CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206995Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	206995
Submission Type; Code	Type 5 –New Formulation or New Manufacturer
Applicant Name	AstraZeneca
Submission Dates	9/17/2014
Brand Name	Iressa
Generic Name	Gefitinib (ZD 1839)
Strength / Dosage Form	250 mg tablets
Proposed Indication	First-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
OCP Division	Clinical Pharmacology V
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1 EXECUTIVE SUMMARY

Gefitinib is an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase proposed for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations. The efficacy and safety of gefitinib were assessed in the Iressa Follow-Up Measure (IFUM) and Iressa Pan-Asia Study (IPASS) trials with a 250 mg daily dose regimen. In the IFUM trial, only Caucasian NSCLC patients with *EGFR*-sensitizing mutations were eligible, and the primary endpoint of objective response rate (ORR) was 69.8% (74 of 106 patients), which was similar to the ORR observed in the *EGFR* mutation-positive subgroup from the IPASS trial (71.2%), in which Asian patients with NSCLC were enrolled without regard to *EGFR* mutation status. A flat exposure-response (E-R) relationship for efficacy (response rate) was observed in the IFUM study. The most common adverse events (AEs) that occurred in at least 10% of patients in the IFUM study were rash, diarrhea, dry skin, nausea, vomiting, cough, and asthenia. Interstitial lung disease (ILD) was reported in 1 (1%) patient in IFUM (Caucasian) and 16 (2.6%) patients in IPASS (Asian).

In the Phase 2 Iressa Dose Evaluation in Advanced Lung cancer (IDEAL) I (D7913C00016) and II (D7913C00039) studies, a doubling of gefitinib dose (500 mg daily vs. 250 mg daily) resulted in an increase in treatment-related toxicities. In patients receiving 500 mg daily of gefitinib, dose reductions due to toxicity ranged from 8.8-10.4% compared to less than 1% in patients receiving 250 mg daily. An E-R analysis based on an observational study in Japanese NSCLC patients (V-15-33) indicated that a higher risk of ILD may be associated with higher exposure to gefitinib.

In a study of subjects with hepatic impairment due to cirrhosis, exposure to gefitinib was approximately 1.4-, 3.6-, and 2.7-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. In a study in healthy subjects, cytochrome P450 (CYP) 2D6 poor metabolizers (PMs) had 2.1-fold higher exposure to gefitinib compared to CYP2D6 extensive metabolizers (EMs). However, dose adjustment is not recommended in patients with hepatic impairment or in CYP2D6 poor metabolizers because exposures in each group overlapped in these studies and dose reduction due to toxicity was relatively low in the Phase 2 studies in NSCLC patients (~10%) when dose was doubled. Caution should be used when using gefitinib in patients with hepatic impairment due to cirrhosis or CYP2D6 poor metabolizers due to the potential increase of gefitinib exposure in these patients. However, PK parameters in CYP2D6 ultra-rapid metabolizers (UMs) remain uncharacterized. We recommend that the applicant conduct a study to characterize the pharmacokinetic properties of gefitinib in CYP2D6 UMs, who may be at risk for treatment failure because of low exposure. This recommendation will be submitted via IND 120992.

1.1 Recommendations

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

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1.2 Phase 4 Commitments

There is no post-marketing requirement (PMR) or post-marketing commitment (PMC) study recommended at this time.

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1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Mechanism of Action and Indication: Gefitinib is a small molecule inhibitor of EGFR tyrosine kinase. Gefitinib inhibits the proliferation of ovarian, breast, and colon cancer cells *in vitro* and demonstrates antitumor activity in a range of xenograft mouse models.

Gefitinib (250 mg daily) is proposed for the first-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have *EGFR* Exon 19 deletions or Exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Refer to the Clinical Review and the appended Genomics and Targeted Therapy Review for details.

Efficacy and Safety: The efficacy and safety of gefitinib were assessed in the IFUM and IPASS trials. In IFUM, only Caucasian NSCLC patients with *EGFR*-sensitizing mutations were eligible, and the primary endpoint of ORR, was 69.8% (74 of 106 of patients), which was similar to the ORR observed in the *EGFR* mutation-positive subgroup from the IPASS trial (71.2%), in which Asian patients with NSCLC were enrolled without regard to mutation status.

The AE profiles for gefitinib were consistent in the IFUM and IPASS trials. Most AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or less; the most common AEs occurring in at least 10% of patients in the IFUM study were rash, diarrhea dry skin, nausea, vomiting, cough, and asthenia. ILD, a known adverse event associated with gefitinib use was reported in 1 (1%) patient in the IFUM (Caucasian) study and 16 (2.6%) patients in IPASS (Asian).

Pharmacokinetics: In cancer patients, the absolute bioavailability of gefitinib is 59% with a T_{max} of 3-5 hours and the mean single-dose terminal half-life is approximately 41 hours. Gefitinib's steady state apparent volume of distribution is 1400 L, suggesting that it is extensively distributed into tissues. Plasma protein binding is approximately 91%, independent of concentration over the range of 50-8000 ng/ml. When administered to healthy volunteers under fed conditions, AUC increased by 37% and C_{max} by 32% compared to that under fasted conditions.

Metabolism and Drug Interactions: Gefitinib is extensively metabolized, and cytochrome P450 (CYP) 3A4 is the major enzyme contributing to metabolism of the parent drug. However, the major metabolite (M523595), which is present in plasma at similar concentrations as gefitinib, is produced exclusively through metabolism of gefitinib by CYP2D6.

In vivo drug interaction studies demonstrated that the strong CYP3A4 inhibitor itraconazole increased gefitinib AUC by 80% and C_{max} by 51% (following a 250 mg oral dose of gefitinib). No dose adjustment is recommended with co-administration of a strong CYP3A4 inhibitor based on the less than 1% dose reduction rate at 250 mg dose and 10% dose reduction rate at 500 mg daily dose observed clinically. The CYP3A4 strong inducer rifampicin decreased gefitinib AUC by 83% and C_{max} by 65% (following a 250 mg oral dose of gefitinib). The proposed labeling recommends that a dose increase from 250 mg daily to 500 mg daily should be considered when gefitinib is administered with a strong CYP3A4 inducer. Increased gastric pH (maintained at >5 with ranitidine and sodium bicarbonate if needed) reduced AUC by 47% (b) (4) FDA

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recommends avoiding concomitant use of proton pump inhibitors, if possible, and scheduling modifications when taking H_2-receptor antagonists or antacids concurrently.

Pharmacokinetics (PK) in Specific Populations: In clinical studies of gefitinib, age, race and body weight did not appear to affect exposure. Caucasian female patients tend to have higher exposure (~27%) to gefitinib than Caucasian male patients following a single 250 mg oral dose; however, this increase in exposure is not considered clinically important. Based on a study of subjects with hepatic impairment due to cirrhosis, exposure to gefitinib is approximately 1.4-, 3.6-, and 2.7-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. However, in subjects with hepatic impairment due to cirrhosis, the PK of gefitinib is highly variable, inconsistent with the degree of hepatic impairment, and exposures in each group overlapped. Considering the low dose reduction rate observed when gefitinib was administered at 2-fold higher than the recommended dose, no specific dose adjustment is recommended in patients with moderate-severe hepatic impairment due to cirrhosis. In a separate study in cancer patients with hepatic impairment secondary to liver metastases, gefitinib exposures were similar in patients with moderate and severe hepatic impairment due to liver metastases compared to patients with normal hepatic function.

Exposure-Response Relationship: Associations between gefitinib exposure and ILD and diarrhea occurrence were identified. No association between exposure and rash was demonstrated. The E-R relationship for response rate appeared to be flat in the target patient population in the IFUM study.

Pharmacogenomics: The IPASS trial was conducted in Asia in a clinically selected population of patients with adenocarcinoma that had never smoked or were light ex-smokers, comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy. *EGFR* mutation status was retrospectively determined in a subset of patients and used for exploratory analyses. In the overall population gefitinib showed a statistically significant advantage in progression free survival (PFS). Patients with *EGFR* mutation positive tumors had a median PFS of 9.5 months with gefitinib versus 6.3 months for carboplatin/paclitaxel (HR: 0.48; 95% CI: 0.36, 0.64; $p<0.0001$). In contrast, in patients without detectable *EGFR* mutations, PFS was significantly shorter for gefitinib (1.5 months) versus carboplatin/paclitaxel (5.5 months) treated patients (HR: 2.85; 95% CI: 2.05, 3.98; $p<0.0001$). The IFUM trial was a single-arm trial restricted to Caucasian patients with *EGFR*-mutation positive NSCLC without regard to clinical characteristics (e.g., smoking history or histological subtype). As reported by the applicant, the primary endpoint of ORR was 69.8%. In both IFUM and IPASS trials, most patients with *EGFR* mutation positive tumors had either exon 19 deletions or L858R substitution mutations. The number of patients with other *EGFR* mutations was very low to conclusively determine whether (or to what degree) *EGFR* mutations other than exon 19 deletions or L858R are sensitizing to gefitinib.

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Gefitinib is metabolized predominately by CYP3A4 and CYP2D6, with CYP3A5 also contributing. The applicant conducted two studies, D7913C00707 and D7913C00019, to evaluate the impact of *CYP3A5* and *CYP2D6* genotypes (and the predicted enzyme phenotypes), respectively, on gefitinib PK in healthy subjects. Genetic variants in CYP3A4, the main CYP isoform contributing to gefitinib biotransformation, were not evaluated by the applicant. *CYP3A5* genotype did not appear to impact gefitinib PK. Regarding CYP2D6, the area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 1430 ng*hr/mL in extensive metabolizers (EMs) vs. 3060 ng*hr/mL in poor metabolizers (PMs), representing a 2.1-fold increase ($p<0.05$ by ANOVA). However, the PK profiles in EMs and PMs were highly variable and overlapping. Moreover, dose reduction rates secondary to drug-related toxicities were low in patients who received 500 mg of gefitinib daily in Phase 2 trials; therefore, a recommendation for dose reduction in CYP2D6 PMs is not warranted.

Conclusion: Overall, the clinical pharmacology information presented in this NDA application is acceptable.

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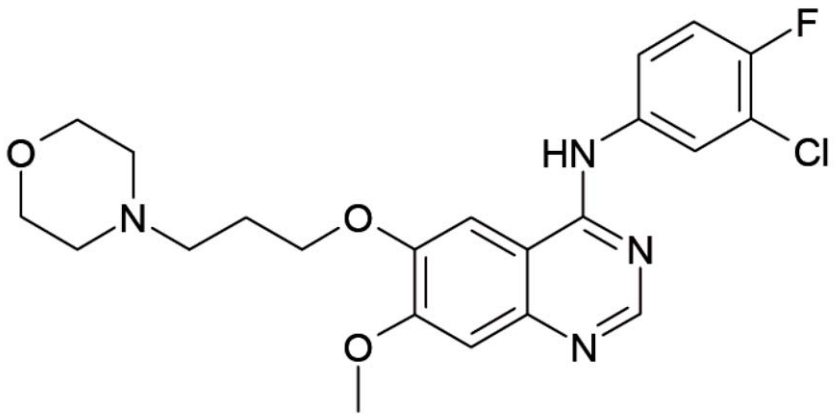
2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

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?

Drug substance

Appearance	Round, biconvex, brown film-coated tablets.
Chemical name	N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (IUPAC)
Molecular formula	$C_{22}H_{24}ClFN_4O_3$
Molecular weight	446.90
Structural formula	
Solubility	• pH dependent solubility • Relatively soluble at pH values below 4 (b) (4) • Insoluble in buffer at pH ≥7
pKa	Gefitinib is a basic molecule, with 2 pK_as of 5.42 and 7.24
Partition coefficients	Gefitinib is (b) (4) with a partition coefficient (log P_{ow}) of 4.15 (b) (4)

See Section 2.5.3 for discussion on effect of gastric pH elevating agents on the exposure of gefitinib.

Drug product

Gefitinib tablets are round, biconvex, brown film-coated tablets containing 250 mg of gefitinib. The excipients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium,

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povidone, sodium lauryl sulfate and magnesium stearate. The tablet coating contains (b) (4), polyethylene glycol 300, red ferric oxide, yellow ferric oxide, and titanium (b) (4).

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Gefitinib is a small molecule inhibitor of EGFR tyrosine kinase (IC_{50}=0.033μM in EGFR-over-expressing squamous carcinoma cells). Gefitinib inhibits the proliferation of ovarian, breast, and colon cancer cells *in vitro* and demonstrates antitumor activity in a range of xenograft mouse models.

Activation of EGFR leads to Ras activation, ultimately resulting in increased cell proliferation and survival. *EGFR*-activating mutations are present in approximately 10% of NSCLC cases in North America and Western Europe, and up to 50% of cases in patients of East Asian descent. The majority of these mutations are exon 19 deletions and a L858R substitution in exon 21, which together account for approximately 90% of *EGFR* mutations in NSCLC (PMID 17318210, 15118073).

The applicant is seeking approval of gefitinib for the first-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

2.1.3 What are the proposed dosages and routes of administration?

The proposed dose is 250 mg orally once daily with or without food.

2.2 General Clinical Pharmacology

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

Regulatory History

Gefitinib received accelerated approval in 2003 for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The initial approval was based on the results of the Phase 2 studies IDEAL I (D7913C00016, conducted primarily in Europe and Japan) and II (D7913C00039, conducted in the United States). The IDEAL studies demonstrated that the 250 mg daily dose was as effective as the 500 mg daily dose with regards to tumor response rates and disease-related improvements, disease control rate, PFS, and survival. However, the 500 mg daily dose was associated with higher rates of treatment-related adverse events. Therefore, the 250 mg dose was selected for approval and further study (See appended Clinical Pharmacology/Biopharmaceutics Review of the original NDA submission).

The clinical confirmatory trial of gefitinib (Iressa Survival Evaluation in Lung cancer (ISEL)) enrolled *EGFR* mutation-positive and -negative patients, and failed to demonstrate a benefit in NSCLC patients. Therefore, in June 2005 the indication was restricted to use in only those patients already receiving and benefitting from gefitinib, and in 2011 the NDA was voluntarily withdrawn. However, the applicant continued to investigate gefitinib in NSCLC patients, including the impact of *EGFR* mutations on gefitinib efficacy.

Major and Supportive Efficacy and Safety Trials

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The IFUM trial was an open-label, single-arm study of gefitinib 250 mg once daily as first-line treatment in Caucasian patients with *EGFR* mutation-positive NSCLC. Patients with *EGFR*-sensitizing mutations were eligible for the trial whereas patients with *EGFR* mutations reported to confer resistance to EGFR TKIs were ineligible. The primary endpoint ORR (objective response rate) was 69.8% (74 of 106 patients).

The IPASS trial was an open label, randomized, parallel group study that compared gefitinib to carboplatin/paclitaxel doublet chemotherapy in clinically-selected Asian patients with NSCLC. In the overall ITT population, gefitinib showed a statistically significant advantage in PFS (HR: 0.74; 95% CI: 0.65, 0.85; $p<0.0001$). However, a strong interaction was observed between *EGFR* mutation status and PFS such that patients treated with gefitinib who had *EGFR* mutation-positive tumors had a statistically significant improvement in PFS compared to carboplatin/paclitaxel whereas patients who had *EGFR* mutation-negative tumors had a statistically significant decrease in PFS when treated with gefitinib compared to carboplatin/paclitaxel.

Clinical Pharmacology Studies

A total of 32 studies were provided to support the Clinical Pharmacology and Biopharmaceutics section of the application (Table 1). Among them, a hepatic impairment study (D7913C00032) and pharmacogenetic study reports evaluating the impact of genetic variation in *CYP3A5* (D7913C00707) and *CYP2D6* (D7913C00019) are newly submitted after the previous NDA review.

Table 1. Clinical pharmacology and biopharmaceutics studies supporting the application.

Study	Title
Clinical Pharmacology Studies	
D7913C00001	A Phase I study to assess the safety, tolerability and pharmacokinetics of ascending oral doses of gefitinib in healthy male volunteers
D7913C00003	A Phase I study to assess the absorption, metabolism and excretion of a single oral dose of 50 mg [14C]-gefitinib in healthy male volunteers
D7913C00005	An open, Phase I, rising multiple-dose tolerability study of gefitinib in patients with solid, malignant tumours
D7913C00010	A Phase I study to assess the safety, tolerability and pharmacokinetics of repeated oral doses of gefitinib given daily over a 3-day period to healthy male volunteers
D7913C00011	A Phase I/IIa exploratory multiple-dose level pharmacokinetic and pharmacodynamic study of gefitinib in subjects with 5 selected tumour types known to over-express epidermal growth factor receptor (EGFR) (US)
D7913C00012	A Phase I/IIa exploratory multiple-dose level pharmacokinetic and pharmacodynamic study of gefitinib in subjects with 5 selected tumour types known to over-express epidermal growth factor receptor (EGFR) (Europe)
D7913C00016 (Trial 16)	A randomized, double-blind, parallel-group, Phase II, multicenter trial to assess the efficacy of ZD1839 (IRESSA™) 250 and 500 mg/day in patients with advanced non-small-cell lung cancer who have failed one or two previous chemotherapy regimens; at least one having contained platinum
D7913C00019	An open-label study to determine the pharmacokinetics of gefitinib and its major circulating metabolite (M523595) following a single 250 mg oral dose to healthy volunteers genotyped for CYP2D6
D7913C00022	A Phase I clinical study to evaluate high-dose gefitinib in patients with solid tumours
D7913C00027	A randomised, open-label, 2-way crossover, Phase I study to assess the effect of itraconazole, a CYP3A4 inhibitor, on the pharmacokinetics of gefitinib in healthy male volunteers

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D7913C00030	A randomised, open-label, 2-way crossover, Phase I study to assess the effect of rifampicin on the pharmacokinetics of a single oral dose of gefitinib in healthy male volunteers
D7913C00032	An open, non-randomised, multi-centre Phase I study to compare the pharmacokinetics and tolerability of gefitinib (IRESSA™) in patients with solid tumours and normal hepatic function, or moderately, or severely impaired hepatic function
D7913C00033	An open, randomised, single-centre study to assess the dose proportionality of single oral doses of gefitinib 50, 100, 250 and 500 mg in healthy male volunteers
D7913C00034	An open, 2-period, single-centre Phase I study to determine the multipledose pharmacokinetics of gefitinib following administration over a 14-day period to healthy male volunteers and to assess the effects of a loading dose regimen on the time to reach steady state
D7913C00036	An open, randomised, Phase I study to separately investigate the effect of food and the effect of an increase in gastric pH on the relative bioavailability of a 250 mg single oral dose of gefitinib in healthy male volunteers
D7913C00038	An open Phase I study to assess the inhibitory effect of gefitinib (IRESSA™) on CYP2D6, by comparing the pharmacokinetics of metoprolol (a CYP2D6 substrate) in the presence and absence of gefitinib, in patients with solid tumours
D7913C00039 (Trial 39)	A randomized, double-blind, parallel-group, Phase II, multicenter trial of two doses of ZD1839 (IRESSA™) in patients with advanced NSCLC who have previously received at least two chemotherapy regimens that contained platinum and docetaxel given concurrently or as separate treatment regimens
D7913C00051	A randomised, open-label, crossover, Phase I study to assess the effect of itraconazole, a CYP3A4 inhibitor, on the pharmacokinetics of gefitinib at doses of 250 and 500 mg in healthy male subjects
D7913C00208	An open-label, single-centre study to assess the intra-subject variability of the pharmacokinetics of gefitinib after single oral doses of the 250 mg tablet in healthy male subjects
D7913C00707	An open, pharmacogenetic pilot study to assess the cytochrome P450 3A5 genotype in healthy male volunteers previously exposed to gefitinib (IRESSA™)
D7913C00718	An open-label, multi-centre, parallel group, Phase I study to compare the pharmacokinetics of gefitinib 250 mg in patients with hepatic impairment and healthy volunteers
D7913C00719	A study to assess the metabolism and excretion of a single oral solution dose of 250 mg [14C]- gefitinib in healthy male and female subjects
V-15-11	A Phase I clinical study to investigate the safety of gefitinib in patients with solid tumours
V-15-33	A nested case-control study to determine the relative risk of and risk factors for interstitial lung disease in a cohort of NSCLC patients treated with and without gefitinib
D4200C00003	A Phase II, randomized, double-blind, 2-part, multicenter study to compare the efficacy of ZD6474 with the efficacy of ZD1839 (Iressa™) in patients with locally advanced or metastatic (IIIB/IV) non-small cell lung cancer after failure of either first-line and/or second-line platinum-based chemotherapy and to assess the activity of ZD6474 in patients following failure of treatment with ZD1839
KPX056	ZD1839: The measurement of ZD1839 metabolites in selected human plasma samples
KPX066	The measurement of ZD1839 metabolites M523595 and M537194 in human plasma samples from Study 1839IL/0032
Biopharmaceutics Studies	
D7913C00002	A randomised, open, 2-period crossover, Phase I study designed to investigate the effect of food on the bioavailability of the tablet formulation of gefitinib in healthy male volunteers
D7913C00028	An open, randomised, 2-way crossover Phase I study to characterise and compare the pharmacokinetic profile of gefitinib when given as a single dose as the brown, biconvex formulation tablet and the yellow, oval formulation tablet
D7913C00031	A randomized, single-center study to assess the absolute bioavailability (BA) of a single

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	oral dose of gefitinib in healthy male volunteers
D7913C00035	An open Phase I study to assess the absolute bioavailability of a 250 mg single oral dose of gefitinib in patients with solid tumours
D7913C00229	An open-label, randomised, single-centre Phase I study to determine the relative bioavailability of gefitinib 250 mg when administered as a tablet dispersion preparation (drink and tube administered) and tablet in healthy male subjects

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

In vitro studies demonstrated correlations between gefitinib concentrations and inhibition of tumor cell growth and inhibition of EGFR and mitogen-activated protein kinase (MAPK). Therefore, EGFR inhibition and MAPK inhibition were quantified in skin biopsies from gefitinib-treated patients in Phase 1 trials. Although EGFR activation and MAPK activation were reduced following gefitinib dosing, no significant correlations between gefitinib dose level and activated EGFR or MAPK were observed. Since gefitinib dose levels and concentrations were poorly correlated with these pharmacodynamic (PD) endpoints, clinical measures of safety were utilized in the selection of dose for the Phase 2 studies and both the 250 mg and 500 mg once daily doses were evaluated.

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

Eight metabolites of gefitinib have been identified in plasma. M523595 (O-desmethyl gefitinib) is the major circulating metabolite formed exclusively through metabolism of gefitinib by CYP2D6 and present in plasma at concentrations similar to gefitinib. M523595 had 14-fold less activity than the parent compound *in vitro*, and in a study of LoVo tumor bearing nude female athymic mice (KMN079) gefitinib administration resulted in statistically significant inhibition of tumor growth while administration of M523595 at doses resulting in similar plasma concentrations to gefitinib had no effect on tumor growth.

Plasma levels of all other metabolites (M537194, M295820, M387783, M527301, M594557, M605211, and M605212) were at least an order of magnitude lower than those of gefitinib. All of the metabolites analyzed (M295820, M387783, M523595, M527301 and M537194) were similar to gefitinib in potency of EGFR tyrosine kinase activity inhibition and selectivity towards EGFR tyrosine kinase compared to other tested kinases (erbB2, KDR, and FTKR). In contrast, all metabolites were less potent than gefitinib when tested for inhibition of EGF-stimulated cell growth. Five metabolites have been identified in fecal extracts. M523595 was the major metabolite in feces; however, it accounted for only 14% of the administered dose. Other metabolites identified in feces include M387783, M605207, M537194 and M605212.

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.

In Phase 1 studies, anti-tumor activity was observed over a range of 150-1000 mg per day. Doses of 250 mg and 500 mg daily were evaluated in Phase 2 trials (IDEAL I and IDEAL II); no apparent relationship between tumor response and dose or plasma concentrations was observed.

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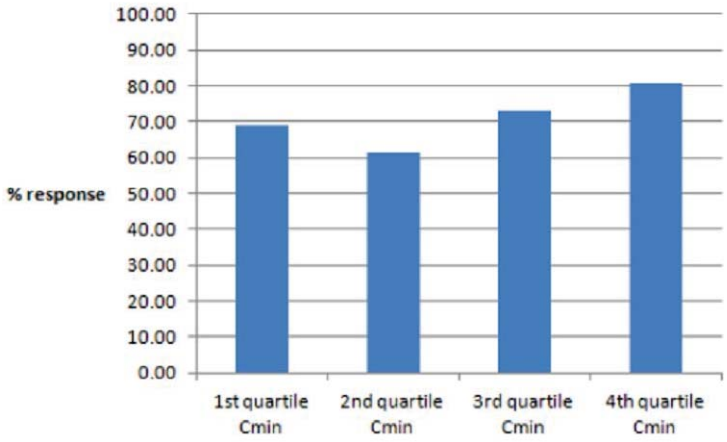
The E-R relationship for response rate in the registration IFUM study (n=103) is flat (Figure 1; see appended Pharmacometrics review for additional details).

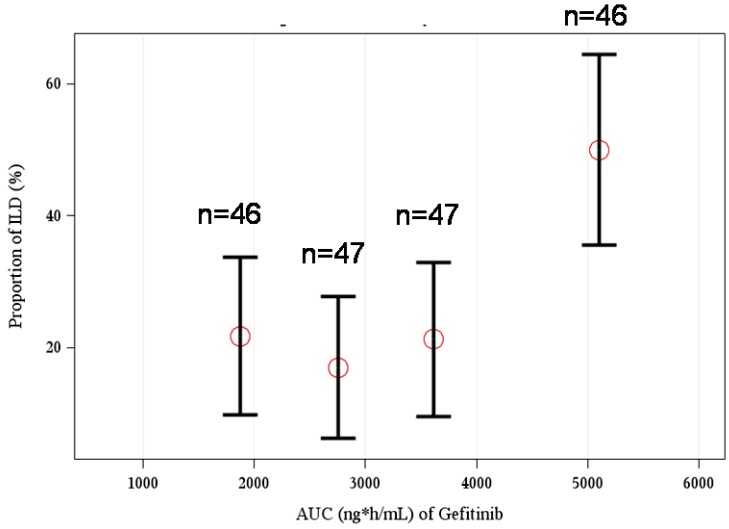
Figure 1. Flat E-R relationship for response rate in IFUM study.



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 most common drug-related adverse AEs observed in Phase 1 studies were skin and gastrointestinal toxicities, which were dose related. In Phase 2 studies, more AEs and an increase in severity of AEs were observed with the 500 mg daily dose. An apparent association between exposure and ILD was identified in an E-R analysis based on an observational study (study code: V-15-33) where sparse PK samples were collected in advanced/recurrent Japanese NSCLC patients (n=186) with ILD and randomly selected patients without ILD (Figure 2; see appended Pharmacometrics review for additional details). No association between exposure and rash was demonstrated. The risk of diarrhea increased in patients with increasing exposure in the IFUM study (n=103).

Figure 2. Relationship between gefitinib exposure (by quartile) and ILD.



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2.2.4.3 Does this drug prolong QT/QTc Interval?

No thorough QT (TQT) study was conducted to evaluate the effect of gefitinib on the QT interval. The relationship between gefitinib concentration and QT measurements was assessed using data collected from study D4200C00003, a randomized double-blind, 2-part, multicenter, Phase 2 study comparing the efficacy of ZD6474 with the efficacy of gefitinib in subjects with locally advanced or metastatic NSCLC. The study report was evaluated by the review from the Interdisciplinary Review Team (QT-IRT) for QT Studies. According to the QT-IRT review, no large change (i.e., > 20 ms) in the QTcF interval was detected when multiple doses of 250 mg gefitinib was administrated. The exposure range in the study is expected to cover the therapeutic exposures in the typical patient population. However, the exposure following 250 mg administration would not be expected to reach the exposure when gefitinib is administered with a strong CYP3A4 inhibitor. Please refer to the review from the QT-IRT review for more detailed information.

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?

In Phase 2 trials, the 250 mg daily dose of gefitinib was as effective as the 500 mg daily dose with regards to tumor response rates and disease-related symptom improvements, disease control rate, and PFS. However, dose-dependent AEs were observed in Phase 1 and Phase 2 studies, and an increase in the frequency and severity of AEs was observed with the 500 mg dose compared to the 250 mg dose. The dose regimen of 250 mg daily selected by the applicant is reasonable and supported by the relationships between dose/concentration and efficacy and safety.

A study report evaluating high-dose once-weekly and twice-weekly administration (starting at 1500 mg once- or twice-weekly) was submitted with the current NDA that was not previously reviewed (study report 7913C00022). High-dose gefitinib was evaluated to determine if higher concentrations could overcome gefitinib resistance. However, the study was stopped before the maximum tolerated dose was reached because the applicant concluded that gefitinib exposure did not increase with increasing dose for either the once- or twice-weekly dosing schedule beyond that determined for the starting dose of 1500 mg.

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

2.2.5.1 What are the PK characteristics of the drug?

In cancer patients, the absolute bioavailability of gefitinib is 59%, with a T_{max} of 3-5 hours and the mean single-dose terminal half-life is approximately 41 hours. Exposures achieved in cancer patients are higher than those achieved in healthy volunteers and the half-life for the majority of individuals in both groups is between 20 and 60 hours. Gefitinib's steady state apparent volume of distribution is 1400 L, suggesting that it is extensively distributed into tissues. Plasma protein binding is approximately 91%, independent of concentration over the range of 50-8000 ng/ml. When administered to healthy subjects under fed conditions at dose of 250 mg, AUC was 37% higher and C_{max} was 32% higher compared to fasted conditions. Based on data from CYP2D6 extensive metabolizers in Study Report 7913C00019, the major metabolite M523595 has a T_{max} of approximately 3 hours, C_{max} of 71 ng/mL, and a half-life of 19 hours, all of which are similar to the parent drug in healthy subjects.

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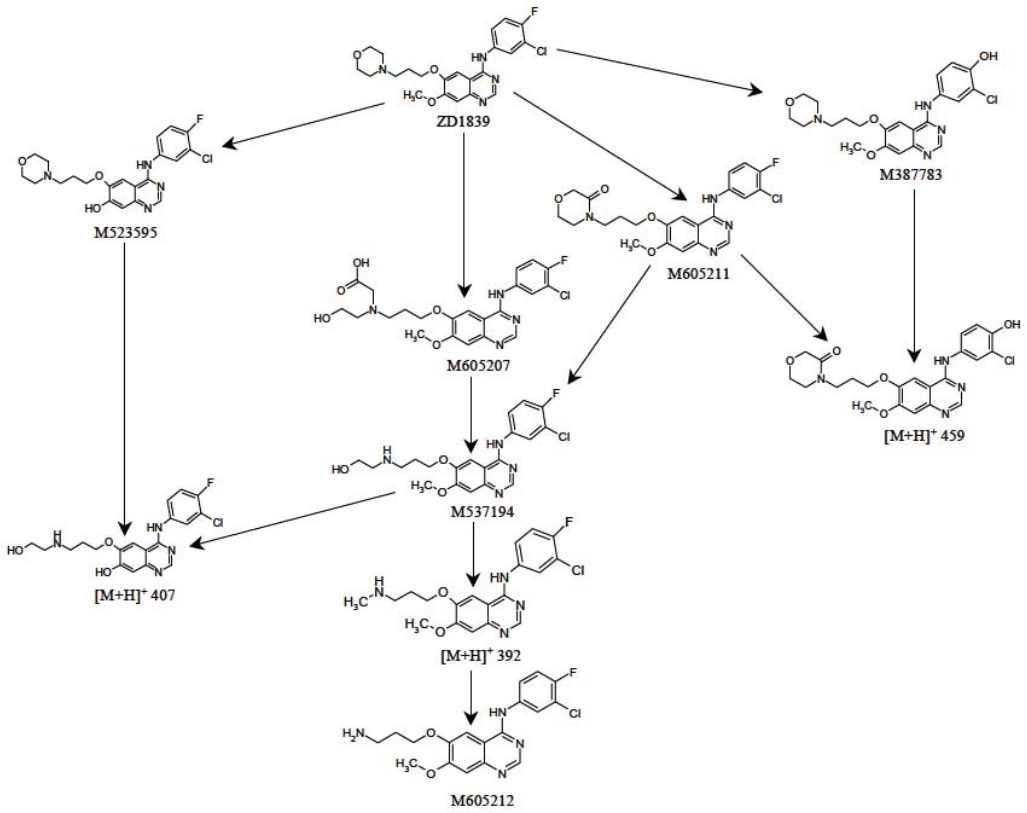
2.2.5.2 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Following oral administration of 250 mg [^{14}C]-gefitinib, 80.8% of radioactivity was recovered in feces and 3.6% of radioactivity was recovered in urine. Only 4% of the dose recovered in feces was unchanged gefitinib, indicating that gefitinib is extensively metabolized in humans. *In vitro* studies indicate that gefitinib is predominately metabolized by CYP3A4 and CYP2D6 with CYP3A5 also contributing. The levels of radioactivity detected in plasma were very low, and did not allow the use of standard methods of metabolite profiling. The proposed metabolic pathway of [^{14}C]-gefitinib is shown in Figure 3.

Figure 3. Proposed metabolic pathway of [^{14}C]-gefitinib in humans.



Source: Applicant's Figure 6, D7913C00719

2.2.5.3 What are the characteristics of drug metabolism?

Gefitinib is extensively metabolized, and CYP3A4 is the major enzyme contributing to metabolism of the parent drug. However, the major metabolite (M523595), which is present in plasma at similar concentrations as gefitinib, is produced exclusively through metabolism of gefitinib by CYP2D6. Seven other metabolites (M537194, M295820, M387783, M527301, M594557, M605211, and M605212) were identified in plasma at significantly lower concentrations.

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

In cancer patients, gefitinib exhibits linear PK over the oral dose range of 50-400 mg daily; however, over the dose range of 50-700 mg daily, gefitinib exhibits non-linear PK.

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

Following chronic daily dosing, steady state plasma concentrations are approximately 2-fold higher than those observed after single-dose administration in both patients and healthy subjects.

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

Gefitinib PK is highly variable in both healthy individuals and patients, with AUC values typically covering a 20-fold and 8-fold range, respectively. In a dedicated study of healthy male subjects to assess intra-subject variability (D7913C00208), the intra-subject range was up to 2-fold for AUC and up to 3-fold for C_{max}; however, the half-life appeared consistent within each subject. In the same study, the inter-subject variability (coefficient of variation) for AUC was 66-67% and for C_{max} was 52-55% across treatment periods.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

In clinical studies of gefitinib, age, race and body weight did not appear to affect exposure. Caucasian female patients tend to have higher exposure (~27%) to gefitinib than Caucasian male patients following a single 250 mg oral dose. This increase in exposure is not considered clinically important and dose reduction is not required in female patients.

In the current NDA submission, a hepatic impairment study (D7913C00032) and pharmacogenetic study reports evaluating the impact of genetic variation in *CYP3A5* (D7913C00707) and *CYP2D6* (D7913C00019) were submitted that were not reviewed in the original NDA submission. The results of the hepatic impairment study and the *CYP2D6* analysis are included in the proposed labeling; however, no recommendations for dose adjustments are made based on these results.

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?

No specific dosage adjustments are recommended based on age, body weight, gender, ethnicity, renal function, hepatic function, or genetic polymorphisms in the applicant's proposed labeling. Data submitted by the applicant shows that subjects with moderate-severe hepatic impairment secondary to cirrhosis have approximately 3-fold higher exposure to gefitinib than subjects with normal liver function, CYP2D6 PMs have approximately 2-fold higher exposure to gefitinib than CYP2D6 EMs, and co-administration of a strong CYP3A4 inhibitor increases exposure to gefitinib nearly 2-fold. However, the PK of gefitinib is highly variable, and exposures in each group overlapped. Based on the low dose reduction rate of 10% observed in Phase 2 trials with

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doubling gefitinib dose (500 mg daily), no specific dose adjustment is recommended in patients with moderate-severe hepatic impairment, CYP2D6 PMs, or with co-administration of strong CYP3A4 inhibitors.

2.3.2.1 What is the status of pediatric studies and/or any pediatric plan for study?

A Phase 1 dose-escalation study was conducted by the Children's Oncology Group in 25 patients younger than 22 years of age with solid malignant tumors and reported in the literature (PMID 16135484) and submitted in the NDA with no data provided. The starting dose was 150 mg/m^2, with subsequent escalation to 300, 400, and 500 mg/m^2 of gefitinib to establish the maximum tolerated dose (MTD). Patients were dosed once daily continuously until disease progression or significant toxicity. Patient characteristics are provided in Table 2 (from PMID 16135484); of the 25 patients enrolled, 17 had evaluable data.

Table 2. Patient characteristics from pediatric PK study.

Characteristic	Number (%)
Age, years Median (range)	 14.8 (1.8-21.2)
Sex Male Female	 10 (40) 15 (60)
Race White Black Asian Other	 18 (72) 2 (8) 2 (8) 3 (12)

No dose limiting toxicity was observed in patients in the 150 or 300 mg/m^2/day dose groups. The MTD was determined to be 400 mg/m^2/day. A summary of the PK parameters for each dose level (from samples collected on day 10, 11, or 12 of course one) is provided in Table 3 (from PMID 16135484).

Table 3. Summary of the PK parameters for each dose level.

	Gefitinib Dose Group			
	150 mg/m^2/day	300 mg/m^2/day	400 mg/m^2/day	500 mg/m^2/day
N	3	3	6	5
C_{max} (ng/mL) Median (range)	831 (436-1158)	1223 (998-1334)	2210 (1187-3550)	2105 (1486-3875)
T_{max} (h) Median (range)	4.2 (2.0-6.0)	4.0 (1.1-4.0)	2.3 (2.0-8.3)	4.2 (2.0-8.3)
$T_{1/2}$ (h) Median (range)	16.4 (9.8-21.3)	8.9 (7.9-22.8)	11.9 (5.6-14.2)	10.9 (5.9-13.6)
CL/F (L/h/m^2) Median (range)	12.8 (4.8-24.8)	14.8 (3.8-24.0)	15.6 (8.4-18.9)	13.1 (5.1-22.2)
AUC_{0-24h} (µg.h/mL) Median (range)	12.9 (6.8-19.5)	19.2 (12.5-32.3)	29.3 (20.4-50.9)	33.8 (22.7-81.4)

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A second Children's Oncology Group study was conducted to assess the MTD of gefitinib when administered in combination with irinotecan in children with refractory solid tumors and reported in the literature (PMID 19687340) and submitted in the NDA with no data provided. The study enrolled 29 patients who were given irinotecan IV at 15 or 20 mg/m^2 for 5 days of 2 consecutive weeks and oral gefitinib concomitantly at 150 or 112.5 mg/m^2 for 12 or 21 days. A single oral dose of irinotecan was given on day 9 of course 2 for PK analysis. The MTD of the combination regimen was 15 mg/m^2/day of irinotecan and 112.5 mg/m^2/day of gefitinib for 12 days. The bioavailability of oral irinotecan was increased 4-fold in the presence of gefitinib compared to historical controls (median 0.09 vs. 0.42; p<0.000001).

(b) (4)

[redacted]

2.3.2.2 Hepatic impairment (Refer to Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, http://www.fda.gov/cder/guidance/3625fnl.pdf .)

The applicant conducted a dedicated study to evaluate the PK of gefitinib in subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment due to cirrhosis compared to control subjects with normal hepatic function (D7913C00718). A total of 10 subjects per group received a single 250 mg dose of gefitinib and plasma concentrations of gefitinib and O-desmethyl gefitinib were determined for 10 days following dosing. The geometric mean exposure to gefitinib was approximately 1.4-, 3.6, and 2.7-fold higher in subjects with mild, moderate, and severe impairment, respectively, compared to control subjects (Table 4). A 2-fold increase in AUC could not be ruled out for the mild, moderate or severe hepatic impairment groups compared to healthy controls (Table 5). Consistent with the increase in exposure, the C_{max} was numerically higher and the half-life was numerically longer in the mild, moderate, and severe hepatic impairment groups compared to controls (Table 4). However, the PK of gefitinib was highly variable, and exposures in each group overlapped. Based on the low dose reduction rate of 10% observed in phase 2 trials with doubling gefitinib dose (500 mg daily), no specific dose adjustment is recommended in patients hepatic impairment due to cirrhosis.

Table 4. Plasma pharmacokinetic parameters of gefitinib.

	Degree of Hepatic Impairment			
Parameter	Normal (n=10)	Mild (n=10)	Moderate (n=10)	Severe (n=10)
AUC (ng.h/mL)	1415 (80.71)	1980 (115.7)	5137 (44.51)	3768 (103.9)
C_{max} (ng/mL)	57.45 (99.53)	82.75 (109.7)	155.7 (52.85)	69.56 (78.76)
T_{max} (h)[a]	4 (2 to 8)	5 (2 to 6)	2 (1 to 10)	3 (1 to 48)
$t_{1/2}$ [b] (h)	23.83 (8.897)	32.13 (15.05)	47.91 (16.21)	47.35 (19.83)
CL/F (mL/min)	2944 (80.71)	2105 (115.7)	811.1 (44.51)	1106 (103.9)

Data from applicant's Table 12 (study report d7913c00718)
Data presented as geometric mean (coefficient of variation (CV%)) unless noted
[a] data presented as median (range)
[b] data presented as mean (standard deviation (SD))

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Table 5. Statistical analysis of plasma AUC of gefitinib.

Group	N	gMean AUC (ng.h/ml)	Ratio	Upper 1-sided 95% CI
Normal	9[a]	1415	N/A	N/A
Mild	10	1980	1.399	2.510
Moderate	10	5137	3.629	6.514
Severe	10	3768	2.662	4.777

Data from applicant's Table 11 (study report d7913c00718)
[a]AUC was not calculable for subject 20 in the normal subject group
gmean, geometric mean; CI, Confidence interval; N/A, Not applicable; Ratio, Ratio of geometric mean AUC for hepatically impaired patients: geometric mean AUC for normal subjects

A separate study (1839IL/0032) was conducted to evaluate the effect of hepatic impairment secondary to liver metastases on gefitinib PK. Patients with solid malignant tumors refractory to other treatments were enrolled to obtain at least 12 evaluable patients with normal hepatic function and 12 with moderate hepatic impairment, plus up to 6 patients with severe hepatic impairment (recruited only after gefitinib was demonstrated to be safe in patients with moderate hepatic impairment). Hepatic impairment was based on baseline CTC grades for aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin. A loading dose of 250 mg oral gefitinib twice daily was given on Day 1, followed by 250 mg daily for 27 additional days. Evaluable data were obtained from 14 patients with normal hepatic function and 13 patients with moderate hepatic impairment, plus 4 patients with severe hepatic impairment. The primary endpoint was $AUC_{24h}ss$. Overall, PK parameters were similar in patients with moderate and severe hepatic impairment secondary to liver metastases compared to patients with normal hepatic function (Table 6 and Table 7).

Table 6. PK parameters of gefitinib at steady state.

	Degree of Hepatic Impairment Secondary to Liver Metastases		
Parameter	Normal (n=14)	Moderate (n=13)	Severe (n=4)
AUC_{24}^{ss} (ng.h/mL)	8896 (55.13)	9553 (66.01)	6226 (23.82)
C_{max}^{ss} (ng/mL)	466.4 (52.64)	517.7 (66.47)	371.8 (23.45)
T_{max} (h)[a]	5.00 (2.98 to 7.17)	3.00 (1.00 to 9.25)	2.00 (1.00 to 7.00)
CL/F (mL/min)	472.1 (54.81)	444.9 (63.79)	669.2 (23.89)

Data from applicant's Table II (study report 1839IL/0032)
Data presented as geometric mean (coefficient of variation (CV%)) unless noted
[a] data presented as median (range)

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Table 7. Statistical analysis of plasma AUC_{24}^{ss} of gefitinib.

Group	N	gMean AUC (ng.h/ml)	Ratio	Upper 1-sided 95% CI
Normal	14	8896	N/A	N/A
Moderate	13	9553	1.07	1.55

Data from applicant's Table I (study report 1839IL/0032)
gmean, geometric mean; CI, Confidence interval; N/A, Not applicable; Ratio, Ratio of geometric mean AUC_{ss} for hepatically impaired patients secondary to liver metastases: geometric mean AUC for patients with normal hepatic function.

2.3.2.3 Does genetic variation in drug metabolizing enzymes impact gefitinib PK?

Gefitinib is metabolized predominately by CYP3A4 and CYP2D6, with CYP3A5 also contributing. Genetic variants in *CYP3A4*, the main CYP isoform contributing to gefitinib biotransformation, were not evaluated by the applicant. However, the applicant conducted studies to evaluate the impact of *CYP2D6* and *CYP3A5* genotypes (and the predicted enzyme phenotypes) on gefitinib PK in healthy subjects. *CYP3A5* genotype did not appear to impact gefitinib PK. Regarding CYP2D6, overall, PK parameters exhibited significant variability, and the ranges overlapped between CYP2D6 EMs and PMs. The mean $AUC_{0-\infty}$ was 1430 ng*hr/mL in EMs vs. 3060 ng*hr/mL in PMs, representing a 2.1-fold increase ($p<0.05$ by ANOVA). However, the PK in both EMs and PMs was highly variable and exposures were overlapping. Based on the low dose reduction rate of 10% observed in Phase 2 trials with doubling gefitinib dose (500 mg daily), no specific dose adjustment is recommended in CYP2D6 PMs. See the appended Genomics and Targeted Therapy Review for more detailed information.

2.3.2.4 Is there a signal for gefitinib activity in patients whose tumors have EGFR mutations other than exon 19 deletions or L858R?

In the few patients whose tumors were positive for less common *EGFR* mutations (L861Q and G719X), gefitinib appears to have some activity; however, it is not conclusive if (or to what degree) these mutations are sensitizing to gefitinib. Inclusion of these data in labeling is an ongoing review issue. While labeling approaches are currently being discussed, it is the provisional opinion of the reviewer that the drug be indicated for populations for whom efficacy and safety have been established, with full description of trial results by mutation status in labeling. See the appended Genomics and Targeted Therapy Review for more detailed information.

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

There are no adequate and well-controlled studies assessing the safety and efficacy of gefitinib in pregnant women. Studies in animals have demonstrated reproductive toxicity; therefore, the proposed labeling recommends women of childbearing potential be advised to avoid becoming pregnant while being treated with gefitinib.

It is unknown whether gefitinib is excreted in human milk and there are no data from use of gefitinib in breast-feeding women. However, gefitinib is excreted into milk in rats. (b) (4)

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(b) (4)

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Effect of Other Drugs on Gefitinib

In vitro studies with human liver microsomes indicate that gefitinib is a substrate of CYP3A4. Therefore, the applicant conducted *in vivo* drug-drug interactions studies to evaluate the impact of strong CYP3A4 inhibitors and strong CYP3A4 inducers on gefitinib PK.

Study 1839IL/0051 evaluated the effect of itraconazole, a strong CYP3A4 inhibitor, on gefitinib PK in healthy male subjects (n=24 in each cohort). In Period 1, subjects received either 200 mg of itraconazole for 12 days, with a single 250 mg (Cohort 1) or 500 mg (Cohort 2) dose of gefitinib on Day 4, or only a single dose of gefitinib on Day 4. In Period 2, following a washout period, subjects crossed over to the treatment that they had not previously received (with a matching gefitinib dose). In the 250 mg cohort, $AUC_{0-\infty}$ was 80% higher and C_{max} was 51% higher in the presence of itraconazole. In the 500 mg cohort, $AUC_{0-\infty}$ was 60% higher and C_{max} was 33% higher in the presence of itraconazole. The proposed labeling does not recommend a dose reduction with co-administration of a strong CYP3A4 inhibitor, which is acceptable based on the low dose reduction rate of 10% observed in Phase 2 trials with doubling gefitinib dose (500 mg daily).

Study 1839/IL/0030 evaluated the effect of rifampicin, a strong CYP3A4 inducer, on gefitinib PK in healthy male subjects (n=18). Subjects received either 600 mg of rifampicin daily for 16 days, on Day 10 of which they received a 500 mg dose of gefitinib, or a single 500 mg dose of gefitinib. Following a washout period of at least 3 weeks, subjects crossed over to the treatment they had not previously received. In the presence of rifampicin, AUC was reduced 83% and C_{max} was reduced 65%. Therefore, administration of gefitinib with CYP3A4 inducers may decrease systemic exposure to gefitinib and reduce efficacy, and the proposed labeling recommends that a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction. FDA recommends resuming gefitinib at 250 mg 7 days after discontinuation of the strong CYP3A4 inducer.

Effect of Gefitinib on Other Drugs

In vitro studies also indicate gefitinib may have a potential to inhibit the metabolism of drugs that are substrates of CYP2C19 and CYP2D6. In an open-label study, cancer patients (n=18) were administered a 50 mg dose of metoprolol (a CYP2D6 substrate); followed by a washout period, gefitinib 500 mg daily was administered for 28 days and a second 50 mg dose of metoprolol was administered on Day 15 of gefitinib dosing. The AUC of metoprolol increased 35% during the gefitinib dosing period. The proposed labeling describes the change in metoprolol exposure in the presence of gefitinib.

See appended Clinical Pharmacology/Biopharmaceutics Review from the original NDA submission for more detailed review of extrinsic factors.

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

In study report D1839KMN081, included in the current NDA which has not been reviewed previously, the applicant assessed the bi-directional permeability of gefitinib (ZD1839) in P-gp-expressing Madin-Darby canine kidney (MDR-MDCK) cell monolayers to determine the potential of gefitinib to be a substrate or inhibitor of P-gp. Gefitinib concentrations of 0.1 μM, 1 μM, and 10 μM were used to determine the bi-directional (A-to-B and B-to-A) permeability in MDR-MDCK cell monolayers. Atenolol, pindolol, and propranolol were used as reference compounds representing low, moderate, and high permeability coefficient compounds, respectively, and cyclosporine A was used as an inhibitor of P-gp. Digoxin was used as a P-gp substrate to assess the potential of gefitinib to inhibit P-gp.

The bi-directional permeability results indicate that gefitinib is a P-gp substrate; however, at the 10 μM concentration gefitinib efflux appears to be reaching saturation (Table 8). In contrast, gefitinib did not appear to be a P-gp inhibitor as addition of 0.1 μM, 1 μM, and 10 μM of gefitinib to 10 μM of digoxin did not affect digoxin permeability (Table 9).

Table 8. Gefitinib bi-directional permeability with and without cyclosporine A in MDR-MDCK cells.

Treatment	Direction	*Average ZD1839 P_{app} ± STD (cm/sec, 10^{-6})	Ratio B-to-A/A-to-B P_{app}	*Average % Recovery ± STD
0.1 μM ZD1839	A-to-B	~ 0.7[#]		73.6 ± 0.2
	B-to-A	32.8 ± 0.4	~ 45.5[#]	56.0 ± 1.2
0.1 μM ZD1839 +10 μM CSA	A-to-B	5.1 ± 1.1		26.0 ± 1.7
	B-to-A	4.4 ± 0.3	0.9	46.3 ± 1.7
1 μM ZD1839	A-to-B	0.9 ± 0.2		77.6 ± 6.9
	B-to-A	46.1 ± 0.9	53.8	87.1 ± 1.4
1 μM ZD1839 +10 μM CSA	A-to-B	9.5 ± 0.1		41.0 ± 1.2
	B-to-A	7.0 ± 0.3	0.7	63.2 ± 5.6
10 μM ZD1839	A-to-B	3.6 ± 0.7		68.2 ± 4.7
	B-to-A	34.5 ± 2.2	9.5	101.8 ± 11.2
10 μM ZD1839 +10 μM CSA	A-to-B	19.3 ± 1.8		55.3 ± 1.0
	B-to-A	11.6 ± 0.6	0.6	70.0 ± 0.3

*Average values and standard deviations are from three replicates.

[#] The measured concentrations of ZD1839 in the receiver compartment were below the lowest limit of quantitation (LLOQ) of 2 nM. Therefore, A-to-B P_{app} values were calculated using the detected concentrations of ZD1839 and are reported as being approximately equal to obtained value. Consequently, the ratio of the B-to-A P_{app} versus A-to-B P_{app} is reported as being approximately equal to the calculated value.

Source: Applicant's Table 4; study report D1839KMN081

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Table 9. Digoxin bi-directional permeability with and without gefitinib in MDR-MDCK cells.

	Direction	*Average P_{app} ± STD (cm/sec, 10^{-6})	Ratio B-to-A/A-to-B	*Average % Recovery ± STD
Digoxin (10 μM) Control treatment	A-to-B	0.29 ± 0.01		95.8 ± 4.4
	B-to-A	10.92 ± 0.30	37.3	102 ± 1.2
Digoxin (10 μM) +ZD1839 0.1 μM	A-to-B	#0.20 ± 0.05		97.5 ± 4.1
	B-to-A	11.39 ± 0.97	56.0	99.5 ± 2.8
Digoxin (10 μM) +ZD1839 1 μM	A-to-B	0.21 ± 0.04		86.9 ± 18.6
	B-to-A	11.58 ± 0.31	56.5	105.8 ± 4.1
Digoxin (10 μM) +ZD1839 10 μM	A-to-B	0.47 ± 0.09		96.5 ± 9.5
	B-to-A	9.19 ± 0.55	19.7	105.8 ± 5.7

*Average values and standard deviations are from three replicates.
#One of the digoxin receiver samples at 60 minutes had a concentration that was below the LLOQ of 4 nM but was included in the analysis.

Source: applicant's Table 5; study report D1839KMN081

2.5 General Biopharmaceutics

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

According to the applicant, the permeability and absorption data support a Biopharmaceutical Classification System (BCS) category of Low Solubility-High Permeability (Class II); however, the absolute bioavailability of gefitinib is only 59% in cancer patients.

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

The major clinical studies utilized gefitinib 250 mg tablets which are qualitatively and (b) (4) identical to the proposed IRESSA 250 mg commercial tablet.

The relative bioavailability of gefitinib when administered as a tablet dispersion preparation (administered orally in a drink or via a nasogastric tube) compared to the tablet formulation was evaluated in healthy male subjects (study report D7913C00229). AUC and C_{max} were similar following administration of the tablet dispersion via drink (Table 10) or nasogastric tube (Table 11).

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Table 10. Statistical Analysis of AUC and Cmax for gefitinib: whole tablet vs. drink.

Parameter (units)	Tablet		Drink		Estimate of treatment ratio[a]	Lower 90% CL	Upper 90% CL	P-value
	n	glsmean	n	glsmean				
AUC (ng.h/ml)	18	2218.7	18	2233.1	1.006	0.876	1.156	0.9374
C_{max} (ng/ml)	18	95.2	18	96.3	1.012	0.864	1.185	0.8998

[a] Treatment ratio=Ratio of drink: whole tablet.
AUC Area under the plasma concentration-time curve from 0 to infinity.
CL Confidence limit.
C_{max} Maximum plasma concentration.
glsmean Geometric least squares mean.
n Number of volunteers.

Source: Applicant's Table 10, D7913C00229 Study Report

Table 11. Statistical Analysis of AUC and Cmax for gefitinib: whole tablet vs. nasogastric tube.

Parameter (units)	Tablet		Nasogastric tube		Estimate of treatment ratio[a]	Lower 90% CL	Upper 90% CL	P-value
	n	glsmean	n	glsmean				
AUC (ng.h/ml)	17	2202.4	17	2043.9	0.928	0.807	1.068	0.3725
C_{max} (ng/ml)	17	94.4	17	91.0	0.964	0.820	1.132	0.6982

[a] Treatment ratio=Ratio of nasogastric tube: whole tablet.
AUC Area under the plasma concentration-time curve from 0 to infinity.
CL Confidence limit.
C_{max} Maximum plasma concentration.
glsmean Geometric least squares mean.
n Number of volunteers.

Source: Applicant's Table 11, D7913C00229 Study Report

The results of the statistical analysis indicate that the AUC and C_{max} are similar when 250 mg of gefitinib is administered as a dispersion (via drink or nasogastric tube) compared to administration of the whole tablet. Instructions on how to prepare and administer the tablet dispersion are included in the proposed labeling for patients who have difficulty swallowing solids.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

The effects of food and increased gastric pH on gefitinib PK were evaluated in a study (d7913c00036) of healthy male subjects. A high-fat breakfast prior to drug administration increased AUC by 37% and C_{max} by 32% compared to fasted conditions following a single 250 mg oral dose of gefitinib. Gastric pH was increased by administration of ranitidine plus sodium bicarbonate if a pH of 5 or greater was not achieved and maintained for 8 hours following gefitinib dosing. Increased gastric pH reduced AUC by 47% and C_{max} by 71%.

The increase in exposure to gefitinib in the fed state is unlikely to be clinically significant and the proposed labeling recommends dosing with or without food, which is consistent with dosing in the IFUM and IPASS studies. FDA recommends avoiding concomitant use of proton pump

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inhibitors, if possible, and scheduling modifications when taking H_2-receptor antagonists or antacids concurrently.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

Gefitinib and its metabolites are identified and measured in plasma using high-performance liquid chromatography assay with tandem mass spectrometry (HPLC-MS/MS). The analytical assay for quantification of gefitinib was initially developed and validated at AstraZeneca UK Limited. During gefitinib development, an improved method was developed and eventually the assay was transferred to the Contract Research Organization [redacted] (b) (4) and then to [redacted] (b) (4) who performed validation of the assay (validation reference number [redacted] (b) (4) and cross-validation with the [redacted] (b) (4) method (validation reference number [redacted] (b) (4). A second assay for the determination of gefitinib and gefitinib-related metabolites was developed and validated at AstraZeneca UK (validation reference number [redacted] (b) (4)). An additional assay solely for the determination of gefitinib and O-desmethyl gefitinib (M523595) in human plasma was developed and validated by [redacted] (b) (4) (validation reference number D1839 KPV069) and the extraction procedure was eventually changed to liquid/liquid extraction in order to improve precision and accuracy of the assay (validation reference number D1839 KPV084).

For each study, the performance of the bioanalytical methods was monitored by the inclusion of quality control samples spanning the range of the standard curve in each analytical run during the analysis of study samples. The limit of quantitation and ranges of accuracy and precision based on the quality control samples from each study is shown in Table 12.

Table 12. Assay information and performance for detection and quantification of gefitinib in PK studies.

Study ID	Analyte	Reference	Calibration Range (ng/ml)	Accuracy (%)	Precision (%)
D7913C00001 (1839IL/0001)	Gefitinib	KPV014	0.5-100	95.0-98	11.5-14.2
D7913C00002 (1839IL/0002)	Gefitinib	KPV014	0.5-100	107-108	11.6-14.0
D7913C00003 (1839IL/0003)	Gefitinib	KPV014	0.5-100	90.0-110	11.8-16.1
	Metabolites	KPV052	2.0-1000	N/A	N/A
D7913C00005 (1839IL/0005)	Gefitinib	KPV014	0.5-100	95.5-117	13.2-18.1
	Metabolites	KPV052	2.0-1000	N/A	N/A
D7913C00010 (1839IL/0010)	Gefitinib	KPV014	0.5-100	99.0-111	11.4-12.1
D7913C00011 (1839IL/0011)	Gefitinib	KPV021	0.5-100	98.9-122	3.0-6.3
D7913C00012 (1839IL/0012)	Gefitinib	KPV021	0.5-100	97.2-116	5.3-7.5
D7913C00016 (1839IL/0016)	Gefitinib	KPV038	0.5-500	90.0-101	6.6-10.7
	Metabolites	KPV052	2.0-1000	N/A	N/A
D7913C00027	Gefitinib	KPV021	0.5-100	100-123	7.6-8.2

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(1839IL/0027)					
D7913C00028 (1839IL/0028)	Gefitinib	KPV049	0.5-100	93.0-107	5.9-9.1
D7913C00030 (1839IL/0030)	Gefitinib	KPV038	0.5-100	92.1-99.3	9.3-12.3
D7913C00031 (1839IL/0031)	Gefitinib	KPV021	0.5-100	99.0-109	4.7-6.4
D7913C00032 (1839IL/0032)	Gefitinib	KPV038	0.5-500	93.5-103	5.8-11.7
D7913C00033 (1839IL/0033)	Gefitinib	KPV021	0.5-100	93.6-117	3.6-7.4
D7913C00034 (1839IL/0034)	Gefitinib	KPV038	0.5-100	90.0-96.0	4.8-7.6
D7913C00035 (1839IL/0035)	Gefitinib	KPV038	0.5-500	91.0-98.4	6.4-13.1
D7913C00036 (1839IL/0036)	Gefitinib	KPV038	0.5-500	88.1-99.6	6.3-11.7
D7913C00038 (1839IL/0038)	Gefitinib	KPV038	0.5-100	96.0-111	4.0-10.3
D7913C00039 (1839IL/0039)	Gefitinib	KPV038	0.5-500	91.9-105	6.9-11.8
D7913C00051 (1839IL/0051)	Gefitinib	KPV038	0.5-500	90.8-100	4.7-12.8
V-15-11	Gefitinib	KPV014	0.5-100	94.3-112	10.8-16.9
	Metabolites	KPV052	2.0-1000	N/A	N/A
D7913C00208 (1839IL/0208)	Gefitinib	KPV057	0.5-500	94.3-97.5	2.9-8.8
D7913C00229 (1839IL/0229)	Gefitinib	KPV069	0.5-500	96.9-98.5	5.7-11.3
	M523595	KPV069	1-1000	95.2-106	8.5-12.5
D7913C00019	Gefitinib	KPV084	0.5-500	90.8-95.2	3.3-13.5
	M523595	KPV084	1-1000	97.2-106	8.2-10.8
D7913C00718	Gefitinib	KPV084	0.5-500	N/A	N/A
	M523595	KPV084	1-1000	N/A	N/A
D7913C00719	Gefitinib	KPV052	2.0-1000	104-115	5.7-9.9
	M523595	KPV052	5.0-1000	5.8-10.5	94.2-112
	M537194	KPV052	5.0-1000	5.8-12.9	103-114
V-15-33	Gefitinib	PBC65-73	0.5-100	89.7-101	0.2-10.3
D791AC00014	Gefitinib	KPV098	5.0-1000	100-102	3.2-8.1
D7913C00022	Gefitinib	KPV084	0.5-500	98.4-100	6.4-12.1

Source: Applicant's Table 9, Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.6.2 Which metabolites have been selected for analysis and why?

The main metabolite M523595 was analyzed in the clinical pharmacology studies that were performed later in the development of gefitinib. In the initial review of gefitinib (NDA 21399), FDA recommended that future clinical pharmacology studies should quantify plasma levels of M523595 because it has comparable exposure to the parent compound and similar *in vitro* potency for inhibition of EGFR tyrosine kinase activity.

2.6.3 For all moieties measured, is free, bound, or total measured?

The total quantity of gefitinib and its metabolites was measured in all studies.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3762549

4 APPENDICES

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3762549

4.1 Pharmacometrics Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

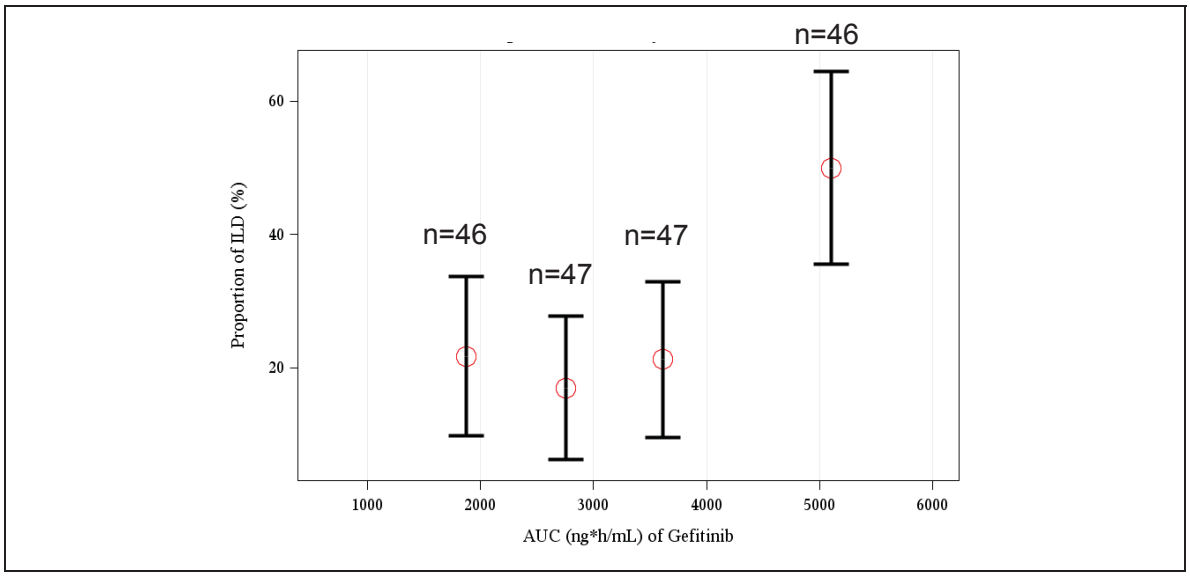
1.1.1 What are the characteristics of exposure-response (E-R) relationship for safety?

Association of gefitinib exposure with ILD, diarrhoea was identified. No association between exposure and rash was demonstrated.

E-R relationship for interstitial lung disease (ILD)

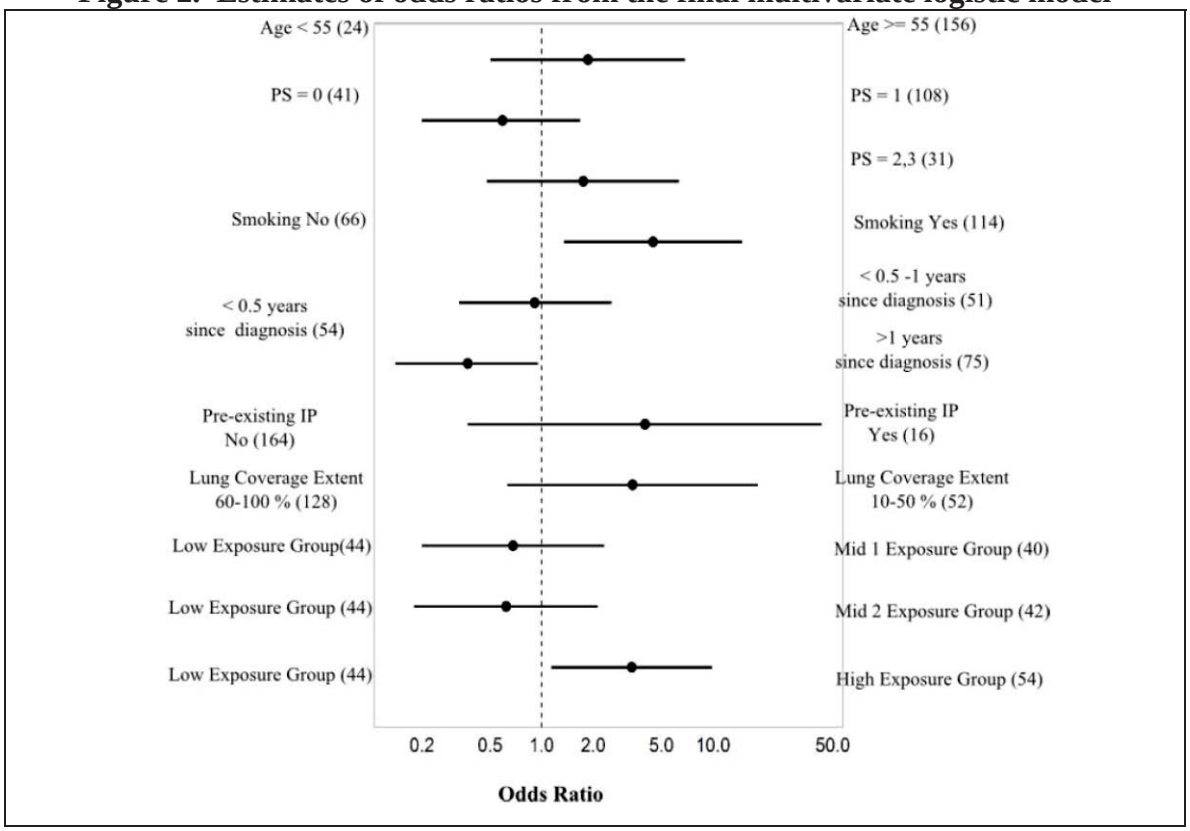
An apparent association between exposure and ILD was identified in E-R analysis based on an observational study (study code: V-15-33) where sparse PK samples were collected in advanced/recurrent Japanese NSCLC patients (n=186) with ILD and randomly selected patients without ILD. The objectives of this study were to determine the risk factors of ILD and assess the potential association between exposure and ILD. Exposure-response analysis showed that patients in the highest exposure group had 2 fold higher exposures and exhibited a higher ILD risk compared with the low exposure groups (Figure 1). Multivariate analysis also showed a similar trend of increasing ILD risk in patients in the highest exposure group after adjusting for other risk factors (Figure 2). While acknowledging the limitations of these exploratory analyses, we can't dispute this apparent association between exposure and ILD based on the available data.

Figure 1. The highest exposure group exhibited a higher ILD risk (n=186)



Reference ID: 3762549

Figure 2. Estimates of odds ratios from the final multivariate logistic model



Sources: Sponsor's Response to the Clinical Information Request from the FDA regarding the study report, "Population Pharmacokinetic Analysis With Non-Small Cell Lung Cancer In Nested Case-Control Study For Gefitinib (Study Code: V-15-33), Page 10.

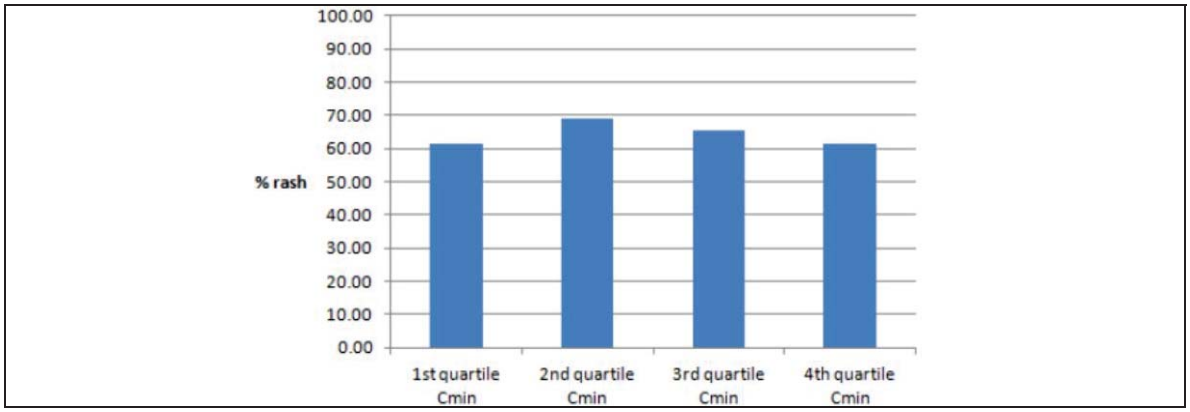
Despite a positive E-R relationship for ILD, diarrhoea, no dose adjustment is recommended in patients with moderate or severe hepatic impairment due to cirrhosis (See Section 2.3 in Clinical Pharmacology Review).

E-R relationship for Rash

No association between exposure and rash was identified in IFUM study (n=103) (Figure 3).

Reference ID: 3762549

Figure 3: Flat E-R relationship for rash in IFUM study

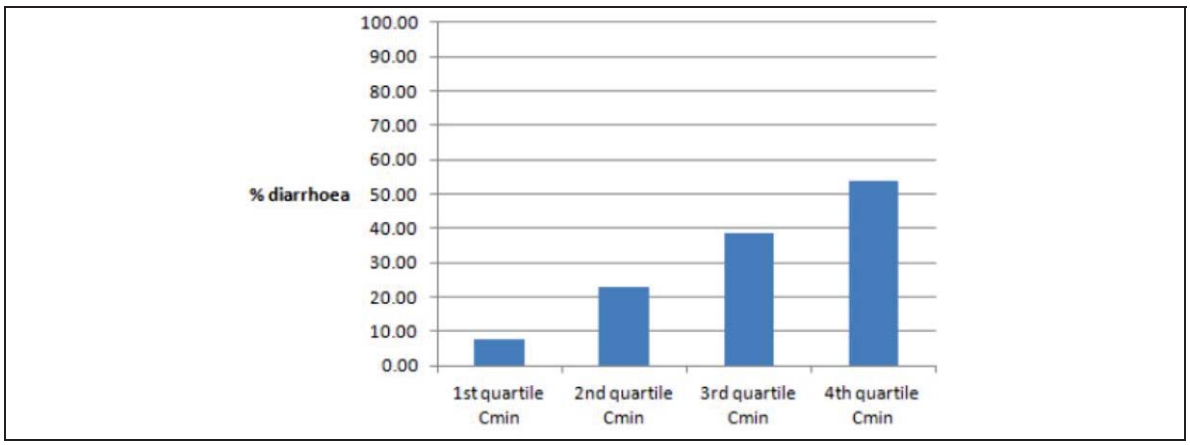


Sources: Sponsor's Population PK/PD report (D791AC00014), page 31

E-R relationship for diarrhoea

An association between exposure and diarrhoea was identified in IFUM study (n=103). The risk of diarrhoea increased in patients with increasing exposure (Figure 4).

Figure 4: Positive E-R relationship for diarrhoea in IFUM study



Sources: Sponsor's Population PK/PD report (D791AC00014), page 32

E-R relationship for other AEs

In Phase 2 studies, in patients receiving 500 mg of gefitinib the incidence of drug-related CTC Grade 3 or 4 adverse events were higher compared to patients receiving 250 mg of gefitinib daily. The increased adverse event rates led to dose reductions of 8.8-10.4% in patients in the 500 mg dose group compared to <1% for patients in the 250 mg dose group (Trial 16 and Trial 39). This suggests a positive E-R relationship for clinical relevant AEs.

Reference ID: 3762549

1.1.2 Is dose adjustment in patients with moderate and severe hepatic impairment (HI) due to cirrhosis warranted?

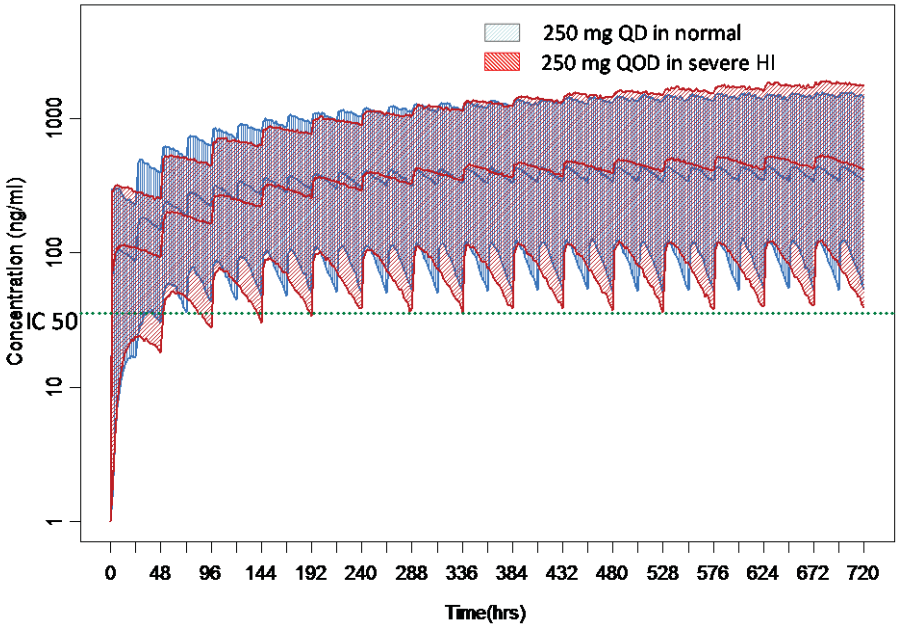
Despite a positive E-R relationship for ILD, diarrhea, no dose adjustment is recommended in patients with moderate or severe HI due to cirrhosis. PK profiles of 250 mg every other day (QOD) regimen, was evaluated in severe HI patients due to cirrhosis by PK simulations based on the findings in dedicated clinical pharmacology study (D7913C00718) (See Section 2.3 in Clinical Pharmacology Review). As shown in **Figure 5**, the median of concentration in normal subjects and patients with severe HI due to cirrhosis are comparable. However, the lower bound (i.e., 5 percentile) of trough concentrations in patients with HI following 250 mg QOD are 27% lower than those in normal subjects following 250 mg QD, largely due to the higher variability observed in patients with severe hepatic impairment (CV% of AUC: 104% in patients with severe hepatic impairment *vs* 81% in normal subjects). This result suggested a potential loss of efficacy in such patients with dose adjustment.

The PK simulations were based on the finding in dedicated clinical pharmacology study (D7913C00718). However, there is an uncertainty about the effect of hepatic impairment on PK due to the high PK variability and other conflicting results (See section 1.3 in clinical pharmacology review). Therefore, purpose of PK simulations was to illustrate the potential loss of efficacy in patients with severe HI following 250 mg QOD dose regimen assuming the dedicated clinical pharmacology study (D7913C00718) provided a reliable estimate of PK in patients with HI.

Given the potential loss of efficacy with dose reduction and acceptable safety profile at 500 mg QD observed in phase 2 studies (Trial 16 and Trial 39), no dose adjustment is recommended in patients with hepatic impairment.

Reference ID: 3762549

Figure 5: Comparison of PK profiles of 250 QD in normal subjects and 250 QOD in patients with severe hepatic impairment due to cirrhosis

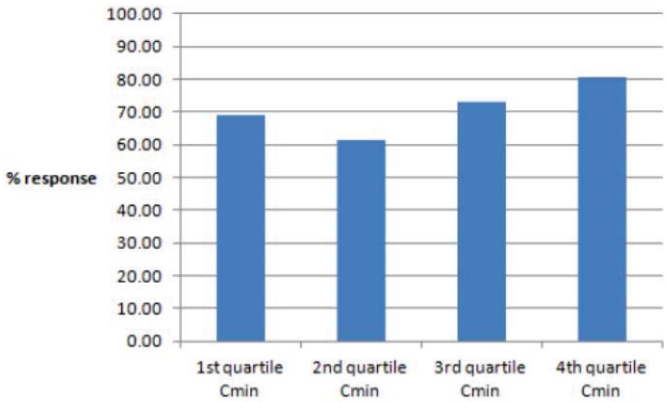


** shaded areas are the 90% simulation intervals with border lines representing 95 percentile, median, 5 percentile of concentrations over the time*
** green dashed line is IC50, the in vitro concentration that reduces the effect by 50% for the inhibition of epidermal growth factor (EGF) stimulated cell growth*

1.1.3 What is the characteristic of E-R relationship for efficacy in pivotal study (IFUM)?

The exposure-response relationship for response rate in pivotal IFUM study (n=103) is flat (Figure 6). This is consistent with the flat dose-response observed in Phase 2 studies (Trial 16 and Trial 39) where 500 mg and 250 mg dose group showed similar efficacy.

Figure 6: Flat E-R relationship for response rate in IFUM study



Reference ID: 3762549

Sources: Sponsor's Population PK/PD report (D791AC00014), page 29

1.1.4 What are the extrinsic and intrinsic factors affecting the PK of gefitinib based on population PK analysis?

Based on population PK analysis, age (37-87 years old), body weight (33-100 Kg), gender, ethnicity and creatinine clearance (26.5-151.6 mL/min) have no meaningful effect on the PK of gefitinib.

1.2 Recommendations

Information regarding the E-R relationship for ILD and diarrhea is recommended in the label.

1.3 Label Statements

See section 3 of Clinical Pharmacology Review

2 PERTINENT REGULATORY BACKGROUND

Gefitinib received accelerated approval from FDA as a 3rd line therapy for NSCLC (unselected) in 2003. In 2005 FDA restricted the indication to patients who in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment as gefitinib showed no survival benefit over the placebo in two studies. In 2009 EMA approved gefitinib "to treat adults who have NSCLC that is locally advanced or metastatic. It is used in patients whose cancer cells have a mutation in the genes that make a protein called epidermal-growth-factor receptor (EGFR)." In 2011 sponsor voluntarily withdrew the NDA. Sponsor is seeking a new indication in biomarker positive patient population in this current submission.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 E-R analysis for safety

3.1.1 ILD

E-R analysis for ILD was based on data collected from an observational study in advanced/recurrence NSCLC patients with ILD (case, n=51) and randomly extracted patients without ILD (control, n=135) from a defined cohort of advanced/recurrence NSCLC Japanese patients. One of the primary objectives of this observational study was to determine the main risk factors associated with its occurrence and to assess the potential association between exposure and occurrence of ILD in advanced/recurrence NSCLC patients treated with gefitinib. Graphical exploration by stratifying patients into exposure quartiles showed that patients in the highest quartile experienced around 2 fold higher ILD risk compared to the rest of patients with lower exposure (Figure 1). Furthermore, this finding was consistent with the results from multivariate logistic regression analysis after adjusting for the risk factors for ILD (Figure 2). Other analyses (i.e., sensitivity analysis) performed by FDA reviewer also reached same conclusion regarding the positive E-R relationship for ILD (See section 4 in this review).

Reference ID: 3762549

3.1.2 Rash and diarrhea

The E-R analysis for rash and diarrhea was graphically explored based on the data collected from the pivotal IFUM study (n=103). There appeared to be an association between exposure and diarrhea (Figure 4). No association was identified between exposure and rash (Figure 3).

3.2 E-R analysis for efficacy

E-R relationship for efficacy (response defined as partial or complete response) was graphically explored based on data from the pivotal study (IFUM, n=103). The E-R relationship for response appeared to be flat (Figure 6).

3.3 Population PK analysis

The population PK study (study code V-15-33) was conducted using 1891 plasma samples taken from 336 Japanese patients. The plasma concentrations of gefitinib were well described by a one compartment model with first order absorption and absorption lag time. Parameter estimates from the final model is provided in Table 1.

Reference ID: 3762549

Table 1. Final estimates of population PK model

Objective Function: -170.223

$$CL/f = 28.6 \times \left(\frac{AGP}{121}\right)^{-0.502} \times 0.759^{AGE\geq 65} \times 1.82^{IND} \times \left(\frac{WGT}{55.5}\right)^{0.503} \times 0.743^{PERI} \text{ (L/h)}$$

$$V/f = 1540 \times \left(\frac{AGP}{121}\right)^{-0.447} \times \left(\frac{WGT}{55.5}\right)^{0.766} \text{ (L)}$$

$k_a = 0.819$ (h^{-1})

$t_{lag} = 0.863$ (h)

Inter-individual variability (CV%)

$\omega_{CL/f} = 49.3\%$ $\omega_{V/f} = 38.5\%$ $\omega_{k_a} = 266\%$ $\omega_{t_{lag}} = 26.5\%$

Intra-individual variability (CV%)

$\sigma = 32.7\%$

Covariate (continuous variable)

- WGT: Body weight (kg)
- AGP: Serum α_1-AGP (mg/dL)

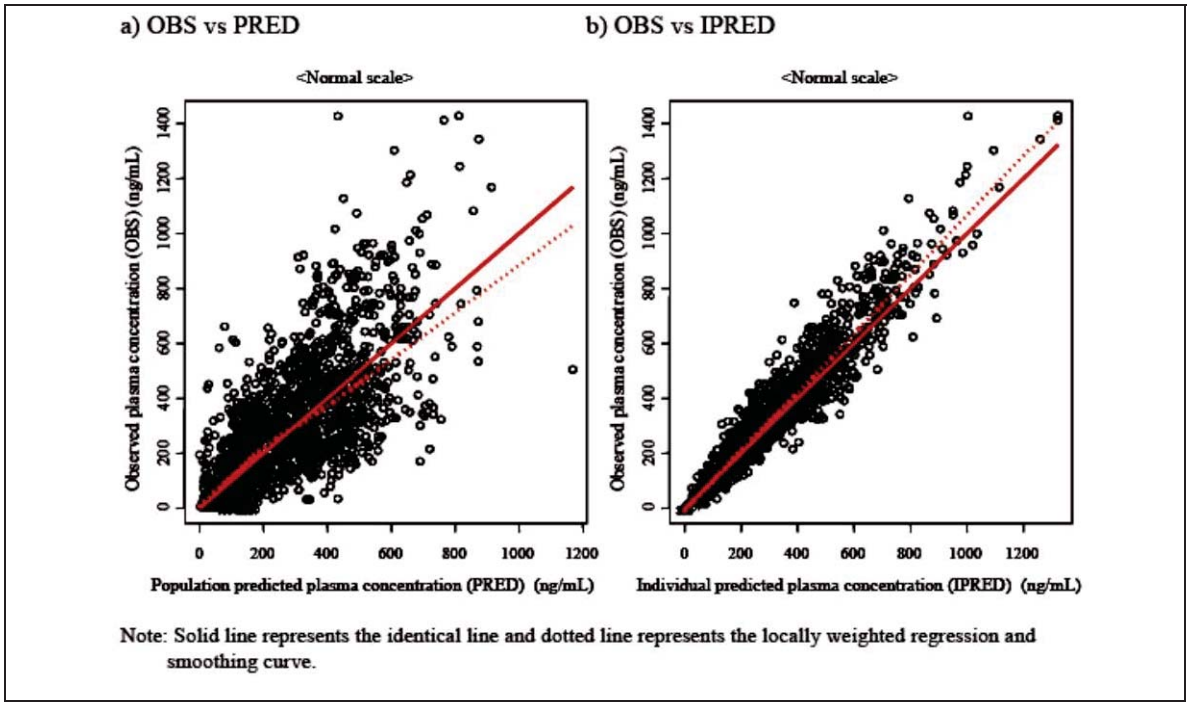
Factor (categorical variable)

- (AGE≥65)=0: <65 years old
  (AGE≥65)=1: ≥65 years old
- PERI=0: without ILD occurrence
  PERI=1: at ILD occurrence
- IND=0: without concomitant use of CYP3A4 inducers
  IND=1: with concomitant use of CYP3A4 inducers

Sources: Sponsor's population pharmacokinetic analysis report (study code V-15-33), page 26

Reference ID: 3762549

Figure 7: Diagnostic plots of final population PK model



Sources: Sponsor's population pharmacokinetic analysis report (study code V-15-33), page 27

Reviewer's comments:

1. The population PK model can adequately describe the observed PK data (Figure 7).

2. Although serum α1-AGP, body weight, age were identified as statistically significant covariate for the PK of gefitinib, however their effect on PK is not meaningful. Therefore, no dose adjustment is warranted with respect to these factors. Concomitant use of CYP3A inducers led to 45% reduction the exposure, which is in line with result from in vivo study. Dose increase to 500 mg is recommended (see section 1.3 in clinical pharmacology review).

3. A separate population PK analysis was conducted with PK data from Caucasian patients (n=103) in IFUM study. However, only few PK samples were collected during the first hours post-dose in IFUM study, therefore it can't provide reliable estimates for some PK parameters, such as the volume of distribution and the rate constant of absorption. The results from this population PK analysis suggested that gender was the only significant covariate. Other covariates identified in study code V-15-33 (n=336) were not significant covariates in IFUM study (n=103), possibly due to the smaller sample size in IFUM study. In IFUM study it appeared that females had higher exposure than males (trough concentration: 392 ng/ml vs. 280 ng/ml). However, such difference in exposure could be (partially) attributed to the body weight difference instead of genders.

Reference ID: 3762549

4 REVIEWER'S ANALYSIS

4.1 Introduction

Sponsor's E-R analysis was based on a subset of NSCLC patients (n=186) with PK collected in study V-15-33 (~6000 patients in the entire cohort). Therefore, the purpose of reviewer's analysis was to examine the robustness of the findings of E-R analysis when additional data is included.

4.2 Methods

E-R analysis

Additional data from 150 NSCLC patients was included to generate a pooled dataset containing 336 patients. Since information regarding the risk factors was not available for these added patients, only graphical exploration was performed to compare the ILD risk across different exposure quartiles.

PK simulations

PK simulations for 5000 subjects were performed using the population PK model (Table 1) constructed in sponsor's population pharmacokinetic analysis report (study code V-15-33). The PK parameters and associated variability in patients with severe HI were based on dedicated clinical pharmacology study (D7913C00718) (See table 4, Section 2.3.2.2 in clinical pharmacology QBR).

4.2.1 Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
V-15-33	est501.xpt	\\cdsesub1\evsprod\nda206995\0013\m5\datasets\d791al00002-pop-pkpd\analysis\legacy\datasets\est501.xpt

4.2.2 Software

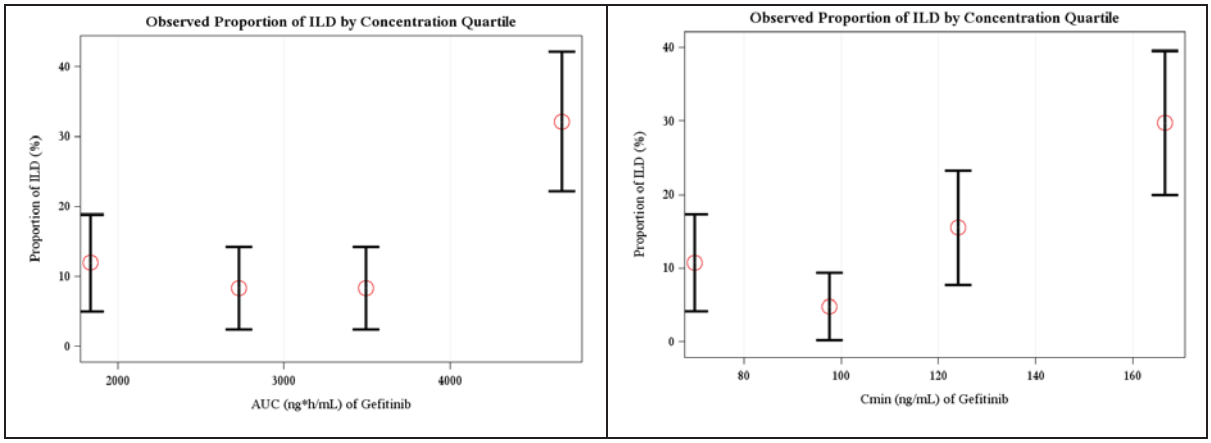
SAS 9.3 was used for graphical exploration. NONMEM 7.3 was used for PK simulations.

4.3 Results

The results based on the pooled dataset demonstrated a higher ILD risk was observed in highest exposure group, which is consistent with the E-R analysis by sponsor (Figure 8).

Reference ID: 3762549

Figure 8: The highest exposure group exhibited a higher ILD risk (n=336)



The results of PK simulations were provided in **Figure 5**.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
[redacted] (b) (4)		
simEOD.csv	Input datasets for simulations of QOD dose regimen	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gefitinib_NDA206995_JYU\PPK_Analyses\simulations
simQD.csv	Input datasets for simulations of QD dose regimen	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gefitinib_NDA206995_JYU\PPK_Analyses\simulations
simQD.txt	Simulation NONMEM code for QD dose regimen	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gefitinib_NDA206995_JYU\PPK_Analyses\simulations
simEOD.txt	Simulation NONMEM code for QOD dose regimen	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gefitinib_NDA206995_JYU\PPK_Analyses\simulations
Sim_Severe_Update.ssc	Analysis code for simulation	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gefitinib_NDA206995_JYU\PPK_Analyses\simulations

Reference ID: 3762549

4.2 Genomics and Targeted Therapy Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

1 Background

Gefitinib is a small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) proposed for the first-line treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Exon 19 deletions and L858R are the most common and best characterized *EGFR* mutations in NSCLC associated with EGFR TKI sensitivity. The clinical significance of other less common *EGFR* mutations is not well established. Gefitinib is predominantly metabolized by cytochrome P450 (CYP) 3A4. However, the major circulating metabolite (M523595), which is present in plasma at similar concentrations as gefitinib, is produced exclusively through CYP2D6 metabolism. The purpose of this review is to evaluate the impact of genetic variation in drug metabolizing enzymes on gefitinib PK and safety, and to assess whether gefitinib has activity in NSCLC patients whose tumors have *EGFR* mutations other than exon 19 deletions or L858R.

2 Submission Contents Related to Genomics

Study reports with genomic contents are listed in Table 1.

Table 1. Studies with contents related to genomics.

Study Identifier	Study Title
Pharmacogenetic –Pharmacokinetic Studies	
D7913C00707	An Open, Pharmacogenetic Pilot Study to Assess the Cytochrome P450 3A5 Genotype in Healthy Male Volunteers Previously Exposed to ZD1839 (IRESSA™)
7913C00019	An open-label study to determine the pharmacokinetics of ZD1839 and its major circulating metabolite (M523595) following a single 250 mg oral dose to healthy volunteers genotyped for CYP2D6
Genome Wide Association Study (GWAS)	
D791AL00002-Addendum (exploratory)	Clinical Study Report Addendum: A nested case-control study to determine the relative risk of and risk factors for interstitial lung disease in a cohort of NSCLC patients treated with and without gefitinib (Study V-15-33): Exploratory Pharmacogenetic Analyses of Single Nucleotide Polymorphism Data in Relation to Interstitial Lung Disease
Assessment of EGFR mutations	
D791AC0014 (IFUM); pivotal trial	An Open-Label, Multicentre, Single-Arm Study to Characterise the Efficacy, Safety, and Tolerability of Gefitinib 250 mg (IRESSA™) as First-Line Treatment in Caucasian Patients Who Have Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)
D791AC00007 (IPASS); supportive study	An Open Label, Randomised, Parallel Group, Multicentre, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib (IRESSA™) (250mg tablet) Versus Carboplatin / Paclitaxel Doublet Chemotherapy as First-Line Treatment in Selected Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) in Asia (IPASS)

Reference ID: 3762549

3 Key Questions and Summary of Findings

3.1 Does genetic variation in drug metabolizing enzymes impact gefitinib pharmacokinetics (PK)?

In vitro studies indicate that gefitinib is metabolized by CYP3A4 and CYP2D6 with CYP3A5 also contributing. The applicant conducted two studies, D7913C00707 and D7913C00019, to evaluate the impact of CYP3A5 and CYP2D6 genotypes (and the predicted enzyme phenotypes), respectively, on gefitinib PK in healthy subjects. Genetic variants in CYP3A4, the main CYP isoform contributing to gefitinib biotransformation, were not evaluated by the applicant. Based on the applicant's analysis, CYP2D6 poor metabolizers (PMs) have approximately 2-fold higher exposure to gefitinib compared to CYP2D6 extensive metabolizers (EMs). CYP3A5 genotype did not appear to impact gefitinib PK.

Published literature:

CYP3A4/CYP3A5: In general, *CYP3A4* genetic variation contributes only to a minor extent or only in specific populations (where loss-of-function variants are more common) to the inter-individual differences in the CYP3A4-mediated drug metabolism. Conversely, CYP3A5 is functional in more than 60% of Africans/African Americans, but only in 5 to 10% of Caucasians. Three alleles, *CYP3A5*3* (12% to 35% in Africans and 88% to 97% in Caucasians), *CYP3A5*6* (15% to 25% in Africans and 12% in African Americans) and *CYP3A5*7* (10% in African Americans) result in non-functional proteins and the non-expressor phenotype [PMID: 24926778, 11740341]. CYP3A4 and CYP3A5 enzymes have overlapping substrates. The *CYP3A4* genotype may impact the metabolism of drugs having overlapping CYP3A4/CYP3A5 enzyme affinities, particularly in CYP3A5 non-expressors [PMID: 24926778].

CYP2D6 is a highly polymorphic enzyme exhibiting large geographical and inter-ethnic differences in the distribution of important genetic variants (Table 2; PMID: 22185816; 15492763).

Table 2: Genetic polymorphisms of *CYP2D6* and their global distribution.

Major variant alleles	*Consequence*	*Allele frequencies (%)*			
		Caucasians	*Asians*	*Black Africans*	*Ethiopians and Saudi Arabians*
*CYP2D6*2xn*	Increased enzyme activity	1–5	0–2	2	10–16
*CYP2D6*4*	Inactive enzyme	12–21	1	2	1–4
*CYP2D6*5*	No enzyme	2–7	6	4	1–3
*CYP2D6*10*	Unstable enzyme	1–2	51	6	3–9
*CYP2D6*17*	Altered affinity for substrates	0	0	20–35	3–9

Source: Modified from PMID: 15492763 (Table 3)

Because of the complexity of the *CYP2D6* locus and of differences in testing platforms, there are considerable differences in how a CYP2D6 phenotype is derived from a genotype in the reported literature [PMID: 245246660].

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Clinical studies submitted by the applicant:

Two healthy subject study reports were submitted by the applicant to evaluate the impact of *CYP3A5* and *CYP2D6* genetic variation on gefitinib PK (D7913C00707 and 7913C00019, respectively). The impact of genetic variation in *CYP3A4*, the main CYP isoform contributing to gefitinib biotransformation, was not evaluated by the applicant. The results presented below correspond to the applicant's analyses.

Study report D7913C00707 (CYP3A5): PK data from subjects with a well-defined, single-dose concentration-time profile enrolled in studies 0002, 0030, 0031, 0033, 0034, and 0051 were pooled for this analysis. DNA was extracted from whole blood and genotyping was performed by the AstraZeneca Clinical Genotyping Group. Subjects were genotyped for the *CYP3A5*3* and *CYP3A5*6* alleles, and a "wild-type" *CYP3A5*1* genotype was inferred when a negative result was obtained from testing for the other two alleles. The genotyping method was not included in the study report.

Study Report 7913C00019 (CYP2D6): DNA was extracted from whole blood of subjects selected based on known CYP2D6 genotype-inferred phenotype. Confirmatory genotyping was performed for the *CYP2D6* alleles *2, *3, *4, *5, *6, *9, *10, *41 and *CYP2D6* gene duplication (for normal function alleles*1, *2, and for the null allele *4) following study enrollment (using 5' exonucleolytic degradation with dually labelled TaqMan® probes or sequencing). The *1 allele was defined by the exclusion of the presence of any of the interrogated poor metabolizer (PM) and intermediate metabolizer (IM) alleles (Table 3). Only individuals with genotype-inferred CYP2D6 phenotypes of extensive or poor metabolizers (EM or PM) confirmed by re-genotyping were included in the study analyses. Phenotypes were assigned according to Table 3.

Table 3. Definition of CYP2D6 allele combinations and predicted phenotypes.

EM – included in study	EM – included in study	PM – included in study	IM – EXCLUDED from study
*1xN/*1, *1xN/*2, *2xN/*1, *2xN/*2	*1/*1, *1/*2, *1/*3, *1/*4, *1/*5, *1/*6, *1/*9, *1/*10, *1/*41, *2/*2, *2/*3, *2/*4, *2/*5, *2/*6, *2/*9, *2/*10, *2/*41, *9/*9, *9/*10, *10/*10, *1x2/*3, *1x2/*4, *1x2/*5, *1x2/*6, *1x2/*9, *1x2/*10, *1x2/*41, *2x2/*3, *2x2/*4, *2x2/*5, *2x2/*6, *2x2/*9, *2x2/*10, *2x2/*41, *4xN/*1, *4xN/*2	*3/*3, *3/*4, *3/*5, *3/*6, *4/*4, *4/*5, *4/*6, *5/*5, *5/*6, *6/*6, *4xN/*3, *4xN/*4, *4xN/*5, *4xN/*6	*3/*9, *3/*10, *3/*41, *4/*9, *4/*10, *4/*41, *5/*9, *5/*10, *5/*41, *6/*9, *6/*10, *6/*41, *9/*41, *10/*41, *41/*41, *4xN/*9, *4xN/*10, *4xN/*41
(N ≥ 2)	(N ≥ 2)	(N ≥ 2)	(N ≥ 2)

Source: Applicant's Table 3, Study Report 7913C00019; N=CYP2D6 gene copy number, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer

*Reviewer comment: Although not inclusive, the CYP2D6 and CYP3A5 alleles selected to be genotyped by the applicant capture relevant genetic variants in these enzymes [PMID: 15492763, 22407409].Potentially relevant alleles not genotyped in these studies include CYP3A5*7, a nonfunctional allele reported mostly in African Americans, and CYP2D6*17, a common IM allele in African-Americans. The CYP2D6 genotype-phenotype calls are mostly consistent with conventional pharmacogenetic designations; however, individuals with ≥2 of the normal function alleles *1 and *2 (i.e., CYP2D6 ultra-rapid metabolizers; UMs) were combined with extensive metabolizers [PMID: 22407409, 19512959].*

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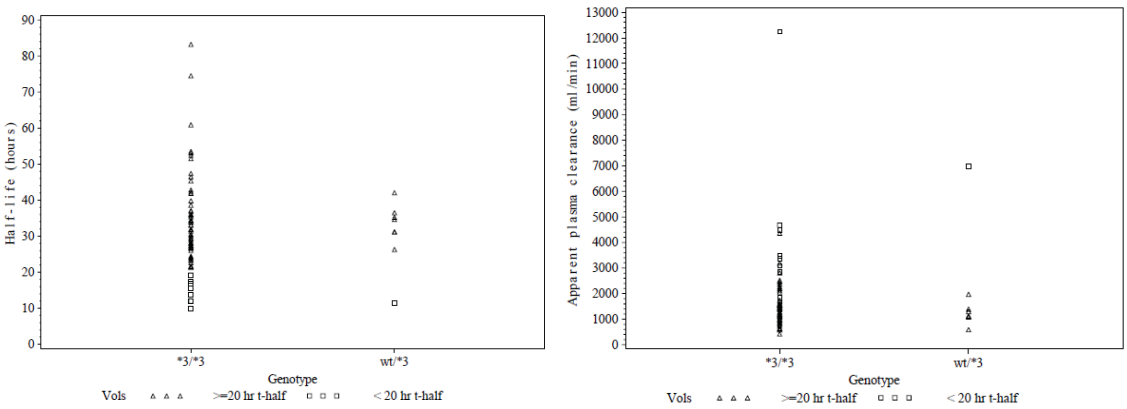
Applicant's genotype-PK Analysis results:

The D7913C00707 dataset consisted of 73 healthy male volunteers who had previously been exposed to gefitinib and had a single dose plasma concentration-time profile; 65 were *CYP3A5*3/*3* genotype (non-expressors) and 8 were *CYP3A5*1/*3* (expressors). No formal statistical analysis was conducted in the study. Apparent plasma clearance and terminal half-life were similar across *CYP3A5* genotypes (Figure 1). Mean clearance of the *CYP3A5*3/*3* group was 1881 mL/min and mean clearance of the *CYP3A5*1/*3* group was 1846 mL/min.

Figure 1. Gefitinib clearance and half-life by *CYP3A5* genotype.



Source: Applicant's Figure 1 and Figure 2, Study Report D7913C00707.

Reviewer comment: Genetic variants in CYP3A4, the main CYP isoform contributing to gefitinib biotransformation, were not evaluated and based on the applicant's analysis, CYP3A5 genotype does not appear to impact gefitinib PK. In general, CYP3A4 genetic variation contributes only to a minor extent or only in specific populations (where loss-of-function variants are more common) to the inter-individual differences in the CYP3A4-mediated drug metabolism.

In 7913C00019, the final dataset included 15 CYP2D6 EMs and 15 CYP2D6 PMs who had received a 250 mg dose of gefitinib. No subjects with duplications of normal function alleles (i.e., *1 or *2), who could be classified as CYP2D6 UMs, were enrolled in the study. Overall, PK parameters exhibited significant variability, and the ranges overlapped between EMs and PMs (Table 4). Following gefitinib dosing, the geometric mean C_{max} was 61.5 ng/mL in EMs vs. 93.0 ng/mL in PMs and the mean terminal half-life was 23.3 hours in EMs compared to 34.1 hours in PMs. $AUC_{0-\infty}$, the primary PK variable, was 1430 ng*hr/mL in EMs vs. 3060 ng*hr/mL in PMs, representing a 2.1-fold increase ($p<0.05$ by ANOVA). The main metabolite M523595 was not quantifiable in the PM group, indicating that CYP2D6 is the only CYP isoform contributing to its formation. No CYP2D6 UMs were enrolled in the study.

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Table 4. Derived PK parameters for gefitinib and M523595 in CYP2D6 EMs and PMs following gefitinib administration.

Derived parameter	Summary statistics	PM		EM	
		ZD1839	M523595	ZD1839	M523595
C_{max} [ng/mL]	gmean (CV%) range	93.0 (81.1) 14.4–211	NC	61.5 (55.3) 20.0–130	70.5 (64.4) 24.7–191
t_{max} [h]	Median range	5.0 (3–12)	NC	5.0 (3–24)	3.0 (1–24)
AUC [ng·h/mL]	gmean (CV%) range	3060 (129) 215–8440	NC	1430 (74.0) 406–5890	1640 (93.6) 292–4780
$t_{1/2}$ [h]	Mean (SD)	34.1 (16.0)	NC	23.3 (13.3)	19.0 (9.90)
Cl/F [mL/min]	gmean (CV%) range	1360 (129) 494–19400	NC	2910 (74.0) 707–10300	NC
Vdss/F [L]	Mean (SD)	4150 (4740)	NC	4710 (2270)	NC

Source: Applicant's Table S2, Study Report 7913C00019; C_{max}=maximum observed plasma concentration, T_{max}=time of maximum plasma concentration, AUC=area under the plasma concentration time curve from time zero to infinity, $T_{1/2}$=terminal half-life, Cl/F=total clearance from plasma following an oral dose, Vd_{ss}/F=apparent volume of distribution, gmean=geometric mean, CV=coefficient of variation, SD=standard deviation, NC=not calculated

Reviewer comment: In study D7913C00019, CYP2D6 PMs had approximately a 2-fold higher exposure to gefitinib compared to CYP2D6 EMs. Although a doubling of dose (500 mg daily vs. 250 mg daily) resulted in an increase in treatment-related toxicities in Phase 2 studies of gefitinib (studies D7913C00016 and D7913C00039), dose reductions due to toxicity ranged from 8.8-10.4% in patients receiving 500 mg daily. The applicant's proposed labeling states that no specific dose adjustment is recommended in patients with known CYP2D6 PM genotype, but these patients should be closely monitored for adverse reactions. Consistent with the applicant's recommendation for CYP2D6 PMs, no dose adjustment is recommended in patients concomitantly taking drugs that inhibit CYP2D6. Given the high level of inter-subject variability for gefitinib PK and low rate of dose reductions due to toxicity observed with doubling the dose, this approach appears reasonable. An Information Request was submitted to the applicant requesting PK data on CYP2D6 UMs (submitted 5/7/2015, response received 5/14/2015). The applicant stated that no data were available to characterize gefitinib PK in CYP2D6 UMs. Therefore, the PK characteristics of gefitinib in this population remain uncharacterized.

3.2 Is there a signal for gefitinib activity in patients whose tumors have *EGFR* mutations other than exon 19 deletions or L858R?

In the few patients whose tumors were positive for less common EGFR mutations (L861Q and G719X), gefitinib appears to have some activity; however, it is not conclusive if (or to what degree) these mutations are sensitizing to gefitinib. Inclusion of these data in labeling is an ongoing review issue. While labeling approaches are currently being discussed, it is the provisional opinion of the reviewer that the drug be indicated for populations for whom efficacy and safety have been established, with full description of trial results by mutation status in labeling.

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EGFR activating mutations more common in Asians (approximately 10% of NSCLC cases in North America and Western Europe, and up to 50% of cases in patients of East Asian descent), and in tumors with adenocarcinoma histology, from women, and never-smokers [PMID: 17318210]). The best characterized mutations associated with EGFR TKI sensitivity are exon 19 deletions and a L858R substitution in exon 21, which together account for approximately 90% of *EGFR* mutations in NSCLC. The remainder of *EGFR* mutations includes a plethora of less characterized mutations generally associated with increased sensitivity (e.g., L861Q, G719 A/C/S – G719X) or resistance (e.g., exon 20 insertions and T790M) to EGFR TKIs [PMID: 23647298; My Cancer Genome]. However, because of the low prevalence and large heterogeneity, the clinical significance of these less common mutations is not clear.

Clinical studies submitted by the applicant:

Pivotal trial D791AC0014 (IFUM): The IFUM trial was a single-arm trial. The primary endpoint was ORR (confirmed CR or PR); other efficacy endpoints included disease control rate (DCR), progression free survival (PFS) and overall survival (OS). The trial was restricted to Caucasian patients with *EGFR*-mutation positive NSCLC without regard to clinical characteristics (e.g., smoking history or histological subtype). The designated central laboratory evaluated the *EGFR* mutation status of individual tumor samples for each of the mutations included in the Qiagen Therascreen EGFR RGQ PCR kit. Eligible mutations (alone or in combination) included exon 19 deletions, L858R, L861Q, and G719X. Patients with tumors positive for T790M, S768I or exon 20 insertions were excluded from the study, including when an eligible mutation was also present.

Overall, 1,060 patients were screened and 118 were deemed eligible based on tumor mutation status. Of the 118 eligible patients, 107 were enrolled in the trial; however, one patient was subsequently found to have a non-eligible mutation. As reported by the applicant, the primary endpoint of ORR was 69.8% (74 of 106 of patients). 102 of 106 patients had either exon 19 deletions (ORR 72.5%) or the exon 21 L858R substitution (ORR 63.6%), with a median duration of response (DoR) of 8.3 months in both groups. The number of patients with tumors positive for less common *EGFR* mutations was very low; however, 1 of 2 patients with the L861Q mutation and 2 of 2 patients with G719X mutations achieved an objective response with gefitinib, suggesting that gefitinib has some activity in tumors with these mutations (Table 5).

Table 5. Response to gefitinib by EGFR mutation type in the IFUM trial.

EGFR Mutation Type	N (%)	Objective Responders	Response Rate (%)	95% CI
Exon 19 deletions	69 (65)	50	72.5	61.0, 81.6
L858R	33 (31)	21	63.6	46.6,77.8
L861Q	2 (2)	1	NC	NC
G719X (G719S/A/C)	2 (2)	2	NC	NC

Source: Applicant's Table 17, Study Report D791AC00014 ;CI=confidence interval; NC=not calculated

Supportive study D791AC00007 (IPASS): The IPASS trial was conducted in Asia in a clinically

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selected population of patients with adenocarcinoma that had never smoked or were light ex-smokers, comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy. The primary endpoint was PFS. Secondary efficacy endpoints included OS and ORR. Tumor samples were collected from consenting patients and *EGFR* mutation status was determined retrospectively in a subset of patients and used for exploratory analyses. Patients were considered to have *EGFR* mutation positive tumors if one (or more) of 29 *EGFR* mutations was detected in the tumor samples by amplification refractory mutation system (ARMS) using the DxS EGFR 29 mutation detection kit, including mutations associated with EGFR TKI resistance.

EGFR mutation status was evaluated in 437 of the 1217 (36%) patients who were randomized in the trial. In the overall population gefitinib showed a statistically significant advantage in PFS (HR: 0.74; 95% CI: 0.65, 0.85; $p<0.0001$). However, a strong interaction was observed between *EGFR* mutation status and PFS. Patients with *EGFR* mutation positive tumors had a median PFS of 9.5 months with gefitinib versus 6.3 months for carboplatin/paclitaxel (HR: 0.48; 95% CI: 0.36, 0.64; $p<0.0001$). In contrast, in patients without detectable *EGFR* mutations, PFS was significantly shorter for gefitinib (1.5 months) versus carboplatin/paclitaxel (5.5 months) treated patients (HR: 2.85; 95% CI: 2.05, 3.98; $p<0.0001$). Overall, 91.9% of patients had exon 19 deletions, the exon 21 L858R substitution, or both. Other EGFR mutations were detected in less than 5 (1.9%) patients (each). For response data on these patients, refer to clinical review (Dr. Dickran Kazandjian).

Reviewer comment: The results support the role of EGFR exon 19 deletions and L858R in conferring sensitivity to gefitinib, as observed for other approved EGFR TKIs. Although results suggest that the less common EGFR mutations L861Q and G719X are sensitizing toward gefitinib at least to some degree, data is very limited for conclusive results.

3.3 Does genetic variation impact gefitinib safety?

Interstitial lung disease (ILD) was observed in 1.3% of patients in Phase 3 clinical trials of gefitinib. The applicant conducted an exploratory GWAS to identify genetic variants associated with the risk of ILD in gefitinib treated Japanese patients. The applicant's GWAS did not identify any genetic variants associated with ILD.

ILD was observed in 1.3% of patients in Phase 3 clinical trials of gefitinib. According to study report V-15-33, a nested case-control study conducted in Japanese patients treated with gefitinib to identify risk factors for ILD, the applicant did not observe marked differences in exposure between cases and controls based on first-dose PK. However, when exposures were calculated at ILD occurrence, there was a tendency for higher exposures compared to the period without ILD occurrence (please refer to the Pharmacometrics review conducted by Dr. Jerry Yu for a more detailed exposure-response analysis).

A Clinical Study Report Addendum (D791AL00002) was submitted to document the findings of an exploratory GWAS conducted to identify genetic variants associated with the risk of ILD in gefitinib treated patients. The analysis included two datasets, a nested case control study V-15-33 (which included 52 ILD cases and 139 controls) and a "Retrospective Study" (which included 28 ILD cases and 55 controls) conducted by the University of Tokyo and AstraZeneca. According

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to the applicant, there was limited evidence in an analysis from the V-15-33 study that top-ranking variants were associated with ILD status; however, these findings were not validated in the retrospective study cohort. Moreover, analysis of the combined datasets by Fisher's exact test did not demonstrate any significant associations between genetic variants and ILD after accounting for the number of comparisons (Table 6). Overall, the applicant's analysis did not identify any genetic associations that are useful for ILD prediction. Data were not re-analyzed by FDA.

Table 6. Top-ranking SNPs from the combined analysis of V-15-33 and the "Retrospective Study".

SNP	P	Risk Allele	OR
rs170020	3.97×10^{-6}	C	2.96
rs4233356	9.1×10^{-6}	T	2.51
rs2072409	1.13×10^{-5}	T	2.45
rs6745588	1.74×10^{-5}	A	3.33
rs11033354	1.78×10^{-5}	T	2.29

Source: Applicant's Table 7, Appendix B of Study Report D791AL00002; SNP=single nucleotide polymorphism, P=p-value from Fisher's exact test, OR=odds ratio

Reviewer comment: The applicant's GWAS, was an exploratory investigation to identify genetic factors that may impact ILD risk. The analysis did not provide convincing data that any of the genetic variants analyzed are associated with ILD status in the Japanese populations included in the nested case-control study and the "Retrospective Study". Genetic variants not present in the Japanese population may impact ILD risk in European or African populations.

4 Summary and Conclusions

According to the applicant, CYP2D6 PMs have approximately a 2-fold increase in exposure to gefitinib compared to CYP2D6 EMs. In Phase 2 clinical trials evaluating 500 mg of gefitinib daily, dose reduction rates secondary to drug-related toxicities were low; therefore, a recommendation for dose reduction in CYP2D6 PMs is not warranted. However, PK parameters in CYP2D6 UMs remain uncharacterized. We recommend that the applicant conduct a study to characterize the pharmacokinetic properties of gefitinib in CYP2D6 UMs, who may be at risk for treatment failure because of low exposure. This recommendation will be submitted via IND 120992.

Gefitinib demonstrated efficacy in NSCLC patients with common *EGFR*-TKI sensitizing mutations (exon 19 deletions and L858R) as assessed by ORR. In patients with tumors positive for less common *EGFR* mutations (L861Q and G719X), gefitinib appears to have some activity, although it is not conclusive if (or to what degree) these mutations are sensitizing to gefitinib. (b) (4) (b) (4)

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5 Recommendations

5.1 Post-marketing studies

No postmarketing commitments or requirements are recommended at this time.

5.2 Label Recommendations

Please see integrated labeling recommendations in Section 3 of the Clinical Pharmacology review.

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4.3 Clinical Pharmacology/Biopharmaceutics Review from Original Iressa NDA Submission (NDA 21399)

Appears This Way On Original

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4.4 Cover Sheet and OCP Filing/Review Form

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206995

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	206995	**Brand Name**	IRESSA
OCP Division (I, II, III, IV, V)	Division V	**Generic Name**	Gefitinib
Medical Division	DOP2	**Drug Class**	Tyrosine kinase inhibitor
OCP Reviewers	Robert Schuck, Pharm.D., Ph.D. (CP, GTT) Jingyu (Jerry) Yu, Ph.D. (PM)	**Indication(s)**	(b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test
OCP Team Leaders	Hong Zhao, Ph.D. (CP) Liang Zhao, Ph.D. (PM) Rosane Charlab Orbach, Ph.D. (GTT)	**Dosage Form**	250 mg tablet
Date of Submission	09/17/2014	**Dosing Regimen**	250 mg once daily
Estimated Due Date of OCP Review	05/22/2015	**Route of Administration**	Oral
Medical Division Due Date	07/17/2015	**Sponsor**	AstraZeneca
PDUFA Due Date	07/17/2015	**Priority Classification**	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to review	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			Module 5.2
HPK Summary	x			Module 2.7.2
Labeling	x			Module 1.14
Reference Bioanalytical and Analytical Methods	x	10	4	New reports: kpv069, 084, 098, 099 Previously reviewed: kpv014, 021, 038, 049, 052, 057
I. Clinical Pharmacology				
Mass balance:	x	2	0	Previously reviewed: d7913c00003, 00719
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:	x	2	1	New report: d7913c00208 Previously reviewed: d7913c00001
multiple dose:	x	2	0	Previously reviewed: d7913c00010, 00034
Patients-				
single dose:				

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multiple dose:	x	8	2	New reports: d7913c00022, d791al00002 Previously reviewed: d7913c00005, 00011, 00012, 00016, 00039, v-15-11
Dose proportionality -				
fasting / non-fasting single dose:	x	1	0	Previously reviewed: d7913c00033
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3	0	Previously reviewed: d7913c00027, 00030, 00051
In-vivo effects of primary drug:	x	1	0	Previously reviewed: d7913c00038
In-vitro:	x	2	0	Previously reviewed: kpx056, 066
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	x	2	1	New report: d7913c00718 Previously reviewed: d7913c00032
PD -				
Phase 2:	x	1	1	New report: d4200c00003 (concentration-QTc)
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	3	2	New reports: d791ac00014, d791ali00002-v-15-33 Previously submitted: d7913c00016-39
Phase 3 clinical trial:	x	1	1	New report: d791ac00007
Population Analyses -				
Data rich:	x	1	0	Previously submitted: d7913c00031-35,
Data sparse:	x	1	1	New report: d7913c00005-v-15-11
II. Biopharmaceutics				
Absolute bioavailability	x	2	0	Previously reviewed: d7913c00031, 00035
Relative bioavailability -	x	2	1	New report: d7913c00229 Previously reviewed: d7913c00028
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	2	0	Previously reviewed: d7913c00002, 00036
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment				
Genotype/phenotype studies	x	2	1	New report: d7913c00707 Previously submitted: d7913c00019
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		48	15	

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206995

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or	x			

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	justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?				

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206995

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Exempt from PREA due to orphan drug designation
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Exempt from PREA due to orphan drug designation
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206995

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Robert Schuck, Jingyu (Jerry) Yu	November 7, 2014
Reviewers	Date
Hong Zhao, Liang Zhao, Rosane Charlab Orbach	November 7, 2014
Team Leaders	Date

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

/s/

ROBERT N SCHUCK
05/21/2015

YANING WANG on behalf of JINGYU YU
05/21/2015

ROSANE CHARLAB ORBACH
05/22/2015

YANING WANG
05/22/2015

HONG ZHAO
05/22/2015
I concur.

NAM ATIQUR RAHMAN
05/22/2015
I concur with the recommendation.

QUALITY-BIOPHARMACEUTICS REVIEW

Division of Biopharmaceutics

OPQ/Office of New Drug Products

Application No.:	NDA 206-995 (000)	**Biopharmaceutics Reviewer:** Salaheldin S. Hamed, Ph.D.	
Division:	DOP2		
Applicant:	AstraZeneca	**Acting Biopharmaceutics Lead:** Okpo Eradiri, Ph.D.	
Trade Name:	IRESSA®	**Acting Branch Chief:** Angelica Dorantes, Ph.D.	
Generic Name:	Gefitinib	**Acting Division Director:** Paul Seo, Ph.D.	
Indication:	First-line treatment of patients with (b) (4) (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test (Qiagen therascreen EGFR RGQ PCR kit).		
Formulation/ strength	Film-coated immediate release tablets, 250 mg	**Date Assigned:**	
Route of Administration	Oral	**Date of Review:**	19-MAY-2015

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	**Date of informal/Formal Consult**	**PDUFA DATE**
17-SEP-2014 (Original NDA)		17-JUL-2015

Type of Submission:	505(b)(1)
Key review points	Acceptability of dissolution method and acceptance criteria

Reference ID: 3795353

EXECUTIVE SUMMARY

Iressa (gefitinib) 250 mg tablets (NDA 21-399) received accelerated approval on May 5, 2003 as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. On June 28, 2005, the indication was restricted to use in only those patients already receiving and benefiting from Iressa therapy; the NDA was voluntarily withdrawn in September, 2011. The current NDA seeks approval for Iressa 250 mg tablets as a first-line treatment for patients with (b) (4) metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutation(s). The sponsor conducted Phase II/III/IV clinical studies with clinical batches that are identical qualitatively and quantitatively to the proposed commercial batches. In support of this NDA, the sponsor provides dissolution data and references a comparative in-vivo bioavailability study from NDA 21-399 to support the selection of the dissolution method and acceptance criterion.

SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

Dissolution Method for Quality Control and Stability Testing

The following dissolution method and acceptance criterion are ACCEPTABLE:

- Dissolution method: USP II, 50 rpm, 1000 mL (5% v/v Tween 80 in water) at 37 °C
- Sampling times: 15, 30, 45, and 60 min
- Acceptance Criterion: Q = (b) (4)%at 45 minutes

Bioequivalence Studies

(b) (4)

(b) (4) The BE study – which was included in NDA 21-399 – is only referenced in the application but not included as part of this NDA submission.

CONSULTS

No consults were issued for this NDA.

RECOMMENDATION

The dissolution method and acceptance criterion, agreed to with the Applicant, and to be implemented for Iressa Tablets, 250 mg are summarized as follows:

Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP Apparatus 2/ 50 rpm	5% v/v Tween 80 in Water	1000 mL	Q = (b) (4)% at 45 min

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From a Biopharmaceutics perspective, The dissolution method and acceptance criterion in NDA 206995 for IRESSA®, Gefitinib 250 mg film-coated immediate release tablets are ACCEPTABLE. The Division of Biopharmaceutics therefore recommends **APPROVAL** of NDA 206995 for Iressa Tablets, 250 mg.

Salaheldin S. Hamed

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QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

GENERAL ATTRIBUTES

1. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

Drug Substance

Gefitinib ($C_{22}H_{24}ClFN_4O_3$) is a [redacted] (b) (4) powder with molecular mass of 446.90. The molecule is achiral, [redacted] (b) (4). Gefitinib exhibits pH dependent solubility. Gefitinib has higher solubility at lower pH [redacted] (b) (4) and becomes practically insoluble at pH ≥ 7.0.

Drug Product

The intended drug product is a round, biconvex, brown film-coated immediate release tablet, 250 mg. The name "IRESSA" and tablet strength marking "250" are impressed on one side and the other side is plain. [redacted] (b) (4) (b) (4) The components and composition of the film-coated tablet, 250 mg are summarized in Table 1.

Table 1 Composition of IRESSA 250 mg film-coated tablets

Ingredient	Quantity (mg/tablet)	Function	Reference to standard
Tablet core			
Gefitinib	250.0	Drug substance	AstraZeneca standard
Lactose monohydrate	[redacted] (b) (4)		USNF
Microcrystalline cellulose			USNF
Croscarmellose sodium			USNF
Povidone			USP
Sodium lauryl sulphate			USNF
Magnesium stearate			USNF
Nominal core tablet weight			
Tablet coating			
Hypromellose [a]			USP
Polyethylene glycol 300			USNF
Red ferric oxide [a]			USNF, 21 CFR 73.1200
Yellow ferric oxide [a]			USNF, 21 CFR 73.1200
Titanium dioxide [a]			USP, 21 CFR 73.575, 21 CFR 73.1575
Nominal coated tablet weight	(b) (4)		

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DISSOLUTION INFORMATION

2. *What is the proposed dissolution method?*

Table 2: Dissolution test method for IRESSA Film-Coated Tablets used during formulation development

Apparatus	USP II (Paddle)
Medium	5% v/v Tween 80 in Water (1000 mL)
Rotation Speed	50 rpm
Sampling Times	15, 30, 45, and 60 min
Analysis	HPLC/UV, λ = (b) (4) nm

(b) (4)

3. *What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?*

The Applicant submitted a dissolution method development report to justify the selection of medium, apparatus, type and amount of (b) (4) and pH. Details of the dissolution method development are provided below (See Question 5).

4. *What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?*

The dissolution assay method was validated with respect to system suitability, specificity, linearity, accuracy by recovery, repeatability and intermediate precision, and stability. The method has been validated for intended use. (see eCTD Section 3.2.P.5.3: Validation Dissolution)

5. *What data are available to support the discriminating power of the method?*

(b) (4)

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(b) (4)

[redacted]

6. ***Is the proposed dissolution method biorelavant? What data are available to support this claim?***

Yes, the proposed dissolution method is biorelevant. The dissolution method was optimized to differentiate between two formulations that are bioinequivalent.

7. ***Is the proposed method acceptable? If not, what are the deficiencies?***

YES, the dissolution method is ACCEPTABLE.

(b) (4)

[redacted]

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ACCEPTANCE CRITERIA

8. ***What are the dissolution acceptance criteria for this product?***

[redacted] (b) (4)

to Q = [redacted] (b) (4)% at 45 minutes.

9. ***What data are available to support the criteria?***

The Applicant provided a detailed dissolution method development report (as discussed above) that focused on optimizing the dissolution method and acceptance criteria to discriminate between bioinequivalent batches.

10. ***Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?***

YES. The dissolution method development report is based on the efficacy study formulation.

11. ***Are mean (n = 12) dissolution profile data used for the setting of the acceptance criteria?***

No. [redacted] (b) (4)

12. ***Are the acceptance criteria acceptable? If not, what the recommended criteria?***

The proposed criterion is NOT acceptable. The Applicant was asked in an Information Request, dated 5/19/2015, to state the dissolution acceptance criteria as "Q = [redacted] (b) (4)% at 45 minutes". The Applicant accepted the recommendation, sent the updated Specifications table to FDA by email on 5/21/2015 and made a commitment to formally submit the update to the NDA through the Electronic Gateway.

Reviewer's Overall Assessment of Dissolution:
The proposed DISSOLUTION METHOD IS ACCEPTABLE. With regard to the

[redacted] (b) (4)

[redacted] (b) (4) ***The Applicant was asked to update the acceptance criterion to Q = [redacted] (b) (4)% at 45 minutes. THE RECOMMENDED ACCEPTANCE CRITERION is Q = [redacted] (b) (4)% at 45 minutes.***

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Upon the Agency's recommendation, the Application updated the dissolution acceptance criterion to Q = (b)(4)*% at 45minutes.*

(b) (4)

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DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING

13. What are the highlights of the drug product formulation development?

(b) (4)

14. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

The proposed product is available in one strength, 250 mg, which is evaluated in the pivotal IFUM trial and the supportive IPASS study.

INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses to these questions are incorporated in QBR above. There are no outstanding review issues

The proposed dissolution method (with 5% v/v Tween 80 in water as the medium) does not exhibit discriminating power when the clinical and commercial batches, that are not bioequivalent, are compared. Based on the presented data (see Table 12, 3.2.P.2.2 Drug Product –Attachment 1), the calculated f2 score is 50.2. Provide a dissolution method that is more suitable and discriminates the two formulations that have been demonstrated to be bioinequivalent. The following general guidelines for the content of a dissolution method development report should be considered:

I. ***Dissolution Test:*** *Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution development report should include the following information:*
   a. *Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45 60, 90 and 120 min;*
   b. *Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);*
   c. *Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the*

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selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables);

II. ***Dissolution Acceptance Criterion:*** *For the selection of the dissolution acceptance criterion(a) of your product, the following points should be considered:*

a. *The dissolution profile data (15, 20, 30, 45, 60, 90, 120 min; n = 12) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) should be used for the setting of the dissolution acceptance criterion(a) of your product (i.e., specification-sampling time point and specification value).*
b. *The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.*
c. *The selection of the specification time point should be where Q= (b)(4)% dissolution occurs. However, if you have a slowly dissolving product, specifications at two time points may be adequate for your product. The first time point should be selected during the initial dissolution phase (i.e., 15-30 minutes about 40-50% dissolution) and the second time point should be where Q = (b)(4)% dissolution occurs.*

Your proposed dissolution acceptance criterion, as stated in the Specifications table, is not acceptable. Update the dissolution acceptance criterion as follows:

Q = (b)(4)% at 45 min

Forward the updated Specifications Table by email and submit it to the NDA through the Electronic Gateway.

The Applicant's responses are summarized in the review.

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