measure total drug. However, plasma AAG concentration is a variable that explains inter-individual variability in pharmacokinetics (see **Section 2.3.1** of this review). This suggests that measurement of free drug may have been more appropriate than measurement of total drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

2.6.4.5 What is the QC sample plan?

The in vivo studies which contributed most significantly to pharmacokinetics decision making are listed below in **FDA Table 26.**

FDA Table 26. Primary In Vivo Clinical Pharmacology Studies

Study	Description of Study
OSI2716g	Relative BA of strengths, Absolute bioavailability
NP16793	ECG (QT)
BR.21	Population PK
BO16411	Population PK
OSI2298g	Population PK
NP16612	DDI: Ketoconazole
NP16638	DDI: Rifampicin

All of these studies used the same analytical method (Applicant's method designation is A2001159). The Applicant's Validation Summary for the method appears on pages 1305-1306 of the report for study OSI2716g and is reproduced below as **FDA Table 27**. The performance of the method during sample analysis for each of the individual studies listed above is included in **Appendix 4.2.** of this review. The method, and its performance during sample analysis for each of the studies listed in **FDA Table 26.** above, is adequate.

FDA Table 27., Applicant's Validation summary for Method A2001159

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24 pages Withheld from this section of the approval package consisted of draft labeling

Appendix 4.2 Clinical pharmacology and biopharmaceutics individual study review

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TABLES

Table 1. Summary of Batches Performed for OSI-774 in Human Plasma

Run ID[a]	Regression Status	Extraction Date	Description	Comment
1	Accepted	29-Jul-2003		OK
2	Accepted	30-Jul-2003		OK
3	Accepted	04-Aug-2003	Subjects 201,202,203	OK
4	Accepted	04-Aug-2003	Subjects 204,205	OK
5	Accepted	05-Aug-2003	Subjects 209, 211, 212	OK
6	Accepted	05-Aug-2003	Subjects 214,215,216	OK
7	Accepted	05-Aug-2003	Subjects 206,207,208	OK
8	Accepted	06-Aug-2003	Subjects 217,218,219	OK
9	Accepted	06-Aug-2003	Subjects 220,213,210	OK
10	Accepted	11-Aug-2003	Subjects 101,102,103	OK
11	Rejected	12-Aug-2003	Subjects 107,108,109	
12	Accepted	12-Aug-2003	Subjects 104,105,106	OK
13	Accepted	13-Aug-2003	subjects 110,111,112	OK
14	Accepted	13-Aug-2003	Subjects 116,117,118	OK
15	Accepted	13-Aug-2003	Subjects 113,114,115	OK
16	Accepted	14-Aug-2003	Subjects 119,120,121,122	OK
17	Accepted	14-Aug-2003	Subjects 123,124,125	OK
18	Accepted	18-Aug-2003	Subjects 126,127,128	OK
19	Accepted	19-Aug-2003	Subjects 132,133,134,135	OK
20	Accepted	19-Aug-2003	Subjects 129,130,131	OK
21	Rejected	20-Aug-2003	Subjects 140,141,142	
22	Accepted	20-Aug-2003	Subjects 107,108,109 and repeats	OK
23	Accepted	20-Aug-2003	Subjects 136,137,138,139	OK

Run ID*	Regression Status	Extraction Date	Description	Comment
24	Accepted	21-Aug-2003	Subjects 104,105,106	OK
25	Rejected	20-Aug-2003	Subjects 140,141,142	
27	Accepted	27-Aug-2003	Subjects 140,141 and 142	OK

* Absence of sequential batch numbering is due to the analysis of multiple analytes (OSI-774 and OSI-420)

Table 2. Summary of Batches Performed for OSI-420 in Human Plasma

Run ID[a]	Regression Status	Extraction Date	Description	Comment
1	Accepted	29-Jul-2003		OK
2	Accepted	30-Jul-2003		OK
3	Accepted	04-Aug-2003	Subjects 201,202,203	OK
4	Accepted	04-Aug-2003	Subjects 204,205	OK
5	Accepted	05-Aug-2003	Subjects 209, 211, 212	OK
6	Accepted	05-Aug-2003	Subjects 214,215,216	OK
7	Accepted	05-Aug-2003	Subjects 206,207,208	OK
8	Accepted	06-Aug-2003	Subjects 217,218,219	OK
9	Accepted	06-Aug-2003	Subjects 220,213,210	OK
10	Accepted	11-Aug-2003	Subjects 101,102,103	OK
11	Accepted	12-Aug-2003	Subjects 107,108,109	OK
12	Rejected	12-Aug-2003	Subjects 104,105,106	
13	Accepted	13-Aug-2003	subjects 110,111,112	OK
14	Accepted	13-Aug-2003	Subjects 116,117,118	OK
15	Accepted	13-Aug-2003	Subjects 113,114,115	OK
16	Accepted	14-Aug-2003	Subjects 119,120,121,122	OK
17	Accepted	14-Aug-2003	Subjects 123,124,125	OK
18	Accepted	18-Aug-2003	Subjects 126,127,128	OK
19	Accepted	19-Aug-2003	Subjects 132,133,134,135	OK
20	Accepted	19-Aug-2003	Subjects 129,130,131	OK
21	Rejected	20-Aug-2003	Subjects 140,141,142	
22	Accepted	20-Aug-2003	Subjects 107,108,109 and repeats	OK
23	Rejected	20-Aug-2003	Subjects 136,137,138,139	

Run ID[a]	Regression Status	Extraction Date	Description	Comment
24	Accepted	21-Aug-2003	Subjects 104,105,106	OK
25	Rejected	20-Aug-2003	Subjects 140,141,142	[redacted]
26	Accepted	26-Aug-2003	Subjects 136,137,138 and 139	OK
27	Accepted	27-Aug-2003	Subjects 140,141 and 142	OK

[a] Absence of sequential batch numbering is due to the analysis of multiple analytes (OSI-774 and OSI-420)

Table 3. Quality Control Sample Data (Between-Batch Precision and Accuracy) for OSI-774 in Human Plasma

Run Date	Curve Number	QC A ~ ng/mL	QC B ~ ng/mL	QC C ~ ng/mL	QC D ~ ng/mL	QC D4 ~ ng/mL
04-Aug-2003	3					
04-Aug-2003	4					
05-Aug-2003	5					
05-Aug-2003	6					
05-Aug-2003	7					
06-Aug-2003	8					
06-Aug-2003	9					
11-Aug-2003	10					
12-Aug-2003	12					
13-Aug-2003	13					
13-Aug-2003	14					
13-Aug-2003	15					
14-Aug-2003	16					

Run Date	Curve Number	QC A ng/mL	QC B ng/mL	QC C ng/mL	QC D ng/mL	QC D4 ng/mL
14-Aug-2003						
18-Aug-2003						
19-Aug-2003						
19-Aug-2003						
20-Aug-2003						
20-Aug-2003						
21-Aug-2003						
27-Aug-2003						
Mean						
%CV						
%Theoretical						
n						

NC = Not Calculated where n ≤ 2

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Table 3. Quality Control Sample Data (Between-batch Precision and Accuracy) for OSI-774 in Human Plasma (Heparin) (Set 1)

Batch	*QC A — ng/mL*	*QC B — ng/mL*	*QC C — ng/mL*	*QC D — ng/mL*
1				
2				
3				
Mean	3.15	27.44	433.15	2683.04
S.D.	0.18	0.37	6.83	49.87
%CV				
%Theoretical				
n	6	6	6	6

Table 4. Quality Control Sample Data (Between-batch Precision and Accuracy) for OSI-774 in Human Plasma (Heparin) (Set 2)

Batch	*QC A ng/mL*	*QC B ng/mL*	*QC C ng/mL*	*QC D ng/mL*	*QC D2 ng/mL*	*QC D4 ng/mL*
4						
5						
7						
8						
9						\
10						
12						
13	\	\	\	\		
14						
15						
16						
17						
18					\	\
19						
20						
21						
22						
23						
24						
25						

Batch	QC A ng/mL	QC B ng/mL	QC C ng/mL	QC D ng/mL	QC D2 ng/mL	QC D4 ng/mL
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						

Batch	QC A ng/mL	QC B ng/mL	QC C ng/mL	QC D ng/mL	QC D2 ng/mL	QC D4 ng/mL
47						
48						
49						
50						
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						
61						
62						
Mean	2.95	24.56	412.24	2541.73	2552.86	2627.61
S.D.	0.18	1.50	19.33	93.26	125.49	166.91
%CV						
%Theoretical						
n	113	114	114	114	16	26

* Lost in Processing

Table 5. Quality Control Sample Data (Between-batch Precision and Accuracy) for OSI-420 in Human Plasma (Heparin) (Set 1)

Batch	*QC A* — *ng/mL*	*QC B* — *ng/mL*	*QC C* — *ng/mL*	*QC D* — *ng/mL*
1				
2				
3				
Mean	2.92	25.48	150.04	795.13
S.D.	0.19	1.30	5.78	11.34
%CV				
%Theoretical				
n	6	6	6	6

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Table 6. Quality Control Sample Data (Between-batch Precision and Accuracy) for OSI-420 in Human Plasma (Heparin) (Set 2)

Batch	*QC A* — *ng/mL*	*QC B* — *ng/mL*	*OC C* — *ng/mL*	*OC D* — *ng/mL*	*QC D2* — *ng/mL*	*OC D4* — *ng/mL*
4						
5						
6						
7						
8						
10						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						

Batch	QC A — ng/mL	QC B — ng/mL	QC C — ng/mL	QC D — ng/mL	QC D2 — ng/mL	QC D4 — ng/mL
25	[					
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						]
45						

Batch	*QC A* — *ng/mL*	*QC B* — *ng/mL*	*QC C* — *ng/mL*	*QC D* — *ng/mL*	*QC D2* — *ng/mL*	*QC D4* — *ng/mL*
46						
47						
48						
49						
50						
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						
61						
62						
Mean	2.88	24.05	148.29	815.69	812.87	833.45
S.D.	0.14	1.28	6.17	31.81	42.03	32.82
%CV						
%Theoretical						
n	113	114	114	114	16	24

* Lost in Processing

Table 11-7 **Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Analyte OSI-774 in Range [ ] ng/mL* (Protocol BO16411)**

Curve Number	QC A	QC B	QC C	QC D
				ng/mL
RJV01				
RJV03				
RJV04				
RJV05				
Mean	3.38	27.1	450	2700
SD	0.165	1.16	11.7	66.9
CV%	[			]
N	8	8	8	8
%nom	[			]

Table 11-8 **Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Analyte OSI-774 in Range [ ] ng/mL' (Protocol BO16411)**

Curve Number	QC A	QC B	QC C	QC D
				ng/mL
SOY01				
SOY02				
SOY03				
SOY04				
SOY05				
SOY06				
SOY07				
SOY08				
SOY09				
SOY10				
SOY11				
SOY12				
SOY13				
SOY14				
SOY15				
SOY16				
SOY17				
Mean	3.12	25.4	425	2520
SD	0.202	0.948	11.5	85.0
CV%	[			]
N	34	34	34	34
%nom	[			]

Table 11-9 **Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Analyte OSI-774 in Range [ ] ng/mL[a] (Protocol BO16411)**

Curve Number	QC A	QC B	QC C	QC D
				ng/mL
TUZ01				
TUZ02				
TUZ03				
TUZ04				
TUZ05				
TUZ06				
TUZ07				
TUZ08				
TUZ09				
TUZ10				
TUZ11				
TUZ12				
TUZ13				
Mean	2.82	23.1	386	2490
SD	0.168	0.699	12.2	94.5
CV%	[			]
N	26	25	26	25
%nom	[			]

B - Lost in Processing

Table 11-10 Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Metabolite (OSI-420) in Range [ ] ng/mL (Protocol BO16411)

Curve Number	QC A	QC B	QC C	QC D
	[			] ng/mL
RJV01				
RJV03				
RJV04				
RJV05				
Mean	3.05	24.2	148	822
SD	0.106	0.662	2.77	14.1
CV%	[			]
N	8	8	8	8
%nom	[			]

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Table 11-11 Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Metabolite (OSI-420) in Range [ ] ng/mL* (Protocol BO16411)

Curve Number	QC A	QC B	QC C	QC D
	[			] ng/mL
SOY01				
SOY02				
SOY03				
SOY04				
SOY05				
SOY06				
SOY07				
SOY08				
SOY09				
SOY10				
SOY11				
SOY12				
SOY13				
SOY14				
SOY15				
SOY16				
SOY17				
Mean	2.96	24.3	151	821
SD	0.135	0.981	4.63	33.7
CV%	[			]
N	34	34	34	34
%nom	[			]

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Table 11-12 Precision and Accuracy from Quality Control Samples (Prepared in Human Plasma) for Metabolite (OSI-420) in Range [ ] ng/mL* (Protocol BO16411)

Curve Number	QC A	QC B	QC C	QC D
	[			] ng/mL
TUZ01				
TUZ02				
TUZ03	\	\	\	\
TUZ04				
TUZ05				
TUZ06				
TUZ07				
TUZ08				
TUZ09				
TUZ10				
TUZ11				
TUZ12				
TUZ13				
Mean	2.78	23.1	141	791
SD	0.122	0.698	3.97	30.7
CV%	[			]
N	26	25	26	25
%nom	[			]

B - Lost in Processing

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