CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review-Addendum	
NDA	201292/0
Brand Name	Gilotrif®
Generic Name	Afatinib
Submission Date	November 14, 2012
Submission Type; Code	505 (b)(1); NME
Review Classification	Priority, Fast Track, Orphan
PDUFA Due Date	July 15, 2013
Proposed Dosage Form / Strength	Film-coated tablets 20, 30, 40 (b) (4)
Proposed Dosing Regimen	40 mg (b) (4)
Proposed Indication	Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test
Related IND	67969
Applicant	Boehringer Ingelheim
OCP Reviewer	Runyan Jin, Ph.D./ Jun Yang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Jun Yang, Ph.D.
Pharmacometrics Secondary Reviewer	Kevin Krudys, Ph.D.
Genomics Reviewer	Rosane Charlab Orbach, Ph.D.
Associate Director for Genomics	Michael Pacanowski, Pharm.D., M.P.H.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 2 (DOP2)

OVERALL SUMMARY

The impact of renal impairment (RI) on the systemic exposure of afatinib was re-evaluated using the data collected in the registration trial at the starting dose of 40 mg only. It was observed that the median afatinib trough concentrations at steady state (day 15) in patients with mild (n=130) and moderate (n=20) RI were 27% and 85% higher than those in patients with normal (n=79) renal function. The impact of mild and moderate RI on the afatinib exposure reported in this addendum is larger than reported in the clinical pharmacology review (DARRTS date of 4/22/13) because the original analysis erroneously included doses other than the recommended starting dose of 40 mg. These updated data analysis results warrant a clinical pharmacokinetic trial in patients with moderate and severe renal impairment under post marketing requirement (PMR).

Key Review Question	Rationale	PMR
Does renal impairment affect the PK of afatinib?	It was observed in the registration trial that the median afatinib trough concentrations in patients with mild and moderate RI were 27% and 85% higher than those in patients with normal renal function, respectively. Patients with severe RI may have even higher afatinib exposures, which could cause more toxicity.	Conduct a pharmacokinetic trial to determine the appropriate doses of afatinib in patients with moderate and severe renal impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*." Submit Draft Protocol: November 2013 Final Protocol Submission: January 2014 Trial Completion: September 2015 Final Clinical Trial Report Submission: December 2015

RECOMMENDATION

The Applicant is required to conduct a clinical pharmacokinetic trial in subjects with moderate and severe renal impairment under the PMR. This study will be included in the Approval Letter with milestones agreed upon after negotiation with the Applicant.

Signatures:

Runyan Jin, Ph.D. Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5
Jun Yang, Ph.D. Pharmacometrics Reviewer Division of Clinical Pharmacology 5	Kevin Krudys, Ph.D. Pharmacometrics Secondary Reviewer Division of Pharmacometrics
	Atiqur Nam Rahman, Ph.D. Division Director Division of Clinical Pharmacology 5
Cc: DDOP2: MO – Shakun Malik; MTL – Anthony Murgo; RPM – Deanne Varney DCP-5: DDD –Brian Booth; DD – Atiqur Nam Rahman	

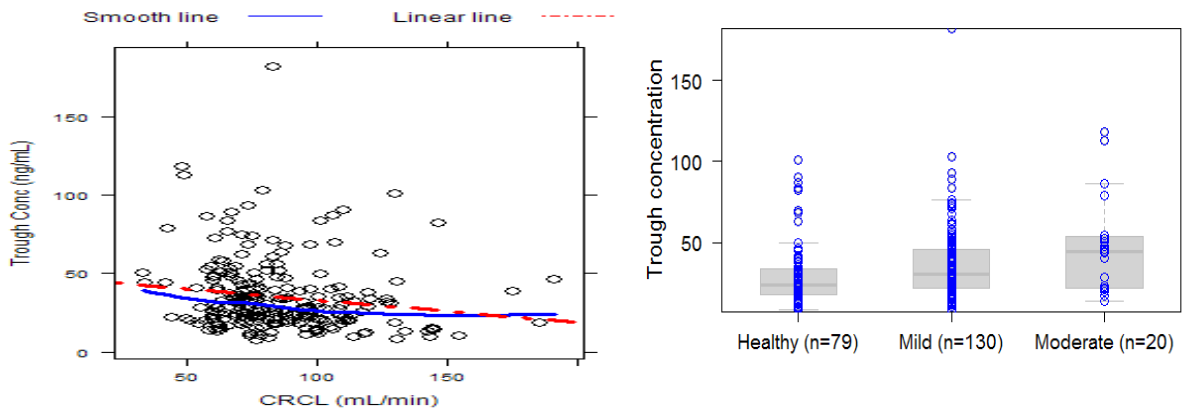
CLINICAL PHARMACOLOGY FINDINGS

The trough afatinib concentration data obtained from the registration trial (1200.32) were used to evaluate the impact of renal impairment and intrinsic and extrinsic covariates on afatinib exposure. It was noted that the steady state afatinib trough concentration data (poppkp.xpt) were defined by the applicant as Day 15 trough concentration ("NDA201292/0007/m5/datasets/1200-iss/analysis"). The updated analysis only includes data from the registration trial at a starting dose of 40 mg. The original analysis (4/22/13) erroneously included data from other doses. The analyses below are therefore meant to replace those in Section 4.1.1.2 of the Pharmacometrics review.

1. Does renal impairment (RI) affect the PK of afatinib?

Yes. The applicant's mass balance study suggests that less than 5% of afatinib is eliminated via renal excretion. However, the absolute bioavailability is unknown and there is a trend that the exposure of afatinib increases as the creatinine clearance (CRCL) value decreases (Figure 1), where the median trough afatinib levels in patients with mild and moderate renal impairment are 27 % and 85 % higher than that of patients with normal renal function. An effect of CRCL on the clearance of afatinib, independent of body weight, was also detected in the population pharmacokinetic model. Afatinib treatment in patients with severe renal impairment has not been studied. Adjustments to the starting dose of afatinib are not considered necessary in patients with mild (CRCL 60-89 mL/min) renal impairment.

Figure 1. Association between trough afatinib levels and CRCL values in the registration trial at a dose of 40 mg.



2. Impact of Other Intrinsic and Extrinsic Factors on PK of Afatinib

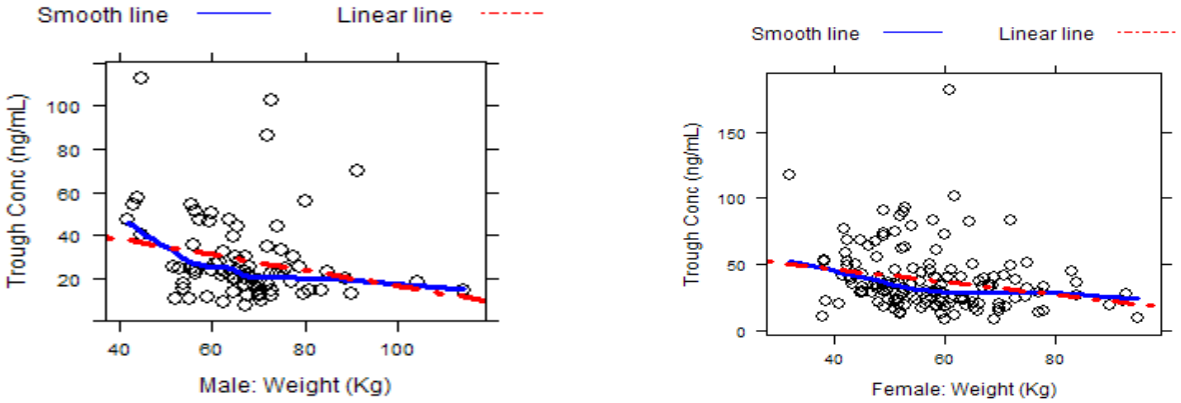
Hepatic Impairment

According to the sponsor's human mass balance study, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose. Hepatic impairment studies have been conducted in subjects with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. The results suggest that hepatic impairment has no influence on the afatinib exposure following a single dose of afatinib. Subjects with severe (Child Pugh C) hepatic impairment have not been studied. Adjustments to the starting dose of afatinib are not considered necessary in patients with mild or moderate hepatic impairment.

Body Weight

The exposure of afatinib in the first cycle (trough concentration, ng/mL) tends to decrease as the body weight increases regardless of the gender (Figure 2) in the registration trial. However, the exposure difference due to body weight is not clinically relevant and no dose adjustment is considered necessary.

Figure 2. Association between trough afatinib levels and body weight in the registration trial at a dose of 40 mg.



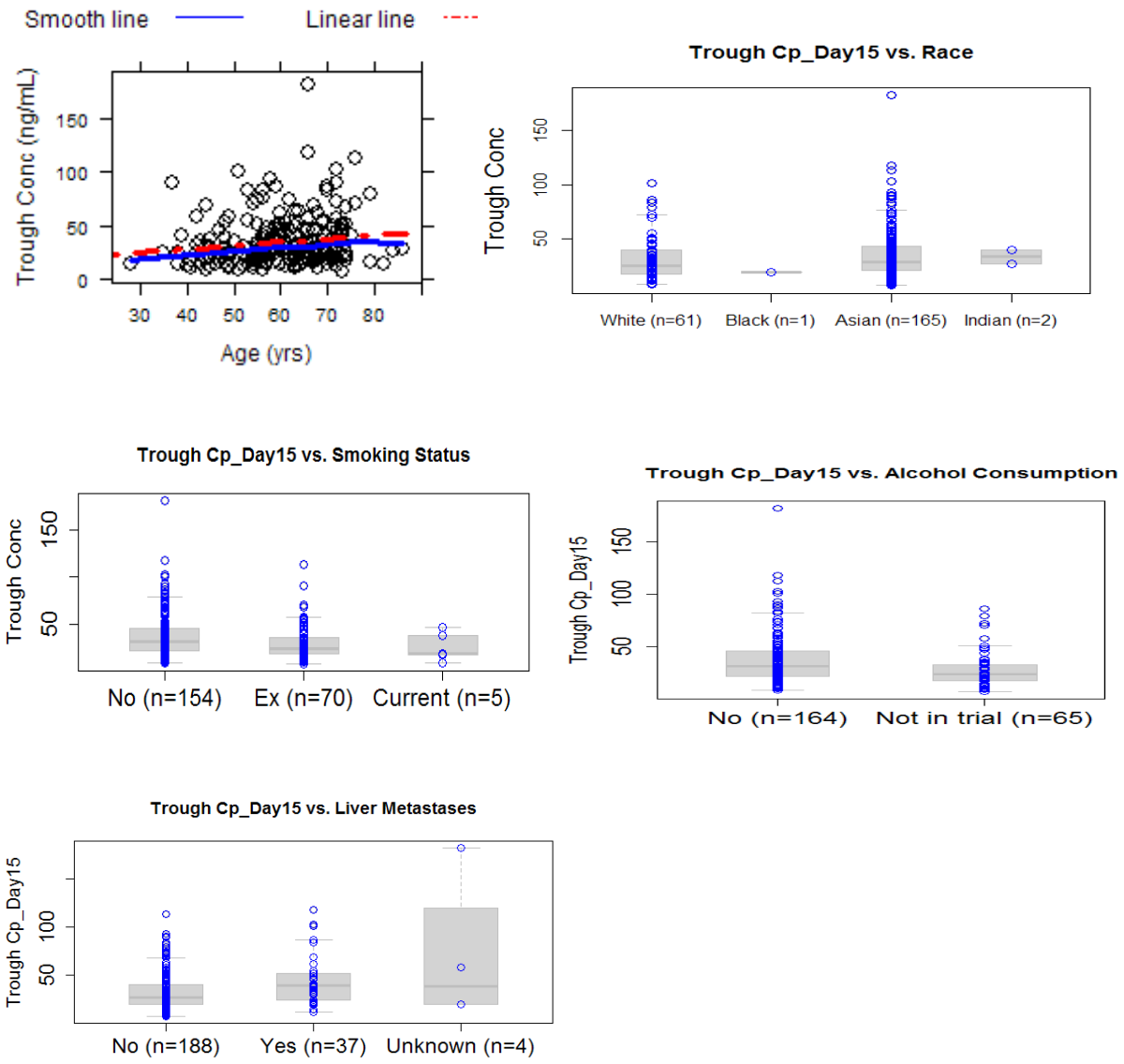
Gender

The median trough plasma concentration of afatinib is approximately 40% higher in females than that of males in the registration trial. According to the applicant's population PK analysis, gender is a significant covariate after adjusting for the body size. However, the exposure difference due to gender is not considered clinically relevant and no dose adjustment is recommended.

Age, Race, and Other Extrinsic/Intrinsic Factors

Age, race, smoking history, alcohol consumption, or presence of liver metastases has no clinical meaningful effect on the exposure of afatinib and no dose adjustment is recommended for these factors (Figure 3).

Figure 3. Association between trough afatinib levels and age, race, smoking status, alcohol consumption, and liver metastases in the registration trial at a dose of 40 mg.



CONCLUSION

These updated data analysis results warrant a clinical pharmacokinetic trial in subjects with moderate and severe renal impairment as post marketing requirement (PMR), which is described as following:

Conduct a pharmacokinetic trial to determine the appropriate doses of afatinib in patients with moderate and severe renal impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

DETAILED LABELING RECOMMENDATIONS

Only relevant renal impairment sections in clinical pharmacology perspective are included. An underline represents FDA recommended labeling modification, and ~~strikethroughs~~ represents content that is taken out from the Applicant proposed labeling.

8 USE IN SPECIFIC POPULATIONS

8.7 Renal Impairment

GILOTRIF has not been studied in patients with severely impaired renal function (creatinine clearance [CLcr] <30 mL/min). Adjustments to the starting dose of GILOTRIF are not considered necessary in patients with mild (CLcr 60-89 mL/min) [redacted] (b) (4) renal impairment. Closely monitor patients with moderate (CLcr 30-59 mL/min) to severe (CLcr < 30 mL/min) renal impairment and adjust GILOTRIF dose if not tolerated [*see Clinical Pharmacology (12.3)*].

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Renal Impairment: The median trough afatinib plasma concentrations in patients with mild (CLcr 60-89 mL/min) and moderate (CLcr 30-59 mL/min) renal impairment were [redacted] (b) (4) 27% and [redacted] (b) (4) 85% higher than those in patients with normal renal function (CLcr ≥ 90 mL/min). GILOTRIF has not been studied in patients with severely impaired renal function (CLcr <30 mL/min) [*see Use in Specific Populations (8.7)*].

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

/s/

JUN YANG
07/11/2013

RUNYAN JIN
07/11/2013

KEVIN M KRUDYS
07/11/2013

HONG ZHAO
07/11/2013
I concur.

NAM ATIQUR RAHMAN
07/11/2013

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1 EXECUTIVE SUMMARY

Afatinib is developed to irreversibly inhibit the tyrosine kinase auto-phosphorylation of the EGFR receptor family with down-regulation of signaling. The applicant proposed indication for afatinib is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. FDA has determined that the clinical trial data only supports the indication for the first line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The efficacy and safety of afatinib were assessed in a randomized (2:1), open-label registration trial in EGFR-TKI treatment naïve patients (N=345) with metastatic NSCLC. A four months improvement in median progression free survival (PFS) was achieved in the afatinib arm as compared to the chemotherapy arm (11.0 vs. 6.9 months) with the hazard ratio (HR) of 0.58 (95% CI: 0.43, 0.78) in favor of afatinib arm. The most common adverse reactions associated with afatinib treatment are diarrhea, rash/acne, stomatitis, and paronychia.

The proposed starting dose for afatinib is 40 mg orally once daily and may be (b) (4) reduced to 30 or 20 mg based on tolerability. FDA recommends capping the maximum daily dose at 40 mg based on clinical observations showing that 10 out of 16 patients who were escalated to 50 mg daily dose subsequently experienced dose reduction to 40 mg or 30 mg. The exposure-response relationship suggests that a titration to (b) (4) dose may not provide additional PFS benefit.

The major form of afatinib presented in human plasma is covalent adducts to plasma proteins and minor metabolites catalyzed by CYP450 enzymes. Fecal elimination of oral afatinib is approximately 85% while 4% is eliminated in urine. Mild to moderate hepatic impairment or mild renal impairment had no effect on afatinib exposure, and moderate renal impairment increased afatinib exposure. The effect of severe hepatic impairment or severe renal impairment on afatinib exposure has not been studied. Patients with severe hepatic impairment or moderate to severe renal impairment should be monitored for toxicity and reduce afatinib dose if not tolerated. Afatinib is a substrate and inhibitor of P-gp transporter. Exposure to afatinib was changed when it was administered with ritonavir (a P-gp inhibitor) or rifampicin (a P-gp inducer). Concomitant use of oral P-gp inhibitors or P-gp inducers with afatinib is not recommended. For patients who require therapy with an oral P-gp inhibitor, reduce afatinib daily dose by 10 mg if not tolerated. For patients who require a chronic oral P-gp inducer, increase afatinib daily dose by 10 mg based on tolerability.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language (see 3. for detailed labeling recommendations).

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

None

Signatures:

Runyan Jin, Ph.D. Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5
Jun Yang, Ph.D. Pharmacometrics Reviewer Division of Clinical Pharmacology 5	Kevin Krudys, Ph.D. Pharmacometrics Secondary Reviewer Division of Pharmacometrics
Rosane Charlab Orbach, Ph.D. Genomics Reviewer Genomics Group	Michael Pacanowski, Pharm.D., M.P.H. Associate Director for Genomics Genomics Group
	Atiqur Nam Rahman, Ph.D. Division Director Division of Clinical Pharmacology 5
Cc: DDOP2: MO – Shakun Malik; MTL – Anthony Murgo; RPM – Deanne Varney DCP-5: DDD –Brian Booth; DD – Atiqur Nam Rahman GG: AD – Michael Pacanowski	

A Required Office of Clinical Pharmacology Office Level Briefing was held on April 18, 2013 attended by Atiqur Rahman, Brian Booth, Julie Bullock, Anthony Murgo, Gideon Blumenthal, John Lazor, Mehul Mehta, Qi Liu, Joe Grillo, Gene Williams, and Ruby Leong.

1.3 CLINICAL PHARMACOLOGY SUMMARY

Mechanism of Action and Indication: Afatinib is a kinase inhibitor that covalently binds to the kinase domains of EGFR, HER2 and HER4 and irreversibly inhibits the tyrosine kinase autophosphorylation of the EGFR receptor family with downregulation of signaling. Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation in cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations that could be achieved clinically. *In vivo* treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with wild type EGFR or HER2 overexpressing tumors.

Afatinib is proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. FDA recommended indication is for the first line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Refer to clinical review and genomic review for details.

Dosing Regimen: The proposed starting dose for afatinib is 40 mg orally once daily and food should not be taken for at least [redacted] (b) (4). Treatment interruption and dose reduction by 10 mg decrements to minimum dose of 20 mg/day are proposed for patients with prolonged/intolerable Grade 2 or Grade ≥3 adverse reactions. (b) (4) [redacted] FDA recommends capping daily dose at 40 mg because [redacted] (b) (4) 10/16 patients who were escalated to 50 mg daily dose experienced dose reduction to 40 mg or 30 mg. The exploratory exposure-response analysis suggests that a titration to 50 mg dose may not provide additional benefit for progression free survival (PFS). Based on the observed decrease in afatinib exposure (39% in $AUC_{0\text{-}inf}$ and 50% in C_{max}) after a high-fat meal as compared to that under the fasted condition, FDA recommends afatinib to be taken at least one hour before or two hours after a meal.

Efficacy and Safety: The efficacy and safety of afatinib were assessed in a randomized (2:1), open-label registration trial in EGFR-TKI naïve patients with metastatic NSCLC. A four-month improvement in the median PFS, the primary endpoint, was achieved in the afatinib arm as compared to the chemotherapy arm (11.0 vs. 6.9 months) with hazard ratio (HR) of 0.58 (95% CI: 0.43, 0.78). The estimated probability to be alive and progression-free after 12 months was 47% in the afatinib arm compared with 22% in the chemotherapy arm. The most frequent (>10%) reported adverse reactions leading to dose reduction in the registration trial were diarrhea, rash/ache, paronychia, and stomatitis. Approximately 39% of patients had a grade 3 event that lead to dose reduction. Thirteen patients (5.7%) in the afatinib arm and 3 patients (2.7%) in the control arm had adverse reactions with fatal outcome.

Pharmacokinetics: The median time to reach peak plasma concentration (T_{max}) was 5 hours after a single oral dose and 3 hours after repeat doses of afatinib tablets. The increase in C_{max} and $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}24hr}$ in the dose range of 20 to 50 mg were more than dose-proportional for both single and multiple doses. Steady state was attained within 8 days of afatinib once daily

administration with overall accumulation ratios of 2.8 for AUC and 2.1 for C_{max}. The elimination half-life was 21-27 hours after a single dose and 45 hours at steady state. The human plasma protein binding of afatinib was 95%. The relative bioavailability was 92% (90% CI: 76%, 112%) based on $AUC_{0\text{-}inf}$ after a single dose of 20 mg tablet compared to the oral solution. A mass balance study suggested that the major route of excretion of afatinib was via feces (85%) while 4% in urine.

Metabolism and Drug Interactions: CYP450 enzyme has a minor role in afatinib metabolism *in vitro* and *in vivo*. The major form of afatinib in human plasma is afatinib covalent adducts to plasma proteins. Afatinib is a substrate and inhibitor (Ki=3.4 μM) for P-gp transporter and exposure to afatinib was changed when it was administered with a P-gp inhibitor, ritonavir (AUC increased by 48%) or with a P-gp inducer, rifampicin (AUC decreased by 34%). Avoid use of orally administered P-gp inhibitors or P-gp inducers is recommended. For patients who require therapy with an oral P-gp inhibitor, reduce afatinib daily dose by 10 mg if not tolerated. For patients who require a chronic oral P-gp inducer, increase afatinib daily dose by 10 mg based on tolerability.

Specific Populations: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinical relevant effect on exposure of afatinib. As compared to the subjects with normal hepatic function, there were no changes in $AUC_{0\text{-}inf}$ in patients with mild or moderate hepatic impairment (HI). While mild renal impairment has no effect on afatinib systemic exposure, moderate renal impairment increased afatinib steady state trough concentrations. The effect of severe hepatic impairment or severe renal impairment on afatinib exposure has not been studied. Patients with severe hepatic impairment or moderate to severe renal impairment should be monitored for toxicity and reduce afatinib dose if not tolerated.

Exposure-Response Relationship: The results of exposure-efficacy analyses for the registration trial suggest that patients in the highest quartile of steady state AUC at final dose (AUC_f Q4) exhibit significant shorter PFS than those of other quartiles and have comparable PFS to control arm. Similar results were obtained for PFS and quartile of first cycle afatinib trough concentration on Day 15 based on a Kaplan-Meier analysis in patients (N=91) who only received the 40 mg daily dose and did not experience a dose reduction. The results of logistic regression analyses suggest that higher exposure of afatinib increases the risk of experiencing CTCAE grade ≥3 toxicity or grade 2 or higher diarrhea event, which are consistent with the clinical observation that majority of patients who were escalated to 50 mg dose required dose reduction. The applicant's proposed dose de-escalation scheme based on patient's tolerability appears reasonable; however, patients in the highest quartile of steady state AUC did not show a PFS benefit, suggesting that the driving force for PFS may not be the afatinib exposure once the exposure has reached certain levels, but the patient's sensitivity to afatinib treatment or other unknown factors.

Pharmacogenomics: EGFR mutations are considered the strongest predictor of response to treatment with EGFR TKIs in metastatic NSCLC. The best characterized mutations associated with EGFR TKI sensitivity are the deletions in exon 19 and the L858R substitution in exon 21, which account for approximately 90% of all reported EGFR mutations. Some other EGFR mutations (e.g., exon 20 insertions, T790M) are associated with lower sensitivity to clinically

achievable doses of EGFR TKIs. Patients with tumors harboring different types of EGFR mutations were enrolled in the afatinib pivotal trial 1200.32. The EGFR mutations were identified with the use of a PCR-based diagnostic test designed to detect 19 deletions in exon 19 (Del 19), L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. The purpose of this review is to assess outcomes in patients according to the EGFR mutation and determine whether the indication should be limited based on the type of EGFR mutation. Randomization was stratified by EGFR mutation status (L858R, Del 19, other). The majority of enrolled patients (89.3%) had Del 19 or L858R positive-tumors. Uncommon or "other" mutations (i.e. EGFR mutations other than Del 19 and L858R alone) were detected in only 37 patients (26 in afatinib and 11 in the chemotherapy arm) and represented a small and genetically heterogeneous group, in which a total of 10 different subtypes of EGFR mutations were identified. Patients with exon 19 deletions or exon 21 L858R showed PFS improvement. This effect was more pronounced in the subset with exon 19 deletions. Conversely, subgroup analysis in patients with "other" EGFR mutations suggested a detrimental effect on both PFS [HR 1.89; (95% CI 0.84, 4.28)] and OS [HR 3.08; (95% CI 1.04, 9.15)] for afatinib-treated patients compared with chemotherapy. The results of the pivotal trial suggest that afatinib may be detrimental to NSCLC patients with some of the uncommon mutation subtypes in the "other" category subset. However, there is limited data to adequately establish efficacy within the subset. We therefore recommend that the afatinib treatment should be indicated to patients with EGFR exon 19 deletion or L858R substitution mutations.

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

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

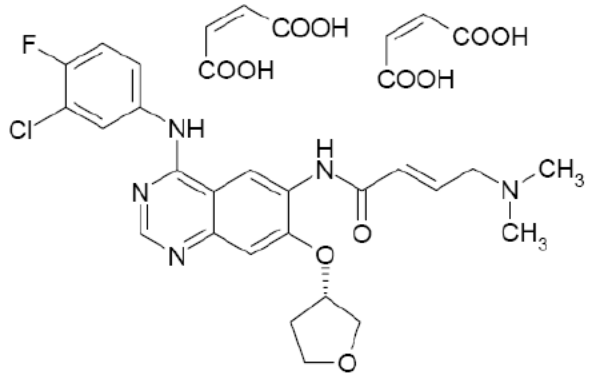
What is the pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Fast Track: Afatinib received Fast Track Designation under IND 67,969 on November 11, 2007, for locally advanced or metastatic NSCLC, which has failed treatment with an EGFR inhibitor and at least one prior line of cytotoxic chemotherapy.

Orphan Drug Designations: Afatinib received Orphan Drug Designation for treatment of EGFR mutation-positive NSCLC as detected by an FDA-approved test on December 3, 2012.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Afatinib base (MW=485.9 g/mol) is the active moiety and afatinib dimaleate (MW=718.1 g/mol) is the salt form (Figure 1).
Figure 1: Chemical Structural of Afatinib Dimaleate



$C_{24}H_{25}ClFN_5O_3 \times 2\ C_4H_4O_4$ or $C_{32}H_{33}ClFN_5O_{11}$

(Source: Figure on Page 5 of Quality Overall Summary)

Afatinib is highly soluble [redacted] (b) (4) in water and in aqueous buffer media up to pH 6. [redacted] (b) (4)

[redacted] (b) (4) dosage strengths (20, 30, 40, [redacted] (b) (4) film coated tablets) are available for oral administration. FDA recommends [redacted] (b) (4) as afatinib maximum

starting dose will be capped at 40 mg/day (see section 1.5.4.4). Afatinib formulation changes during clinical development and their use in the different clinical trials is summarized in section 2.5.

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

Afatinib is a kinase inhibitor that covalently binds to the kinase domains of EGFR, HER2 and HER4 and irreversibly inhibits the tyrosine kinase autophosphorylation of the EGFR receptor family with downregulation of signaling. Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation in cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations that could be achieved clinically. *In vivo* treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with wild type EGFR or HER2 overexpressing tumors.

Afatinib is proposed for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. Based on clinical data provided in the NDA, FDA recommended indication is for the first line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

2.1.3 What are the proposed dosage and route of administration?

The proposed starting dose for afatinib is 40 mg orally once daily. Treatment interruption and dose reduction by 10 mg decrements are proposed for patients with prolonged/intolerable Grade 2 or Grade ≥3 adverse reactions. (b) (4) FDA recommends capping the maximum daily dose at 40 mg because clinical observations do not support the titration to a 50 mg dose as 10/16 patients who were escalated to 50 mg daily dose experienced dose reduction to 40 mg or 30 mg. The exposure-response relationship suggests that a titration to 50 mg dose may not provide additional PFS benefit.

Applicant proposed that food should not be taken for at leas (b) (4) after taking afatinib. FDA recommends taking afatinib at least 1 hour before or 2 hours after a meal (see food effect section 2.5.6).

2.2 GENERAL CLINICAL PHARMACOLOGY

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

The clinical pharmacology program for afatinib is composed of 17 Phase 1 trials, 2 Phase 1/2 trials, 10 Phase 2 trials and 2 Phase 3 trials. The Phase 1 trials include pharmacokinetic (PK) characterization, mass balance, relative BA, food-effect, drug-drug interaction (DDI) and hepatic impairment studies. The clinical pharmacology studies to support afatinib monotherapy for the indication of NSCLC are listed in Table 1. In addition, a PK meta-analysis was conducted across

monotherapy studies 1200.1, 1200.2, 1200.3, 1200.4 and 1200.24 using noncompartmental analysis.

Table 1: Summary of Clinical Pharmacology Studies of Afatinib

Study Report	Phase	Objective	Design	Treatments	Population
1200.1	1	MTD, safety, efficacy, PK and PD	dose escalation, dense PK sampling	10-100 mg, qd, 14/28-day treatment cycle	Patients with advanced solid tumors
1200.2	1	MTD, safety, efficacy, PK and PD	dose escalation, dense PK sampling	10-65 mg, qd, 21/28-day treatment cycle	Patients with EGFR/HER2 expressing solid tumors
1200.3	1	• MTD, safety, efficacy, PK and PD • Food effect	dose escalation, dense PK sampling	10-50 mg, qd, continuously over 28-day treatment cycle	Patients with advanced solid tumors
1200.4	1	MTD, safety, efficacy and PK	dose escalation, dense PK sampling	10-60 mg, qd, continuously over 28-day treatment cycle	Patients with advanced solid tumors
1200.25	1	ADME and PK	Mass balance	Single oral dose of 15 mg containing [^{14}C] radiolabelled afatinib	Healthy male subjects (n=8)
1200.35	1	Relative BA and PK of 20 mg film-coated IR afatinib (FF/TF 2) vs. drinking solution	3-way crossover	a single dose of 20 mg	Healthy male subjects (n=22)
1200.80	1	PK, safety, and tolerability	single rising dose, 4 sequential dose groups	Single oral dose of 20-50 mg (FF)	Healthy male subjects (n=48)
1200.86	1	The impact of mild and moderate hepatic impairment on afatinib PK	Single dose, dose escalation, intensive PK sampling	A single dose of 30-50 mg	• Mild (n=8) and moderate (n=14) hepatic impairments • Healthy subject (n=16)

1200.79	1	Pgp DDI: effect of ritonavir on afatinib PK	2-way crossover	• A single oral dose of 20 mg afatinib • Ritonavir 200 mg bid for 3 days	Healthy male subjects (n=22)
1200.151	1	Pgp DDI: effect of ritonavir on afatinib PK	3-way crossover	• A single oral dose of 40 mg afatinib • Ritonavir 200 mg simultaneously with afatinib • Ritonavir 200 mg given 6 hours after afatinib	Healthy male subjects (n=24)
1200.152	1	Pgp DDI: effect of rifampicin on afatinib PK	two-period, fixed sequence	• A single oral dose of 40 mg afatinib • Rifampicin 600 mg qd for 7 days	Healthy male subjects (n=22)
1200.33	1/2	MTD, PK, efficacy,	dose escalation	20-50 mg, qd, continuously over 28-day treatment cycle	Japanese NSCLC patients
1200.22	2	Efficacy, safety, and PK	Open-label, multi-center, monotherapy	• A starting dose of 50 or 40 mg, qd • Dose reduction to 40 and 30 mg qd if intolerance	NSCLC patients
1200.26	2	Efficacy and PK	Open-label, non-controlled, multi-centre	• A starting dose of 50 mg, qd • Dose reduction to 40 and 30 mg qd if intolerance	EGFR positive cancer patients
1200.24	2	Cardiac safety (QTcF) and efficacy	Open-label, multicenter,	50 mg, qd	Cancer patients with advanced solid tumors
1200.23	2b/3	Efficacy,	Double-blind,	• A starting	NSCLC

		safety, and PK	randomized, two-arm (afatinib + BSC vs. placebo + BSC)	dose of 50 mg, qd • Dose reduction to 40 and 30 mg qd if intolerance	patients and EGFR TKI pre-treated
1200.32	3	Efficacy, safety, and PK	Open-label, randomized (2:1), active-controlled, parallel-grouped, two-arm (afatinib vs. pemetrexed/cisplatin)	• A starting dose of 40 mg, qd • Dose escalation to 50 mg qd or reduction to 40, 30, or 20 mg qd if required	NSCLC patients and treatment naive

Four population PK analyses were performed to characterize the PK profile of afatinib and evaluate the effect of intrinsic and extrinsic factors on the PK of afatinib (Table 2).

Table 2: Summary of Population PK Analyses of Afatinib

	Combined PK studies	Objective	Clinical Phase
PopPK1	1200.1-3	Development of a PPK model and simulation of different administration schedules	1
PopPK2	1200.1-4 and 1200.20	Characterizing dose nonlinearity of afatinib and PK after single and multiple administration	1
PopPK3	1200.10-11 and 1200.22-23	Development of a PPK model in NSCLC and breast cancer patients to assess the effects of intrinsic and extrinsic factors on afatinib PK	2/3
PopPK4	Data in PopPK3 + 1200.28 and 1200.32-33	Development of a PPK model in patients with various cancer types and to re-assess the effects of intrinsic and extrinsic factors on afatinib PK	2/3

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

The evaluation of afatinib efficacy is mainly based on one registration trial (1200.32) and three supportive trials (1200.22, 1200.23, and 1200.42 Part A) in patients with NSCLC (Table 3).

Table 3: An Overview of the Clinical Efficacy and Safety Trials

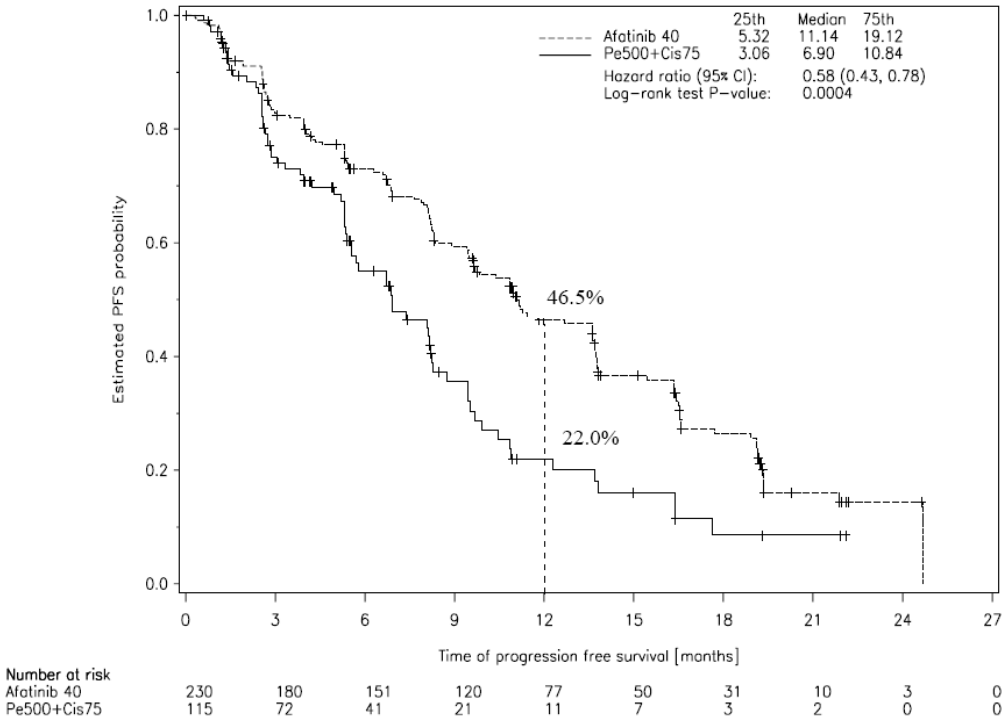
Trial	Primary endpoint	Major Secondary endpoints	Line of treatment	Prior EGFR TKI	Afatinib starting dose	Control group
1200.32	PFS	PRR, DCR, OS, QoL	First	No	40 mg (n=230)	Pemetrexed/ cisplatin (n=115)
1200.22	ORR,	PFS, OS	First or second	No	40 or 50 mg (n=129)	uncontrolled
1200.23	OS	PFS, ORR, HR QoL	Third or fourth	Yes	50 mg (n=390)	Placebo
1200.42	PFS	ORR, OS	Second or later	Yes	50 mg (n=1154)	uncontrolled

The PFS was chosen as the primary endpoint in the first-line chemotherapy-controlled trial 1200.32 (registration trial) for the following reasons:

- Any study drug effect on overall survival (OS) would likely be obscured because the patients in the control arm were expected to cross over to the test arm after disease progression.
- Any study drug effect on OS could be further confounded due to the high likelihood of multiple lines of subsequent therapy considering the relatively long expected survival time of patients with NSCLC receiving first-line treatment.

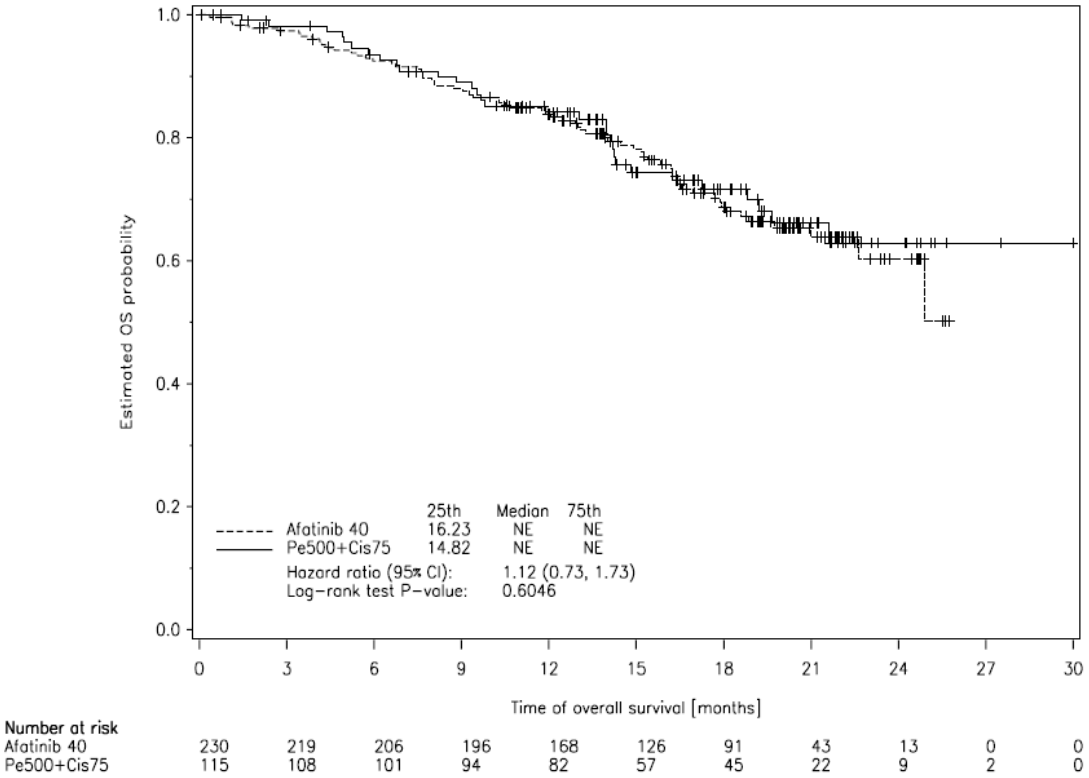
The median PFS in the afatinib arm was reported 4 months longer than that in the controlled arm (afatinib: 11.0 months; chemotherapy: 6.9 months) in the registration trial (Figure 2). The estimated probability to be alive and progression-free after 12 months was 46.5% in the afatinib arm compared with 22% in the chemotherapy arm. As the cutoff of February 2012, the OS data of trial 1200.32 were not conclusive (Figure 3). The probability to be alive at 24 months was estimated to be 60.3% in the afatinib arm and 62.9% in the chemotherapy arm.

Figure 2: Kaplan-Meier Estimates of PFS by Central Independent Review in Trial 1200.32



(Source: Figure 4.3.1:1 on Page 28 of Clinical Overview)

Figure 3: Kaplan-Meier Estimates of Overall Survival in Trial 1200.32 at Cutoff of February 2012)



(Source: Figure 4.3.1:3 on Page 31 of Clinical Overview)

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

Yes, afatinib in the human plasma and urine was appropriately identified and measured using a validated high performance liquid chromatography assay coupled to tandem mass spectrometry (HPLC-MS/MS). No metabolites were measured due to trace amount. See Section 2.6.

2.2.4 Exposure-response

2.2.4.1 Is there an exposure-response (E-R) relationship for progression free survival (PFS), the primary efficacy endpoint?

The E-R relationship between the primary efficacy endpoint, PFS and quartiles of steady state AUC at final titration dose (AUC_f) in patients treated with afatinib in the registration trial was evaluated by a Kaplan-Meier analysis. The results indicate that patients in the highest exposure quartile (Q4) have comparable PFS to the control arm and exhibit shorter PFS than those of other quartiles (Figure 4A). EGFR status, smoking status, ECOG performance, baseline tumor size, gender, body weight, Asian status, and final titration dose were all approximately evenly distributed across different quartiles of AUC_f. Similar results were obtained for PFS and quartile of first cycle afatinib trough concentration on Day 15 (CP_day15) based on a Kaplan-Meier analysis in patients (N=91) who only received the 40 mg daily dose and did not experience a dose reduction (Figure 4B), suggesting that patients with higher exposure may not have PFS benefit. Because the dose de-escalation is based on a patient's tolerability, the E-R analysis results indicate that patients who can not tolerate high exposure may be more sensitive to afatinib treatment. These results suggest that titration to a 50 mg dose may not provide additional PFS benefit in NSCLC patients (See pharmacometrics review for detail analyses).

Figure 4: E-R Relationship for PFS Stratified by Quartiles of Steady State AUC at Final Dose (AUC_f (4A) and First Cycle Afatinib Trough Level (4B) in Afatinib Arm.

Figure 4A: PFS vs. Afatinib AUC_f

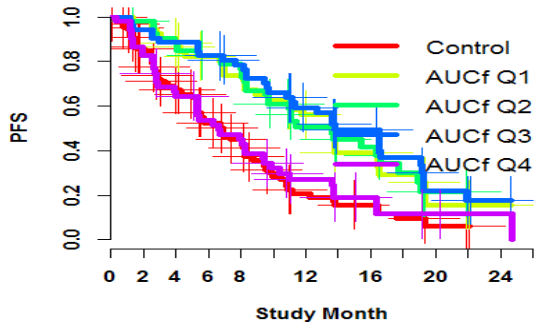
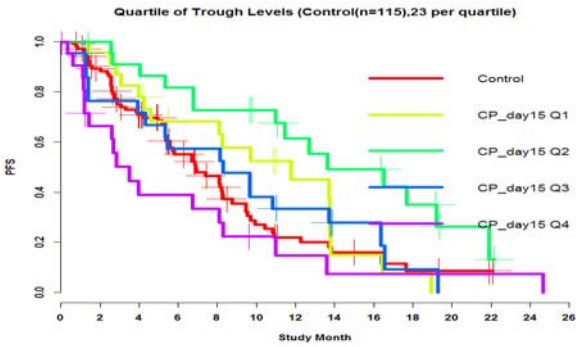


Figure 4B: PFS vs. First Cycle Afatinib Trough Level on Day15



2.2.4.2 Is there evidence of exposure-response (E-R) for safety?

Patients in the afatinib treatment group also experienced higher incidence of adverse events (AEs) with the most frequent AEs leading to dose reduction being diarrhea (19.7%), rash/acne (19.2%), nail effects (13.5%), and stomatitis (10.0%). In the registration trial 1200.32, 83.5% of patients experienced their first diarrhea episode within 14 days of beginning afatinib treatment at the 40 mg starting dose. Therefore, the observed afatinib trough concentration at day15 (CP_day15) were used for the E-R analyses for Common Terminology Criteria for Adverse Events (CTCAE, grade ≥3) and the two most common AEs, diarrhea and skin rash/acne (grade ≥2). The results of logistic regression analyses suggest that higher exposure of afatinib increases the risk of experiencing CTCAE grade ≥3 toxicity (Figure 5) or grade 2 or higher diarrhea event (Figure 6A). There was no E-R relationship between grade 2 and higher rash/acne event and afatinib exposure (Figure 6B). The E-R for safety analyses is consistent to the clinical observation that 10 of the 16 patients who were escalated to 50 mg QD dose experienced dose reduction (See pharmacometrics review for detail analyses).

Figure 5: Relationship between Experiencing CTCAE grades >=3 Toxicity and Trough Afatinib Levels in Cycle 1 (CP_day15)

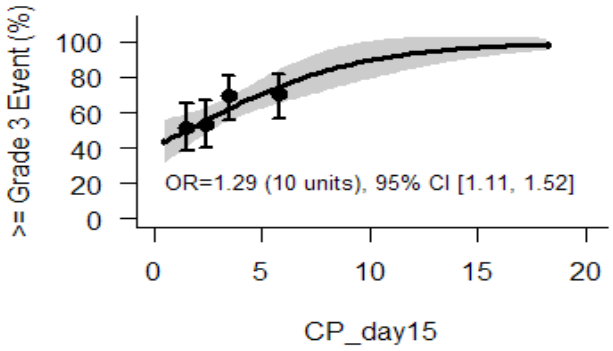
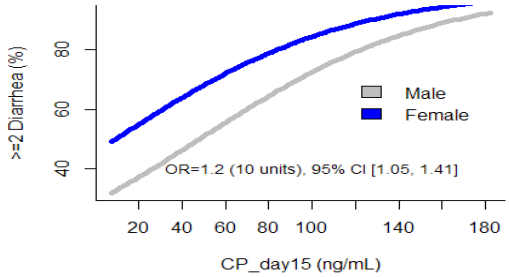
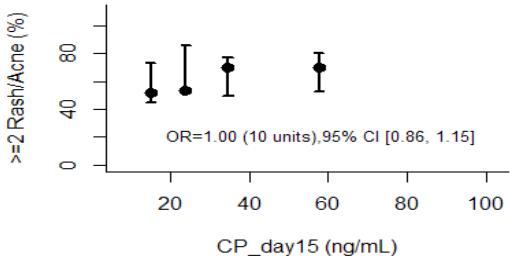


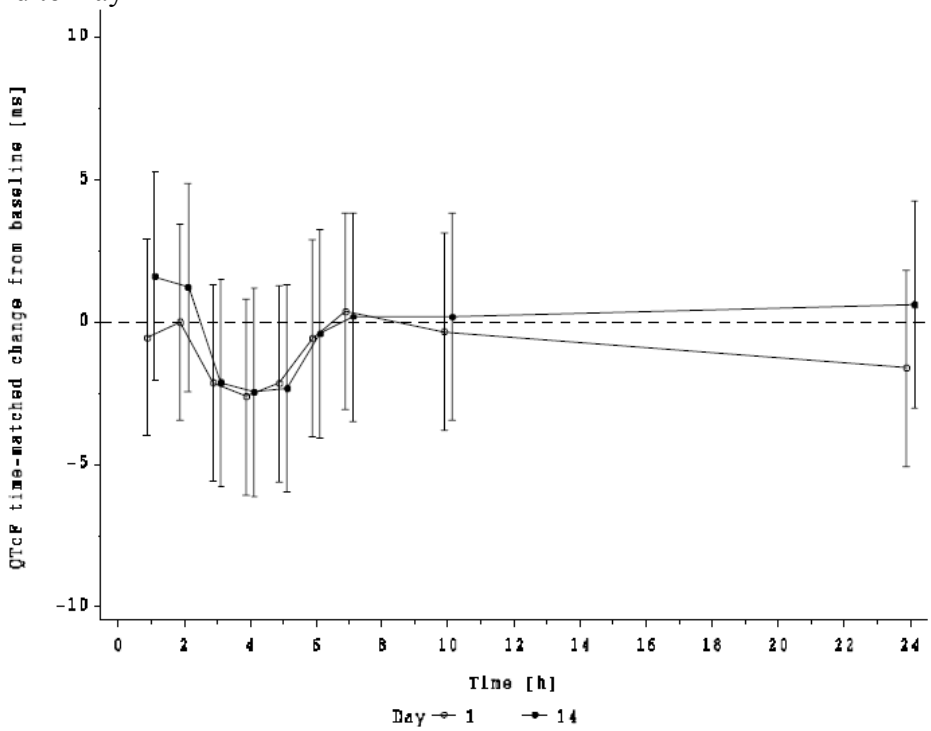
Figure 6: Relationship between Experiencing grade >=2 Diarrhea or Rash/Acne and Trough Afatinib Levels in Cycle 1 (CP_day15).

Figure 6A: Cp_day15 vs. grade >=2 Diarrhea	Figure 6B: Cp_day15 vs. grade >=2 Rash/Acne
	

2.2.4.3 Does this drug prolong the QT or QTc interval?

The effect of orally administered 50 mg afatinib once daily for 14 days on QTc interval was evaluated in an open-label, single arm study (1200.24) in 49 cancer patients. The mean time-matched QTcF over 1 to 24 hour showed a decrease of 0.3 ms (90% CI -2.8, 2.3) between baseline and Day 14 and a decrease of 1.0 ms (90% CI -2.2, 0.2) from baseline to Day 1. The time profiles of mean QTcF changes and the corresponding 90% CI between 1 and 24 hours from baseline to Day 1 and to Day14 are shown in Figure 7. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

Figure 7: Time Profile of Time-matched Adjusted Mean QTcF Changes from Baseline to Day 1 and to Day 14



(Source: Figure 5.2:6 on Page 174 of Summary of Clinical Pharmacology Studies)

A linear mixed model was used to quantify the potential relationship between plasma concentration of afatinib and the time-matched changes in QTcF and QT between baseline and Days 1 and 14. The estimated slopes were close to zero, which indicated that there was no relationship between exposure to afatinib and prolongation of QTcF or QT.

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

The Maximum Tolerated Dose (MTD) of afatinib tablet was determined as 50 mg once daily in 3 Phase 1 dose-escalation trials (1200.2-4) in patients with various solid tumors. Diarrhea and dehydration occurred more frequently at daily dose of 55 mg and above. Based on the identified MTD in phase 1 trials, 50 mg afatinib was chosen as starting dose for once daily dosing in the Phase 2 and 3 trials. Similar efficacy was demonstrated between 50 mg and 40 mg as starting

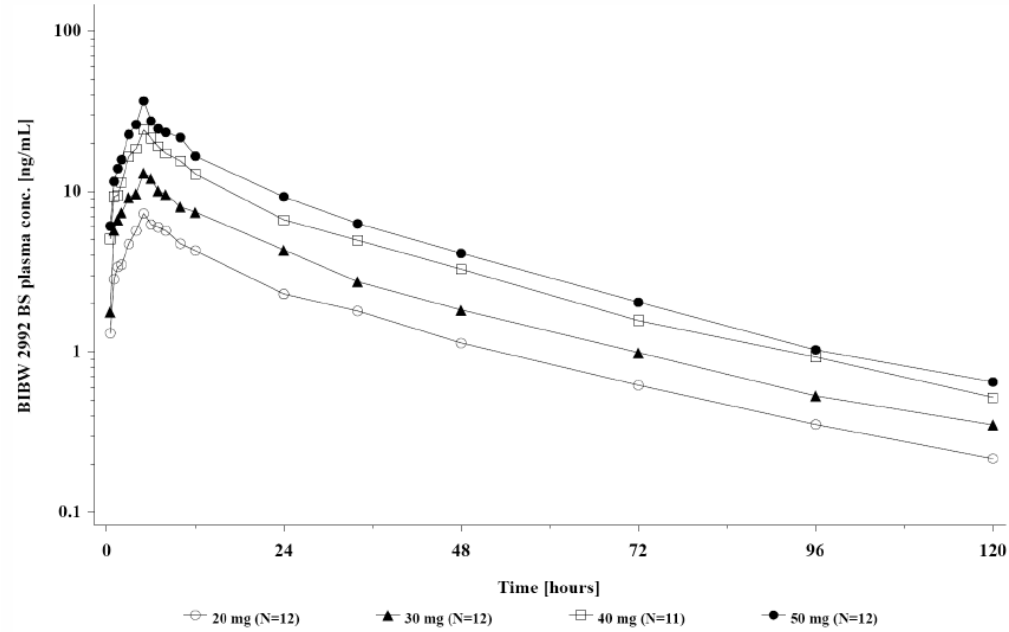
dose in the trial 1200.22 while a better tolerability was seen for the 40 mg starting dose. Therefore, the 40 mg starting dose was selected for the registration trial 1200.32. After the first cycle treatment with daily 40 mg dose, 16 patients had the dose escalated to 50 mg as they tolerated 40 mg well. However, 13 of those 16 patients at the 50 mg regimen experienced dose reduction. Therefore, 40 mg as the starting dose provided a better balanced profile of efficacy/toxicity than 50 mg, which is consistent with the E-R relationship identified (see Section 2.2.4.1 and 2.2.4.2). The high frequency of dose reduction (63%) at 50 mg in trial 1200.32 and no additional PFS benefit provided at 50 mg dose [redacted] (b) (4) FDA recommends capping the maximum daily dose at 40 mg.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single-dose and multiple dose pharmacokinetic parameters?

The PK after single oral doses of 20 to 50 mg afatinib final formulation (FF) tablets was characterized in healthy subjects (study 1200.80). The mean plasma concentration-time profiles in log scale are shown in Figure 8. The peak plasma concentration (C_{max}) was reached approximately 5 hours post-dose (Table 4). The estimated elimination half-life ranged 28.5 to 32.9 hours. The increase in C_{max} and $AUC_{0\text{-}inf}$ in the dose range of 20 to 50 mg appears to be more than dose-proportional.

Figure 8: Mean Plasma Concentration-Time Profiles of Afatinib after Single-Dose of 20-50 mg to Healthy Male Subjects



(Source: Figure 5.2:3 on Page 171 of Summary of Clinical Pharmacology Studies in the NDA)

Table 4: Comparison of PK Parameters of Afatinib after Single Dose of 20-50 mg

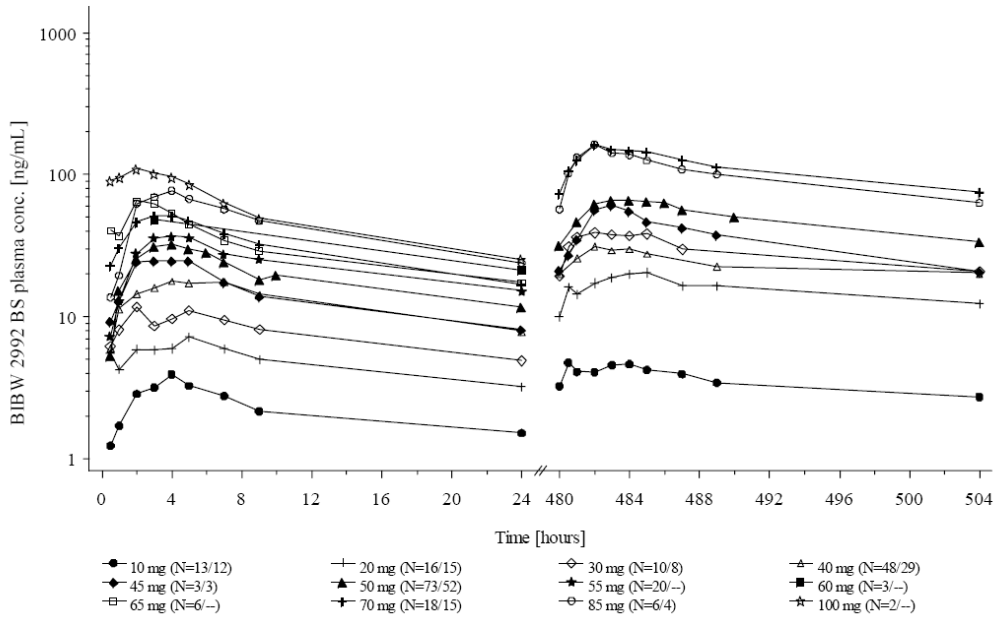
		20 mg (N=12)		30 mg (N=12)		40 mg (N=11)		50 mg (N=12)	
Parameter	Unit	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{0-\infty}$	[ng h/mL]	189	35.1	327	35.5	549	32.1	724	48.7
$AUC_{0-\infty,norm}$	[ng h/mL/mg]	9.43	35.1	10.9	35.5	13.7	32.1	14.5	48.7
C_{max}	[ng/mL]	7.78	42.3	13.7	44.7	24.3	33.1	37.1	37.4
$C_{max,norm}$	[ng/mL/mg]	0.389	42.3	0.457	44.7	0.608	33.1	0.741	37.4
t_{max} [1]	[h]	5.00	(2.00-8.00)	5.00	(1.00-6.00)	5.00	(5.00-6.00)	5.00	(4.00-5.00)
$t_{1/2}$	[h]	30.7	10.6	32.9	24.8	29.6	12.6	28.5	15.5
MRT_{po}	[h]	36.8	12.3	36.1	22.8	33.6	10.1	32.0	13.4
CL/F	[mL/min]	1770	35.1	1530	35.5	1210	32.1	1150	48.7
V_z/F	[L]	4700	43.9	4350	42.7	3110	39.1	2840	54.8

[1] Median and range are given.

(Source: Table 3.2.2:2 on Page 94 of Summary of Clinical Pharmacology Studies)

The PK of single and multiple doses of 10 to 100 mg afatinib tablets in cancer patients was assessed in a meta-analysis including studies 1200.1-4 and 1200.24. The mean plasma concentration-time profiles in log scale are shown in Figure 9. The median time to reach maximum plasma concentration (T_{max}) was around 3 hours after a single dose (range: 2-4 hours) and after multiple doses (range: 2-5 hours) (Table 5). The overall estimated elimination half-life was 21.4 hours (range: 21.3 to 26.9 hours) after a single dose and 37.2 hours (range: 22.3 to 47.1 hours) at steady state. The steady state was attained within 8 days of afatinib once daily treatment. The overall accumulation ratios was 2.8 (range: 2.5 to 3.4) based on AUC and 2.1 (range: 2.0 to 2.7) based on C_{max}.

Figure 9: Mean Plasma Concentration-Time Profile of Afatinib after Daily Dosing of 10 to 100 mg tablets in Cancer Patients



(Source: Table 3.2.2:1 on Page 91 of Summary of Clinical Pharmacology Studies)

Table 5: Comparison of PK Parameters of Afatinib in Cancer Patients after Taking 20 to 50 mg and 10-100 mg Tablets in Cycle 1

		20 mg			30 mg			40 mg			50 mg			Overall (10- 100 mg)		
Parameter	Unit	N	gMean	gCV[%]	N	gMean	gCV[%]	N	gMean	gCV[%]	N	gMean	gCV[%]	N	gMean	gCV[%]
AUC_{0-24}	[ng·h/mL]	12	119	56.6	10	189	95.9	30	324	68.9	69	459	68.0			
$AUC_{0-24,norm}$	[ng h/mL/mg]	12	5.93	56.6	10	6.29	95.9	30	8.10	68.9	69	9.17	68.0	184	8.72	73.3
$AUC_{\tau,ss}$	[ng·h/mL]	15	380	77.2	8	660	92.4	26	631	85.9	51	1130	59.6			
$AUC_{\tau,ss,norm}$	[ng h/mL/mg]	15	19.0	77.2	8	22.0	92.4	26	15.8	85.9	51	22.6	59.6	148	20.2	80.5
C_{max}	[ng/mL]	13	11.6	85.1	10	16.3	139	30	25.2	73.3	73	40.8	76.6			
$C_{max,norm}$	[ng/mL/mg]	13	0.582	85.1	10	0.545	139	30	0.629	73.3	73	0.817	76.6	189	0.761	81.7
$C_{max,ss}$	[ng/mL]	15	24.5	88.5	8	46.5	120	27	38.0	105	51	77.0	63.6			
$C_{max,ss,norm}$	[ng/mL/mg]	15	1.23	88.5	8	1.55	120	27	0.950	105	51	1.54	63.6	149	1.33	92.0
t_{max}[1]	[h]	13	3.00	(0.500-24.0)	10	2.00	(0.567-6.92)	30	3.98	(0.583-9.10)	73	3.13	(0.900-9.05(	189	3.02	(0.467-24.0)
$t_{max,ss}$[1]	[h]	15	4.98	(0.500-9.08)	8	2.01	(0.517-4.00)	27	3.00	(0.467-23.8)	51	3.82	(1.00-7.05)	149	3.00	(0.467-23.8)
$t_{1/2}$	[h]	11	22.3	80.3	10	21.3	82.1	30	26.9	61.1	13	21.9	54.8	127	21.4	56.5
$t_{1/2,ss}$	[h]	15	47.1	51.6	7	33.4	56.8	23	36.3	57.1	7	22.3	25.4	100	37.2	45.5
CL/F	[mL/min]	11	1430	64.7	10	1370	72.9	30	952	86.2	13	1090	94.0	127	1050	76.3
$CL/F_{,ss}$	[mL/min]	15	877	77.2	8	758	92.4	25	1070	87.9	7	1390	47.3	104	898	89.2
V_z/F	[L]	11	2770	61.8	10	2520	109	30	2220	71.4	13	2080	123	127	1940	87.7
$V_z/F_{,ss}$	[L]	15	3570	107	7	2000	67.8	23	2870	101	7	2690	47.8	99	2770	99.3
$R_{A,AUC}$		11	3.14	27.6	8	3.40	83.1	9	2.53	48.0	49	2.61	59.1	120	2.77	63.1
$R_{A,Cmax}$		12	2.23	26.5	8	2.67	98.8	9	2.08	57.7	51	2.00	69.2	123	2.11	70.2

[1] Median and range are given.

(Source: Table 3.2.2:3 on Page 96 of Summary of Clinical Pharmacology Studies)

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

The PK parameters (mean and % CV) of afatinib in healthy subjects (study 1200.80) and in cancer patients (study 1200.1-4 and 1200.24) after single dose administration of 20 to 50 mg

tablets were summarized in Table 6. It appears that the mean values of PK parameters for healthy subjects are in the range of those for cancer patients at each dose level.

Table 6: Comparison of PK Parameters of Afatinib between Cancer Patients and Healthy Volunteers

Afatinib		20 mg			30 mg			40 mg			50 mg		
		N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]
Cancer patients													
AUC_{0-24}	[ng·h/mL]	12	119	56.6	10	189	95.9	30	324	68.9	69	459	68.0
C_{max}	[ng/mL]	13	11.6	85.1	10	16.3	139	30	25.2	73.3	73	40.8	76.6
t_{max}[1]	[h]	13	3.00	(0.500 -24.0)	10	2.00	(0.567 -6.92)	30	3.98	(0.583 -9.10)	73	3.13	(0.900 -9.05)
$t_{1/2}$	[h]	11	22.3	80.3	10	21.3	82.1	30	26.9	61.1	13	21.9	54.8
CL/F	[mL/min]	11	1430	64.7	10	1370	72.9	30	952	86.2	13	1090	94.0
V_z/F	[L]	11	2770	61.8	10	2520	109	30	2220	71.4	13	2080	123
Healthy subjects													
AUC_{0-24}	[ng·h/mL]	12	98.5	41.3	12	177	40.9	11	307	33.2	12	416	44.0
C_{max}	[ng/mL]	12	7.78	42.3	12	13.7	44.7	11	24.3	33.1	12	37.1	37.4
t_{max}[1]	[h]	12	5.00	(2.00-8.00)	12	5.00	(1.00-6.00)	11	5.00	(5.00-6.00)	12	5.00	(4.00-5.00)
$t_{1/2}$	[h]	12	30.7	10.6	12	32.9	24.8	11	29.6	12.6	12	28.5	15.5
CL/F	[mL/min]	12	1770	35.1	12	1530	35.5	11	1210	32.1	12	1150	48.7
V_z/F	[L]	12	4700	43.9	12	4350	42.7	11	3110	39.1	12	2840	54.8

[1] Median and range are given.

(Source: Table 3.2.3:1 on Page 102 of Summary of Clinical Pharmacology Studies)

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of a single dose of afatinib FF tablet, the median T_{max} was 5 hours post-dose (Table 7). Mean C_{max} and AUC_{0-inf} increased more than dose proportional in the range from 20 to 50 mg of afatinib. The T_{max} after repeat doses ranged 2-5 hours across studies (Table 5). Mean C_{max} and AUC_{0-24hr} at steady state also increased more than dose proportional.

The absolute bioavailability of afatinib has not been studied. The mean relative bioavailability was determined with the single dose of 20 mg FF tablet in comparison with the oral solution in study 1200.35, which was 92% (90% CI: 76%, 112%) based on AUC_{0-inf} and 85% (90% CI: 69%, 106%) based on C_{max} (Table 8). The PK parameters of afatinib after single oral administration of 20 mg as a FF tablet, trial formulation II (TFII) or as oral solution are shown in Table 8.

Table 7: Adjusted Geometric Means and Relative Bioavailability Comparison of Afatinib 20 mg as Final Formulation (FF) vs. Oral Solution

Parameter	Adjusted gMean		Adjusted gMean ratio FF/drinking solution	Two-sided 90% confidence interval		Intra-individual gCV	p-value for ratio outside [0.80, 1.25]
	Tablet FF	Drinking solution	[%]	Lower limit [%]	Upper limit [%]	[%]	
C_{max} [ng/mL]	4.223	4.950	85.31	68.745	105.878	42.3	0.3059
$AUC_{0-\infty}$ [ng·h/mL]	105.697	114.588	92.24	76.301	111.512	36.7	0.1048

(Source: Table 11.5.2.1.3:1 on Page 60 of Study 200.35)

Table 8: PK Parameters of Afatinib after Single Oral Administration of 20 mg as Tablet (FF, TFII) or as Oral Solution

	20 mg BIBW 2992 Tablet FF			20 mg BIBW 2992 Tablet TFII			20 mg BIBW 2992 Drinking solution		
	N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]
AUC_{0-24} [ng·h/mL]	21	54.3	63.0	20	61.9	36.3	22	61.8	35.2
AUC_{0-tz} [ng·h/mL]	21	93.0	68.8	20	105	37.1	22	105	36.9
$AUC_{0-\infty}$ [ng·h/mL]	21	103	65.5	20	115	37.6	22	114	37.5
$\%AUC_{tz-\infty}$ [%]	21	8.94	41.1	20	8.24	34.6	22	7.33	26.1
C_{max} [ng/mL]	21	4.14	65.6	20	5.02	38.2	22	4.93	31.5
t_{max} [h][1]	21	5.00	2.02 - 12.0	20	5.00	2.02 - 6.00	22	5.00	0.517 - 10.0
$t_{1/2}$ [h]	21	28.9	20.9	20	30.4	16.0	22	27.5	13.3
MRT_{po} [h]	21	35.9	17.3	20	35.9	15.9	22	34.2	12.1
CL/F [mL/min]	21	3230	65.5	20	2900	37.6	22	2920	37.5
V_Z/F [L]	21	8100	64.4	20	7620	40.5	22	6960	34.8

[1]Median and range

(Source: Table 11.5.2.3:1 on Page 68 of Study 1200.35)

As afatinib has a non-linear PK in the dose range of 20 to 50 mg, the relative bioavailability at the dose of 20 mg between FF and oral solution may not apply to the other dose levels.

2.2.5.4 What are the characteristics of drug distribution?

The human plasma protein binding of afatinib was determined to be 95% (SD=0.5) in an i*n vitro* study (A004/03FU). The fraction of protein bound was shown to be independent of the drug concentration from 50 to 500 nM. The protein binding of total radioactivity of [^{14}C]-labelled afatinib was measured in human plasma samples *ex vivo* in a mass balance study (1200.25) and the measured plasma protein binding was between 57.2% and 88.4% at 6 hours post dosing. The results should be interpreted with caution since the values were all in the low range of the validated range with large variation in the calculated values of plasma protein binding.

The ratio of afatinib concentration between blood cells and plasma (C_c/C_p) was tested at a drug concentration of 150 nM (study A004/03FU). The C_c/C_p was determined to be 2.21 at 2 min and 1.02 at 3 hours after spiking into the human blood indicating a predominant distribution into blood cells initially. A mass balance study (1200.25) suggested that the ratio of the $AUC_{0\text{-}24hr}$ of [^{14}C]-radioactivity in whole blood to plasma was 1.25 *ex vivo*.

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

The major route of elimination of afatinib was determined to be via feces in the human mass balance study (1200.25). The fecal fraction of total [^{14}C]-radioactivity was 85.4% within 312 h after a single oral administration of 15 mg afatinib (2.25 MBq [^{14}C]-labelled afatinib) solution in healthy subjects. The contribution of renal excretion to the total body clearance of [^{14}C]-radioactivity was 3.1% until 120 hours after dosing. The fraction excreted in urine for afatinib was 0.7 %. The PK parameters of afatinib (BIBW2992 BS) and [^{14}C]-radioactivity in urine and feces are shown in Table 9.

Table 9: Comparison of PK Parameters of Afatinib in Urine and [^{14}C]-labelled Afatinib in Urine and Feces after Single Oral Administration of 15 mg Solution

		BIBW 2992 BS in urine		[^{14}C]-BIBW 2992 BS-EQ in urine			[^{14}C]-BIBW 2992 BS-EQ in faeces		
		(N=8)		(N=8)			(N=7)		
Parameter	Unit	gMean	gCV [%]	Unit	gMean	gCV [%]	Unit	gMean	gCV [%]
$Ae_{0\text{-}120}$	[µg]	103	54.9	[µgeq]	467	31.9	[µgeq]	---	---
$fe_{0\text{-}120}$	[%]	0.687	55.0	[%]	3.11	31.3	[%]	---	---
$CL_{R,0\text{-}96}$	[mL/min]	11.4	45.2	[mL/min]	22.4	19.2	[mL/min]	---	---
$Ae_{0\text{-}312,\ faeces}$	[µgeq]	---	---	[µgeq]	---	---	[µgeq]	12800	5.79
$fe_{0\text{-}312,\ faeces}$	[%]	---	---	[%]	---	---	[%]	85.4	5.82

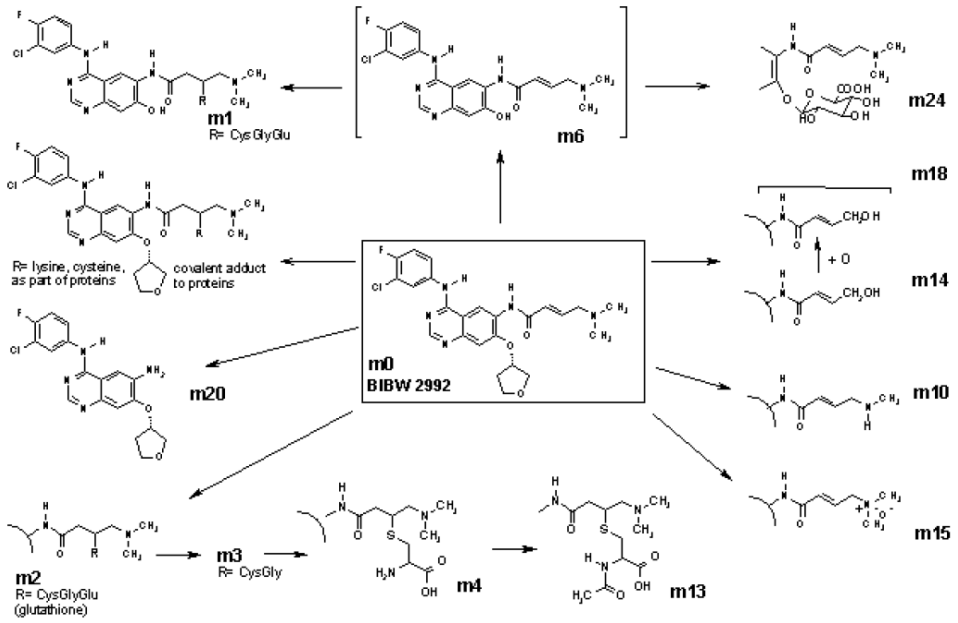
Urine from subjects 4 and 5 was mixed up in the time interval 72 - 96h

(Source: Table 11.5.2.5:2 on Page 75 of Study 1200.25 in the NDA)

2.2.5.6 What are the characteristics of drug metabolism?

Two metabolites were formed *in vitro* using human liver microsomes: the N-desmethyl-afatinib (m10) by CYP3A4, and afatinib-N-oxide (m15) by flavin-containing monooxygenase 3 (FMO3). In the model of sandwich-cultured human hepatocytes, approximately half (48%) of the total metabolic turnover was observed as m15 and 42% was accounted for afatinib conjugates (i.e., glutathione conjugates m2 and its breakdown products m3, m4 and m13) (Figure 10). Metabolites that were potentially formed by CYP450-dependent reactions were observed with 9.0% of the total metabolic turnover and m10 was in trace amounts. Therefore, CYP450 enzyme has a minor role in afatinib metabolism *in vitro.*

Figure 10: Major Metabolic Pathways of Afatinib in Humans



Please note: all pathways can be classified as minor/ trace metabolic pathways, some of these pathways were observed by LC-MS only in the samples of cancer patients after 14 days of continuous dosing

(Source: Figure 3.2.2:4 on Page 98 of Summary of Clinical Pharmacology Studies in the NDA)

Afatinib metabolism was investigated in a mass balance study in healthy subjects after a single oral solution of 15 mg containing [^{14}C]-afatinib (1200.25). The study suggested that [^{14}C]-afatinib was the predominant radioactive compound detected in plasma. The afatinib covalently bound to plasma protein was increased with time from 7% (1-2 hours) to 48% (72 hours). A few metabolites of afatinib were detected in trace amount in plasma. Approximately 88% of the excreted ^{14}C-radioactivity in the urine and feces was identified as parent compound afatinib, followed by 6.7% as m4, 3.7% as m13 and 0.4% as m15.

Afatinib metabolism was also investigated in cancer patients with various solid tumors following multiple oral doses of 70 mg once daily (study 1200.1). Afatinib was the major analyte in plasma and m3 was detected in a low amount. Additional metabolites (i.e., m10 and m20) that were not detected in mass balance study were found in a low amount in patients' urine samples.

All together, afatinib metabolism catalyzed by CYP450 enzymes is to a minor extent *in vitro* and *in vivo*. Afatinib covalent adducts to plasma proteins (i.e., serum albumin and hemoglobin) is the major circulating moiety in human plasma.

2.2.5.7 What are the characteristics of drug elimination and excretion?

The results of a mass balance study (1200.25) suggested that the major route of afatinib excretion after oral administration was via feces. The renal excretion of afatinib was low. The mean terminal half-life was in a range of 29 to 33 hour in health subjects after a single dose of 20 to 50 mg of afatinib tablet (study 1200.80). The mean estimated apparent clearance (CL/F) ranged from 1,150 to 1,770 mL/min.

The estimated elimination half-life was about 45 hours after repeat doses in a population PK analysis (PopPK4) based on the datasets in the Phase 2 and 3 trials including the registration trial. The estimated afatinib PK patameters including CL/F, apparent volume of distribution (V/F), T_{max}, C_{max}, $AUC_{0\text{-}24hr}$ at steady state (ss) for a typical female patient are shown in Table 10.

Table 10: Model Predicted Population Mean Values of Afatinib PK Parameters after Repeat Daily Doses of 20 -50 mg

Afatinib		20 mg	30 mg	40 mg	50 mg
NSCLC patients		Model predicted population mean values[1]			
$AUC_{\tau,ss}$	[ng·h/mL]	329	600	920	1280
$C_{max,ss}$[2]	[ng/mL]	17.7	32.3	49.6	69.0
$t_{max,ss}$[2]	[h]	4.25	4.25	4.25	4.25
$t_{1/2}$	[h]	45.4	45.4	45.4	45.4
CL/F	[mL/min]	1010	833	725	651
V_z/F	[L]	3990	3280	2850	2560

[1] The model prediction were based on the typical patient defined by the median/mode of the respective baseline covariate values of all patients from studies 1200.22, 1200.23 and 1200.32 receiving at least one dose of afatinib (female, 62 kg, CRCL of 77 mL/min, ECOG performance score of 1, AP of 104 U/L, LDH of 252 U/L and TPRO of 72 g/L).
[2] To determine $C_{max,ss}$ and $t_{max,ss}$ per profile the model predicted concentration was requested for every 0.25 h.

(Source: Table 3.2.4:1 on Page 104 of Summary of Clinical Pharmacology Studies in the NDA)

The same population PK model identified that body weight (WT), creatinine clearance (CLcr), gender and total protein (TPRO) are significant covariates affecting afatinib clearance. However, the change in afatinib exposure due to different body weight, decrease in CLcr, male/female or total protein level appears not clinical relevant and no dose adjustment is needed (see pharmacometrics review for detail analyses).

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

Dose proportionality was assessed using FF tablets in healthy subjects (study 1200.80). After single dose administration of 20 to 50 mg afatinib, C_{max} and $AUC_{0\text{-}inf}$ increased more than dose-proportional (Table 4). The estimated mean ratios of AUC for 20, 30 and 40 mg as to 50 mg were 0.650, 0.752 and 0.945, respectively.

The non-linear PK was also characterized in the dose range from 10 to 160 mg in a population PK analysis (PopPK2) combining single and multiple doses from studies 1200.1-4 and 1200.20. Applicant used a power model of dose-dependent F1 to explain the more than dose-proportional increase in exposure. The F1 increased with increasing dose up to 70 mg and no further significant increase observed for doses greater than 70 mg. The predicted F1 for 20, 30 and 40 mg as to 50 mg were 0.626, 0.770 and 0.892, respectively, which are consistent with the estimates in the single dose proportion study 1200.80.

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

The overall accumulation ratio was 2.8 (2.5 to 3.4) for AUC and 2.1 (2.0 to 2.7) for C_{max} after repeat doses in the dose range of 10 to 160 mg. The $T_{max, ss}$ was in the same range of 2-5 hours as that after a single dose. The steady state was attained within 8 days of afatinib tablets once daily treatment. The elimination half-life was prolonged from 30 hours to 45 hours following chronic dosing.

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

The inter-subject variability of PK parameters was analyzed using data from four phase 1 studies and one QT study conducted in cancer patients by a meta-analysis (Table 11). The variability for 40 mg dose group ranged from 57.1 to 105%. A similarly high variability of PK parameters was also observed in the other dose groups. In addition, the variability of PK parameters is higher in cancer patients compared to healthy volunteers (Table 11), which may be due to different characteristics of the patient population, co-medications that are P-gp inhibitors or inducers, and control of food effects. The intra-subject variability of afatinib plasma trough concentrations was estimated from day 8 to 28 over all treatment courses in the same meta-analysis and ranged from 22.2% to 67.5% over doses of 10 to 100 mg as shown in Table 12.

Table 11: Comparison of PK Parameters of 20 to 50 Dose Groups

BIBW	20 mg			30 mg			40 mg			50 mg		
2992 BS	N	gMean	gCV	N	gMean	gCV	N	gMean	gCV	N	gMean	gCV
AUC_{0-24}	12	119	56.6	10	189	95.9	30	324	68.9	69	459	68.0
$AUC_{\tau,ss}$	15	380	77.2	8	660	92.4	26	631	85.9	51	1130	59.7
C_{max}	13	11.6	85.1	10	16.3	139	30	25.2	73.3	73	40.8	76.6
$C_{max,ss}$	15	24.5	88.5	8	46.5	120	27	38.0	105	51	77.0	63.6
t_{max}*	13	3.00	0.500 -24.0	10	2.00	0.567 - 6.92	30	3.98	0.583 -9.10	73	3.13	0.900 -9.05
$t_{max,ss}$*	15	4.98	0.500 - 9.08	8	2.01	0.517 - 4.00	27	3.00	0.467 -23.8	51	3.82	1.00 - 7.05
$t_{1/2}$	11	22.3	80.3	10	21.3	82.1	30	26.9	61.1	13	21.9	54.8
$t_{1/2,ss}$	15	47.1	51.6	7	33.4	56.8	23	36.3	57.1	7	22.3	25.4
CL/F	11	1430	64.7	10	1370	72.9	30	952	86.2	13	1090	94.0
$CL/F_{,ss}$	15	877	77.2	8	758	92.4	25	1070	87.9	7	1390	47.3
Vz/F	11	2770	61.8	10	2520	109	30	2220	71.4	13	2080	123
$Vz/F_{,ss}$	15	3570	107	7	2000	67.8	23	2870	101	7	2690	47.8
$R_{A,AUC}$	11	3.14	27.6	8	3.40	83.1	9	2.53	48.0	49	2.61	59.1
$R_{A,Cmax}$	12	2.23	26.5	8	2.67	98.8	9	2.08	57.7	51	2.00	69.2

* median and range

(Source: Table 2.1 on Page 5 of Afatinib PK Meta-analysis in the NDA)

Table 12: Intra-subject Variability of Afatinib C_{trough} Values over All Courses by Dose Group

Treatment group	[mg]	10	20	30	40	45	50	55	60	65	70	85	100
Intra-subject gCV	[%]	36.88	35.72	35.38	33.20	54.40	30.95	37.32	22.19	24.87	36.92	51.16	67.50

(Source: Table 7.3.2:1 on Page 40 of Afatinib PK Meta-analysis in the NDA)

2.3 INTRINSIC FACTORS

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

A population PK analysis (PopPK4) was performed on a combination of the dataset from the PopPK3 model and a Phase 2 trial in head & neck squamous cell carcinoma (HNSCC) patients (1200.28), a Phase 2 trial in Japanese patients with stage IIIB or IV NSCLC (1200.33) and a registration trial in NSCLC patients (1200.32). The PK analysis dataset contained 4460 observations from 927 patients (764 NSCLC, 73 HNSCC and 90 BC (breast cancer) patients) which were used for the model development and covariate analysis.

The afatinib plasma concentration-time profiles were described by a 2-compartment model with first order absorption and linear elimination. F1 increases with increasing dose following a power function up to a dose of 70 mg; for doses greater than 70 mg F1 stays constant. Food intake, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase levels (LDH) and alkaline phosphatase levels (AP) were identified as statistically significant covariates influencing the afatinib exposure by affecting F1. Body weight (WT), creatinine clearance (CLcr), gender and total protein (TPRO) were significant covariates affecting afatinib clearance.

2.3.1.1 Body size and Gender

Pharmacometrics (PM) reviewer's independent popPK analyses revealed that the exposure of afatinib in the first cycle (CP_day15, ng/mL) tends to decrease as the body weight increases regardless of the gender. However, the exposure difference due to body weight is not clinically relevant (see PM review for detailed analyses).

According to the sponsor's population PK analysis, the gender is a significant covariate after adjusting for the body size. However, the exposure difference due to gender is not clinical relevant (see PM review for detailed analyses).

2.3.1.2 Race

The PK of afatinib did not exhibit statistically significant difference between Asian (Chinese, Japanese, Korean, Southeast Asian, Taiwanese, and other Asian) and White patients. No apparent difference in PK could be detected for American Indian/Alaska native or African American due to the limited data available in the analyses datasets.

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, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

1.6.2.1 Pregnancy
Afatinib is classified as Pregnancy Category D.

1.6.2.2 Nursing Mothers
It is not known whether afatinib is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 fold higher than those found in plasma from 1 to 6 hours after administration. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from BRAND, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

2.3.2.1 Pediatric Patients
Safety and effectiveness of afatinib in pediatric patients have not been established. Current submission is exempt from pediatric use assessments based on afatinib orphan-drug status for the proposed indication.

1.6.2.4 Geriatric Use
Of the 3865 patients in the clinical studies of afatinib, 32% of patients were 65 years and older, while 7% were 75 years and older. No overall differences in safety were observed between patients 65 years and over and younger patients. In registration trial, 39% of the 345 patients were 65 years of age and 4% were 75 years or older. No overall differences in effectiveness were observed between patients 65 years and over and younger patients.

2.3.2.2 Renal Impairment
No dedicated study was conducted to assess the effect of renal impairment on the PK of afatinib. The results of a PopPK analyses (PopPK4) suggested that CL/F declined linearly by 0.5% for one unit decrease in CLcr for patients with a CLcr lower than 120 mL/min. The model predicted 42% increase in afatinib $AUC_{0\text{-}24hr}$ in patients with severe (CLcr < 30 mL/min) renal impairment; however, the PopPK analyses only included data from 2 patients with severe renal impairment.

PM reviewer's independent analyses revealed that there was a trend that the trough concentration of afatinib at day 15 (Cp_day15) increased as the CLcr value decreases (Figure 11A). The median afatinib trough plasma concentration in patients with mild and moderate renal impairment were 14% and 37% higher, respectively than that in patients with normal renal function. The effect of severe renal impairment on the PK of afatinib was inconclusive as the Cp_day15 of one patient was in the range of those of the patients with mild and moderate renal impairment and the Cp_day15 of another patient was almost two times higher than the rest of the patients with renal impairment (Figure 11B) (see PM review for detailed analyses).

Figure 11: Association between Trough Afatinib Levels at Day 15 and Creatinine Clearance

Figure 11A: Cp_day15 vs CLcr

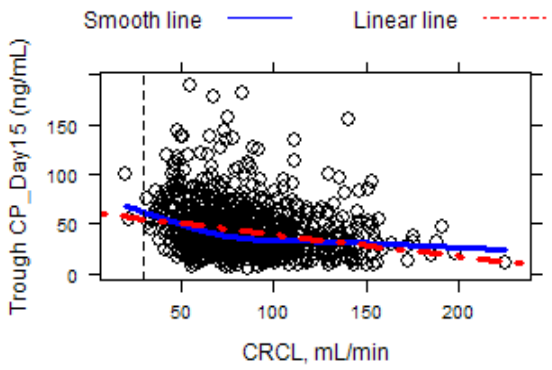
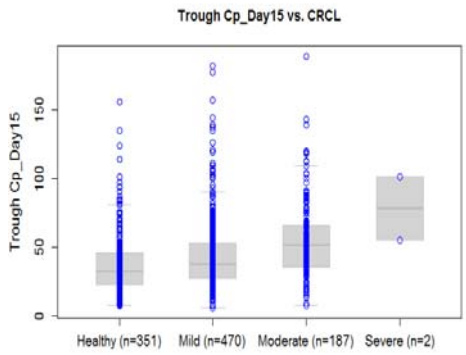


Figure 11B: Cp_day15 by Renal Impairment level



No adjustment to the starting dose is needed for patients with mild renal impairment. Patients with moderate or severe renal impairment should be monitored closely and reduce afatinib dose if not tolerated.

2.3.2.3 Hepatic Impairment

A dedicated study (1200.86) was conducted to assess the effect of mild (Child Pugh A, 5 or 6 points) and moderate (Child Pugh B, 7 to 9 points) hepatic impairment (HI) on the PK of afatinib. The exposure parameters of a 50 mg single dose of afatinib in subjects with mild or moderate HI were compared to healthy subjects with matched age, weight, gender, and creatinine clearance (Table 13). No clinically relevant differences in $AUC_{0\text{-}inf}$ and C_{max}) were observed except a 27% increase in C_{max} in the moderate HI group. This increase in C_{max} is not considered clinically meaningful due to the magnitude and small sample size in each group (n=8). Severe HI was not studied in this trial.

Table 13: Mean Ratios of AUC and C_{max} for Subjects with Mild or Moderate Hepatic Impairment Compared with Subjects with Normal Hepatic Function (n=8 in each group)

	Adj gMean ratio mild HI/HC [%]	90% CI [%]	Adj gMean ratio mod HI/HC [%]	90% CI [%]
$AUC_{0\text{-}\infty}$	92.6	68.0 to 126.3	94.9	72.3 to 124.5
$AUC_{0\text{-}tz}$	90.6	66.9 to 122.7	94.5	71.6 to 124.8
C_{max}	109.5	82.7 to 144.9	126.9	86.0 to 187.2

(Source: Table on Page 8 of Study Report 1200.86)

The influence of hepatic impairment on the PK of afatinib was further evaluated by studying the relationship between CP_day15 and the surrogate liver markers such as billirubin, ALT, AST, lactate dehydrogenase levels (LDH) and alkaline phosphatase levels (AP) and no correlation was identified for these liver markers and the afatinib exposure (see PM review for detailed analyses).

Overall, plasma exposure of afatinib was comparable between subjects with mild or moderate HI

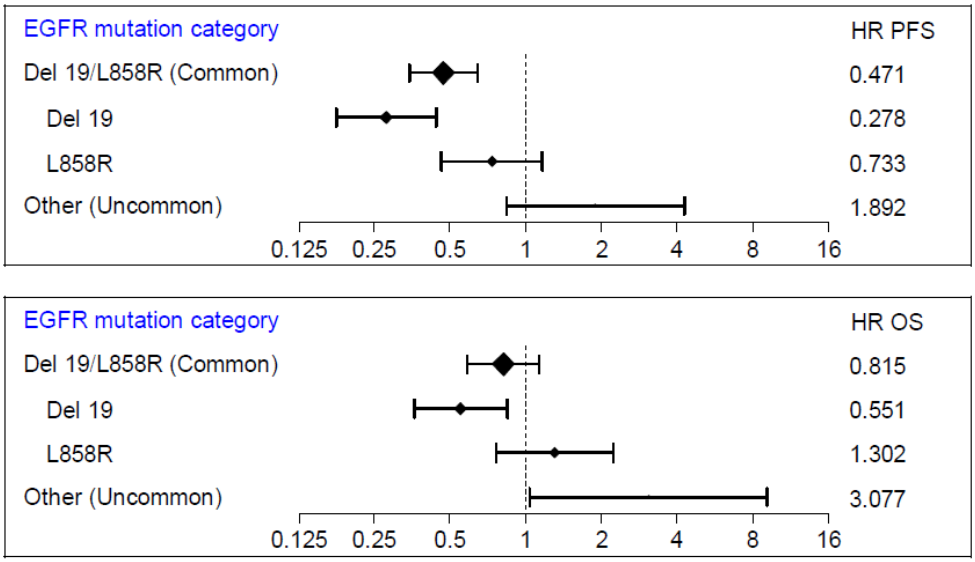
and subjects with normal hepatic function. No adjustment to the starting dose is needed for patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should be monitored closely and reduce afatinib dose if not tolerated.

2.3.3 Should the indication be limited based on the type of EGFR mutation?

Randomization was stratified by EGFR mutation status (L858R, Del 19, other) in the pivotal trial 1200.32. Afatinib showed PFS improvement in the overall population, however different EGFR mutations appear to have demonstrated different sensitivities to afatinib inhibition in clinical trial 1200.32. Tumors positive for exon 19 deletion mutations appear more likely to respond to afatinib than those with L858R mutations. Similar results were reported in the published literature for reversible EGFR TKIs.

The applicant pooled several different mutations associated to either increased sensitivity or therapeutic resistance to EGFR TKIs in the category "other". Exploratory analyses showed lower objective response rates and a worse estimate of PFS and OS for afatinib compared with chemotherapy for the uncommon mutation subset, as shown in Figure 12.

Figure 12: Forest Plot of PFS based on Central Independent Review (top) and OS (bottom) for EGFR Mutation Category / RS

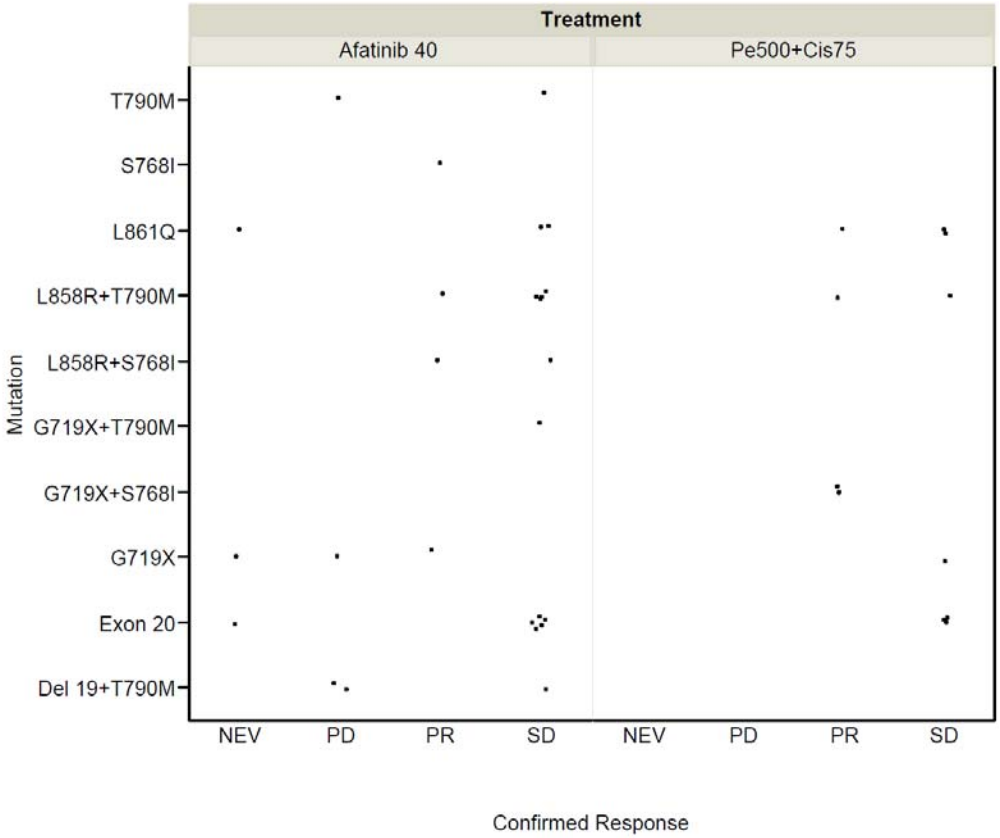


Favors Afatinib Favors Chemotherapy

[*Source: Applicant's figure, modified from figures 3.3.1: 1 (Summary of Clinical Efficacy) and 15.2.3.3: 17 (overall survival data; January 2013 update).* Number of patients: Del 19/L858R (common) n=308, Del 19 n=170, L858R n=138, Other (Uncommon) n= 37; RS-randomized set]

Despite a possible detrimental effect of afatinib in the "other" EGFR mutation category, some of the individual responses from afatinib-treated patients with "other" EGFR mutations suggested evidence for activity of afatinib, in a manner that was generally consistent with in vitro assessments. However, because of the small sample size, numeric imbalances and biological heterogeneity, this subset is not adequately powered to draw firm conclusions (Figure 13).

Figure 13: Individual Patient Responses* to Afatinib or Chemotherapy in the Category "Other" (Investigator Assessments)



[*Confirmed response (*source data: Applicant's listing 96.1*); Response = Complete response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Non-evaluable (NEV); Exon 20 = exon 20 insertions]

The early studies in EGFR-mutated NSCLC were dichotomized in wild-type and mutant for simplicity. It is now clear that many tumor genotypes occur and may confer differential sensitivity to treatment (PMID: 23485129). The high variability identified in these mutations may translate into distinct functional consequences. The mechanisms that underlie differential responses to EGFR tyrosine kinase inhibitors need to be better elucidated before uncommon mutations can be categorized into "responsive" or "resistant". The therapeutic decision-making in EGFR-mutated NSCLC patients seems to be contingent on the type of mutation present and, therefore, strategies to understand these mutations in the clinical setting are needed. We therefore recommend that the afatinib treatment should be indicated to patients with EGFR exon 19 deletion or L858R substitution mutations.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no dedicated studies or PopPK analyses designed to evaluate the effects of herbal products on the PK of afatinib.

The effect of alcohol use on CL/F, relative bioavailability (R-BA) and absorption rate constant (K_{abs}) of afatinib was explored using sparse PK data from several Phase 2 and 3 trials. Alcohol use was classified as: patient does not drink any alcohol, patient does drink alcohol but degree of consumption should not interfere with trial participation and patient does drink alcohol and degree of consumption could interfere with trial participation. One third of the patients (302 of 927) included in the PopPK analyses consumed alcohol. The effect of alcohol use on the above PK parameters of afatinib is not clinical relevant (see pharmacometrics review for details).

The effect of smoking status on CL/F, relative bioavailability and absorption rate constant of afatinib was explored in the same PopPK analyses. Smoking status was classified as: never smoked, current smoker and ex-smoker. Of the 927 patients, 60% never smoked, 34% quit smoking and 5.5% were currently smoking. The effect of smoking status on the above PK parameters of afatinib is not clinical relevant (see pharmacometrics review for details).

2.4.2 Drug-drug interactions

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

Yes, afatinib is a substrate and inhibitor (Ki=3.4 μM) for P-gp transporter. See Section 1.7.2.4 for details.

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

CYP450 enzyme has a minor role in afatinib metabolism *in vitro* and *in vivo.* The metabolites of afatinib potentially formed by CYP450-dependent reactions were 9.0% of the total metabolic turnover in sandwich-cultured human hepatocytes. The metabolite (m10) formed by CYP3A4 was in trace amounts. In addition, no metabolites formed by CYP450 enzymes were detected in the excreta after the administration of a single-dose 15 mg [^{14}C]-labeled afatinib oral solution in a human mass balance study. A trace amount of metabolites formed by CYP450 enzymes were obtained by LC-MS analyses of urine samples in cancer patients treated with 70 mg afatinib once daily for 14 days.

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

<u>*In vitro* inhibition</u>

The inhibition potential of afatinib is low. Afatinib up to 100 μM (600-fold higher than mean C_{max}) did not show potent inhibition of ten tested CYP450 isoenzymes that are most relevant for drug metabolism in humans (CYP1A1/2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A11) in liver microsomes of humans (Table 14). The

mean plasma C_{max} of afatinib at steady state is 0.16 µM for 50 mg dose in a PK meta-analysis of clinical trials 12001-4 and 1200.24.

Table 14: Inhibition of Test Reactions by Afatinib Compared to Model Inhibitors

test reaction	CYP iso-enzyme	inhibitor	IC_{50} [µM]
coumarin 7-hydroxylation	2A6	BIBW 2992 MA2	>100
coumarin 7-hydroxylation	2A6	tranylcypromine	0.16
bufuralol 1'-hydroxylation	2D6	BIBW 2992 MA2	>100
bufuralol 1'-hydroxylation	2D6	quinidine	0.24
erythromycin N-demethylation	3A4	BIBW 2992 MA2	>100
erythromycin N-demethylation	3A4	ketoconazole	0.11
lauric acid 11-hydroxylation	2E1	BIBW 2992 MA2	>100
lauric acid 11-hydroxylation	2E1	diethyldithiocarbamate	289
lauric acid 12-hydroxylation	4A11	BIBW 2992 MA2	>100
nifedipine oxidation	3A4	BIBW 2992 MA2	>100
nifedipine oxidation	3A4	ketoconazole	0.15
paclitaxel 6α-hydroxylation	2C8	BIBW 2992 MA2	>100
phenacetin O-deethylation	1A2	BIBW 2992 MA2	>100
phenacetin O-deethylation	1A2	furafylline	3.31
S-mephenytoin N-demethylation	2B6	BIBW 2992 MA2	>100
S-mephenytoin N-demethylation	2B6	orphenadrine	>100
S-mephenytoin 4'-hydroxylation	2C19	BIBW 2992 MA2	>100
testosterone 6ß-hydroxylation	3A4	BIBW 2992 MA2	>100
testosterone 6ß-hydroxylation	3A4	ketoconazole	0.07
tolbutamide hydroxylation	2C9	BIBW 2992 MA2	79.3
tolbutamide hydroxylation	2C9	sulphaphenazole	0.67

*: competitive inhibitor
†: mixed inhibitor
✱: mechanism based inhibitor
a: non competitive

(Source: Table 10:23 on Page 84 of Study Report A130/03LU in the NDA)

In vitro induction

The induction potential of afatinib is low. Afatinib up to 5 µM (30-fold higher than mean C_{max}) did not show potent induction of six testedCYP450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4) in primary human hepatocytes.

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

Substrate of P-gp transporter

Afatinib is a P-gp substrate. The potential transport of afatinib by P-gp was investigated in a bi-directional assay system using Caco-2 cell monolayers (Study U04-1771) and human P-gp expressing LLC-PK1 cells (Study U07-3504). The results showed that apically-directed vectorial transport of afatinib in both cell lines was completely blocked in the presence of cyclosporine A, verapamil and zosuquidar (P-gp inhibitors). The efflux ratio (in human P-gp expressing LLC-PK1 cells divided by that in the parental cell) was 1.44. The estimated K_m was 10 to 30 μM and 9.25 μM in Caco-2 cells and human P-gp expressing cells, respectively. See Section 1.7.2.7 for drug interaction study results.

Inhibition of P-gp transporter

Afatinib is a P-gp inhibitor. The potential inhibition of afatinib on the transport of digoxin (substrate of P-gp) was investigated using Caco-2 cell monolayers and human P-gp expressing LLC-PK1 cells. The results showed that the inhibition was in a concentration-dependent manner with the mean apparent IC_{50} of 24 μM and 1.6 μM in Caco-2 cells and human P-gp expressing cells, respectively. A separate *in vitro* study was conducted to determine the value of the inhibitory constant (Ki) of afatinib using bi-directional transport model in Caco-2 cell monolayers. Three concentrations of digoxin (50, 100, 200 μM) and six concentrations of afatinib (0.1, 0.3, 1, 3, 10 and 30 μM) were tested. The results showed a K_i value of 3.4 μM for afatinib. Applicant stated that the ratio of $C_{max,ss}$ over K_i (corresponding to I/K_i) was below 0.1, which indicates that an *in vivo* DDI study with P-gp substrates is not necessary.

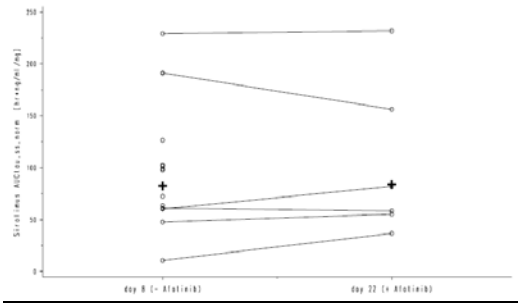
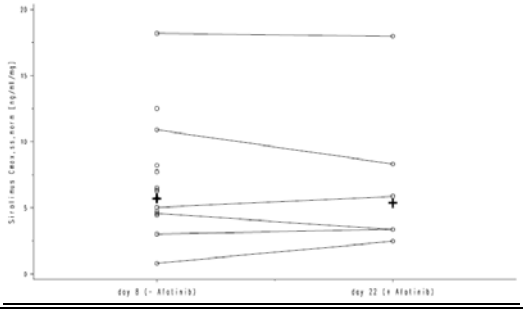
As afatinib is orally administered, inhibition concentration (I) is preferred to use the dose of afatinib over 250 mL. In the scenario of 40 mg afatinib used in clinic, the ratio should be [40mg/(485.9 g/mol) /250 mL]/3.4 μM =97, which is much higher than the cut-off value suggested in the FDA drug interaction draft guidance. Therefore, an *in vivo* DDI study with a P-gp substrate such as digoxin is necessary.

Information was requested to the applicant to address the issue of potential effect of afatinib on the PK of oral P-gp probe substrates *in vivo*. Applicant submitted data from three clinic settings to demonstrate no clinically relevant effect of afatinib on orally administered P-gp substrates.

- First, concomitant administration of 10 mg of afatinib with an investigational new drug (BIBF 1120) did not result in a significant change in the exposure of BIBF 1120 (study 1239.1) comparing that when co-administered with ketoconazol.
- Second, concomitant 30 or 40 mg of afatinib with sirolimus did not result in a clinical relevant change in sirolimus exposure (study 1200.70) as shown in Figure 14.
- Third, among 34 patients received concomitant digoxin and afatinib, the frequency of patients experienced anorexia, nausea, vomiting and visual disturbances (digoxin toxicity) was less than that in the overall patients population receiving afatinib (n=3,865). Nine patients experienced cardiac symptoms.

Based on above evidence, applicant claimed that further investigations of the effect of afatinib on the PK of P-gp probe substrates are not warranted.

Figure 14: Comparison of Sirolimus Exposure at Steady State before and after Administration of Multiple Doses of Afatinib

Figure 14A: AUC of Sirolimus at Steady State with or without Afatinib	Figure 14B: C_{max} of Sirolimus at Steady State with or without Afatinib
	

In reviewer's opinion, the results from the combination therapy of afatinib and BIBF 1120 are inconclusive as the lower (10 mg) than clinical dose (40 mg) of afatinib was used. The results from the second setting demonstrated no clinically meaningful effect of afatinib on the exposure of a PgP substrate (sirolimus). The results from the third setting demonstrated no clinically meaningful effect of afatinib on the safety profile of a PgP substrate (digoxin). The above clinical data suggest that afatinib is unlikely to affect plasma concentrations of concomitant P-gp substrates although it was deteremined as an inhibitor of P-gp (Ki=3.4 μM) *in vitro*.

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

Afatinib-N-oxide (m15) formed by flavin-containing monooxygenase 3 (FMO3) was found in human liver microsomes accounting for 47.8% of the total metabolic turnover of afatinib in sandwich-cultured human hepatocyte model. However, only 0.4% of m15 were detected in the excreta after administration of a single-dose 15 mg [^{14}C]-labeled afatinib oral solution in a human mass balance study. Considering no clinically relevant DDIs have been described for drugs that are metabolized by FOM3 and no specific FMO3 inhibitors have been identified yet, no drug interaction study with a FMO3 inhibitor was conducted.

An *in vitro* study (U11-2809) showed that apically-directed vectorial BCRP-mediated transport of afatinib in Caco-2 cell monolayers was partially blocked in the presence of Fumitremorgin (BCRP inhibitor). The same study also showed that afatinib was an inhibitor of BCRP transporter using E-sul as the probe substrate with an IC_{50} value of 0.75.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No co-administration of other drugs is specified in the label as afatinib is used as monotherapy in the proposed indication.

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

Drug interaction studies were conducted in healthy subjects to evaluate the effect of a P-gp inhibitor ritonavir at 200 mg BID on afatinib exposure when ritonavir was given at 1 hour before, simultaneous, or 6 hours after afatinib administration. The relative bioavailability of afatinib based on $AUC_{0\text{-}inf}$ and C_{max} in the presence of ritonavir to afatinib alone is shown in Table 15. The $AUC_{0\text{-}inf}$ and C_{max} of afatinib were increased by 48% and 39%, respectively, when a single 20 mg dose of afatinib was taken 1 hour after ritonavir. No clinical meaningful change in afatinib exposure when the 3rd dose of ritonavir was administered simultaneously with or 6 hour after a single 40 mg dose of afatinib. However, the effect of relative dosing time of ritonavir on afatinib exposure may not be extrapolated to other P-gp inhibitors as the PK profiles of P-gp inhibitors are confounded by the CYP3A4 component. Therefore, avoid concomitant use of oral P-gp inhibitors with afatinib is recommended. For patients who require therapy with an oral P-gp inhibitor, reduce afatinib daily dose by 10 mg if not tolerated.

Table 15: Relative Bioavailability of Afatinib in Presence and Absence of 200 mg Ritonavir BID for 3 Days

Dosing time of ritonavir relative to afatinib	1 hour before	Simultaneously	6 hours after
Single dose of afatinib	20 mg	40 mg	40 mg
Number of Patients	22	24	24
Mean C_{max} Ratio (%)	139	104	105
Mean $AUC_{0\text{-}inf}$ Ratio (%)	148	119	111

A drug interaction study was also conducted to assess the effect of rifampicin (a P-gp inducer) on the exposure of afatinib in healthy subjects. Pre-treatment of rifampicin 600 mg BID for 7 days resulted in a 34% decrease in $AUC_{0\text{-}inf}$ and a 22% decrease in C_{max} of afatinib (Table 16). Therefore, avoid concomitant use of oral P-gp inducers is recommended. If an oral P-gp inducer is required for chronic treatment, increase afatinib daily dose by 10 mg as tolerated.

Table 16: Adjusted Geometric Means and Relative Bioavailability of $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tz}$ and C_{max} of Afatinib

Parameter[a]	Adjusted gMean		Adj. gMean ratio (Test/Reference) [%]	Two sided 90% CI [%]		Intra-individual gCV [%]
	Test	Reference		Lower limit	Upper limit	
$AUC_{0\text{-}\infty}$ [ng·h/mL]	604.0	912.4	66.20	60.82	72.06	16.1
$AUC_{0\text{-}tz}$ [ng·h/mL]	569.4	860.3	66.18	60.66	72.21	16.5
C_{max} [ng/mL]	30.02	38.28	78.41	72.36	84.97	15.6

[a]For the reference treatment, N=22; for the test treatment, N=22 for C_{max} and N=21 for $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}tz}$

(Source: Table 11.5.2.3:1 on Page 60 of Study Report 1200.152 in the NDA)

2.5 GENERAL BIOPHARMACEUTICS

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

Afatinib is considered either a BCS class 1 or 3 drug substance. Afatinib is highly soluble in water (>50 mg/mL) and in aqueous buffer media up to pH 6. The permeability determination in CaCo-2 cells is inconclusive because afatinib exhibits both high passive permeability and a substrate of P-gp and breast cancer resistance protein (BCRP). As a result, the permeability of afatinib could not be classified conclusively based on currently available *in vitro* data on the permeability behavior.

2.5.2 What moieties should be assessed in bioequivalence studies?

Afatinib dimaleate (MA2) is the salt form (MW=718.1 g/mol) and afatinib is the free base (BS, MW=485.9 g/mol). Afatinib free base, the active ingredient of drug product, should be assessed in BE studies.

(b) (4)

[redacted]

2.5.3 What is the composition of the to-be-marketed formulation?

The composition of the to-be-marketed formulation (Table 17) is very similar to film-coated afatinib final formulation (FF) tablets used in the registration trial. FF tablets were debossed on one side only with the Boehringer Ingelgeim company symbol. The to-be-marketed tablets are debossed on both sides to include the Boehringer Ingelheim company symbol on one side and the dosage strength related code (e.g. “T30 for the 30 mg tablet) on the other side.

Table 17: Qualitative and Quantitative Composition of Afatinib Film-coated Tablets

Dosage strength		[20 mg]**	20 mg	30 mg	40 mg	(b) (4)		
Part of tablet	Ingredient		[mg/coated tablet]				Function	Reference to Standards
Core	BIBW 2992 MA2 (BIBW 2992 free base)	29.5600 (20.0000)	29.5600 (20.0000)	44.3400 (30.0000)	59.1200 (40.0000)		Active	Company Standard
	Lactose monohydrate				(b) (4)		(b) (4)	NF
	Microcrystalline cellulose							NF
	Colloidal silicon dioxide							NF
	Crospovidone							NF
	Magnesium stearate							NF
Film-coat	Hypromellose (b) (4)							USP
	Polyethylene glycol (b) (4)							NF
	Titanium dioxide							USP
	Talc							USP
	FD&C Blue No. 2 (b) (4) (b) (4)							21 CFR 74.1102
	Polysorbate 80							NF
	(b) (4)							USP
	Total mass	185.00	185.00	277.00	368.00			

(Source: Table 2.3.P.1:1 on Page 38 of Quality Overall Summary in the NDA)

The to-be-market afatinib tablets are provided in four different strengths:

- 20 mg: white to slightly yellowish, round, biconvex, bevel-edged tablets
- 30 mg: dark blue, round, biconvex, bevel-edged tablets
- 40 mg: light blue, round, biconvex, bevel-edged tablets
- (b) (4)

Four tablet formulations and one oral solution have been developed in the clinical development and their use in the different clinical phases is summarized in Table 18.

Table 18: Overview of Formulations Used in Clinical Trials

Type of clinical formulation	Manufacturing changes	Clinical phase	Key clinical studies
Trial formulation 1 (TF I): uncoated tablets, 5, 20 and 100 mg	(b) (4)	Phase I	• Study 1200.1: MTD finding in cancer patients (10 to 100 mg) • Study 1200.2: MTD finding in cancer patients (10 to 65 mg)
Drinking solution (20 mg/bottle)		Phase I	• Study 1200.25: [^{14}C] Human ADME trial (15 mg solution single dose) • Study 1200.35: Relative BA trial (20 mg solution)

	(b) (4)		
Trial formulation 2 (TF II): film-coated tablets, 5, 20 and 100 mg		Phase I Phase II/IIa/IIb	<u>Phase I:</u> • Study 1200.3: MTD finding in cancer patients (10, 20, 30, 40 & 50 mg) • Study 1200.4: MTD finding in cancer patients (10, 20, 40 & 60 mg) • Study 1200.35: Relative BA trial (20 mg TF 2) <u>Phase II:</u> • Study 1200.22: Monotherapy in NSCLC patients (start at 40 or 50 mg)
Intended final formulation (iFF): film-coated tablets, 20, 30, 40, 50 and 70 mg		Stability studies; Not in clinical trials	Never used in clinical trials
Final formulation (FF): film-coated tablets, light blue (20 and 40 mg); dark blue (30 and 50 mg)		Phase I Phase III	<u>Phase I:</u> • Study 1200.35 (20 mg): Relative BA trial (20 mg FF) • Study 1200.80: Single rising dose trial (20, 30, 40 & 50 mg) <u>Phase III:</u> • Study 1200.23 Monotherapy in NSCLC patients (30, 40 and 50 mg): • Study 1200.32: Monotherapy in NSCLC patients (start at 40 mg)

A similar dissolution profiles for trial formulation II (TFII) and final formulation (FF) was reported as (b) (4) dissolved in 15 minutes at pH 4.0 for all dosage strengths although TFII tablets had significant differences in the quantitative composition from FF (Figure 15). A relative bioavailability study (1200.35) was conducted comparing FF tablets to TFII at the dose strength of 20 mg. Results showed that the TFII tablets had a higher geometric mean (gMean) $AUC_{0\text{-inf}}$ and C_{max} values compared with the FF. The adjusted gMean ratios FF/TFII for $AUC_{0\text{-inf}}$ and C_{max} were 87% (90% CI: 70%, 106%) and 80% (90% CI: 65%, 100%), respectively. The FF tablets in the dosage strengths of 20 to 50 mg were used in the registration trial (1200.32) for the proposed indication. The formulation development and their use in the different clinical phases are summarized in section 2.5.

(b) (4)

(Source: Figure 2.3.P.2.2:1 on Page 45 of Quality Overall Summary)

2.5.4 What is the absolute bioavailability of afatinib?

The absolute BA of afatinib has not been determined.

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

The relative bioavailability of the proposed to-be-marketed formulation to FF used in the registration clinical trial has not been determined as the difference in debossing is not expected to impact the overall quality and *in vivo* performance of the drug product.

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

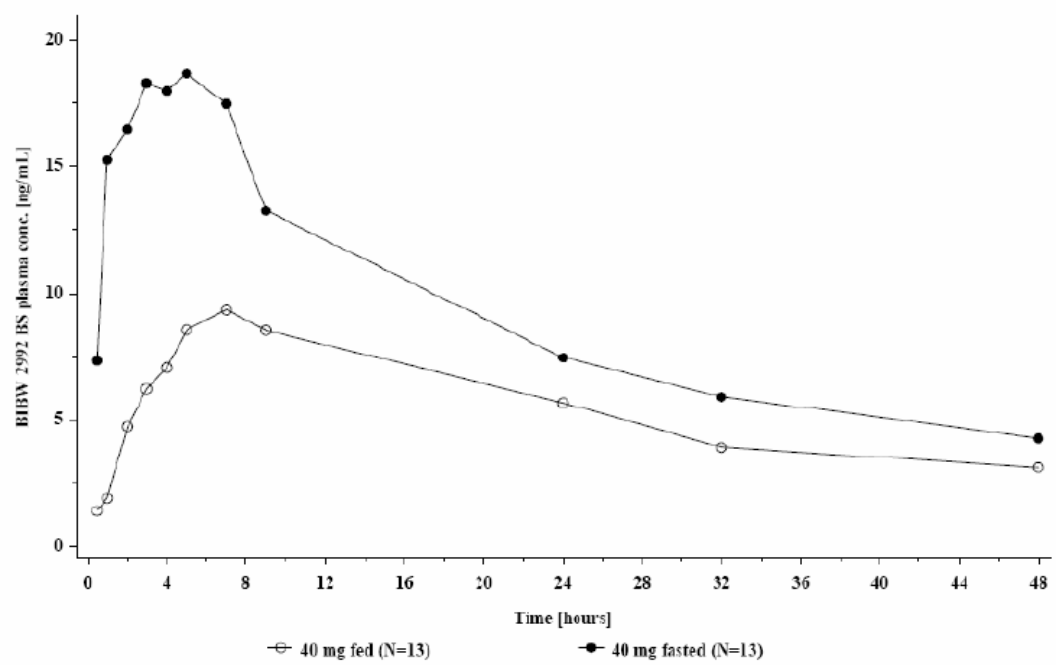
The effect of food was investigated in 13 cancer patients with various advanced solid tumors in a sub-study of trial 1200.3. The effect of a high fat/high caloric meal taken 30 minutes before afatinib on the PK of a single dose of 40 mg afatinib (TFII) was evaluated comparing to fasted conditions. Afatinib exposure was decreased by 39% in $AUC_{0\text{-}inf}$ and 50% in C_{max}, respectively (Table 19). The median T_{max} was delayed from 3.0 hour to 6.9 hour after a high-fat meal (Figure 16). Based on these findings in food effect study, the requirement for fasted administration of afatinib has been implemented in all clinical trials including the registration trial for the proposed NSCLC indication.

Table 19: Adjusted Geometric Means and Relative Bioavailability Comparison of Afatinib under Fed vs. Fasted Condition

Parameter	Adjusted gMean ratio (Fed/Fasted) [%]	Two-sided 90 % CI Lower limit [%]	Two-sided 90 % CI Upper limit [%]	intra-indiv. gCV [%]	p-value for ratio outside interval 0.8-1.25
C_{max}	49.52	35.98	68.15	47.6	0.9896
$AUC_{0-\infty}$	61.17	49.64	75.38	30.2	0.9793

(Source: Table 11.5.22:2 on Page 75 of Study Report 1200.3 in the NDA)

Figure 16: Mean Afatinib Plasma Concentration-Time Profile after Single Oral Dose of 40 mg Afatinib under Fed and Fasted Conditions



(Source: Figure 3.2.1:1 on Page 48 of Summary of Biopharmaceutics and Associated Analytical Methods in the NDA)

The results of 2 PopPK analyses (PopPK3 and 4) also supported decreased systemic exposure when food was consumed within 3 hours before (↓34%) or 1 hour after (↓26%) afatinib administration. Applicant also evaluated the magnitude of food effect on afatinib PK when a high fat meal was consumed at different intervals within the range of 3 hours before to 1 hour after afatinib administration. There is an 18% difference in the decreased exposure between food consume 3 hours before and 2 hours before afatinib administration, FDA recommends that take afatinib at least 1 hour before or 2 hours after a meal.

2.6 ANALYTICAL SECTION

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

High performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) methods were developed and validated for the identification and quantification of afatinib in the human biological matrices (plasma and urine). For all bioanalytical methods, isotope labeled [D6]-afatinib was used as the internal standard (IS).

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites of afatinib were selected for analysis because they are in trace amount in the human plasma and urine samples.

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

Total plasma afatinib concentrations were measured. Measurement of the total drug instead of free drug concentration appears acceptable as afatinib is approximately 95% bound to plasma protein.

2.6.4 What bioanalytical methods are used to assess concentrations?

The concentrations of afatinib were quantified by HPLC-MS/MS using electrospray ionization in the positive ion mode. The transition forms for afatinib and the IS were m/z=486 → 371 and m/z=492 →371, respectively. The chromatography at Boehringer Ingelheim site included reversed phase (C18), 30 x 2 mm analytical HPLC columns with gradient elution of aqueous vs. methanolic ammonium formate solutions. The chromatography at (b) (4) site (contract research organization) included reserved phase (C18), 50 x 2 mm analytical HPLC column with gradient elution of aqueous ammonium formate solution vs. methanol.

Eleven bioanalytical assays have been developed to assess afatinib concentrations. The validation data of eight assays for analysis of afatinib in human plasma are summarized in Table 20 and three assays in human urine are summarized in Table 21. A list of bioanalytical methods used for the quantification of afatinib in individual clinical studies is provided in Table 22.

Table 20: Summary of Validation Data of Bioanalytical Assays for Analysis of Afatinib in Human Plasma Samples

Method reference	[U04-1421]	[U05-2022]	[U08-1226]
Matrix	Plasma	Plasma	Plasma
Calibration range (ng/mL)	0.500 - 250	0.500 - 250	0.500 - 250
Max. overall accuracy % (QCs low/mid/high)	-10.5	-7.7	+5.6
Max. overall precision % (QCs low/mid/high)	12.5 (N=15/16/16)	6.6 (N=9/10/10)	4.6 (N=11/12/11)
Overall accuracy % at LLOQ	+0.4	-0.2	+8.8
Overall precision % at LLOQ	14.3 (N=18)	9.1 (N=18)	8.3 (N=12)
Method reference	[U11-2675]	[U07-1311]	[U09-2026]
Matrix	Plasma	Plasma	Plasma
Calibration range (ng/mL)	0.500 - 250	0.100 - 20.0	0.100 - 20.0
Max. overall accuracy % (QCs low/mid/high)	-5.2	+3.4	-5.0
Max. overall precision % (QCs low/mid/high)	12.3 (N=8/8/8)	8.1 (N=10/10/10)	6.0 (N=10/10/10)
Overall accuracy % at LLOQ	+1.7	+3.0	-1.9
Overall precision % at LLOQ	5.9 (N=18)	8.4 (N=18)	14.1 (N=18)
Method reference	[U09-2367]	[U11-2675]	
Matrix	Plasma	Plasma	
Calibration range (ng/mL)	0.100 - 20.0	0.100 - 50.0	
Max. overall accuracy % (QCs low/mid/high)	+10.0	+12.5	
Max. overall precision % (QCs low/mid/high)	6.1 (N=6/6/6)*	6.7 (N=6/6/6)	
Overall accuracy % at LLOQ	Not done	+1.5	
Overall precision % at LLOQ	Not done	8.4 (N=6)*	

* data obtained from sixfold analyses within one sequence

(Source: Table 1.4.1.1:3 on Page 28 of Summary of Biopharmaceutics and Associated Analytical Methods in the NDA)

Table 21: Summary of Validation Data of Bioanalytical Assays for Analysis of Afatinib in Human Urine Samples

Method reference	[U06-2289]	[U11-2821]	[U12-1021]
Matrix	Urine#	Urine&	Urine&
Calibration range (ng/mL)	0.500 - 250	5.00 - 1000	5.00 - 1000
Max. overall accuracy % (QCs low/mid/high)	-3.1	-4.7	+7.0
Max. overall precision % (QCs low/mid/high)	6.1 (N=10/10/10)	5.2 (N=12/12/12)	5.2 (N=6/6/6)
Overall accuracy % at LLOQ	-0.8	-7.0	+1.8
Overall precision % at LLOQ	8.1 (N=18)	4.4 (N=18)	3.1 (N=18)

\# urine acidified with 1 % citric acid to prevent adsorption losses
& urine with 1 % Tween 20 to prevent adsorption losses

(Source: Table 1.4.1.1:4 on Page 29 of Summary of Biopharmaceutics and Associated Analytical

Methods in the NDA)

Table 22: Summary of Bioanalytical Methods Used in Clinical Studies

Study no.	Short Title	Clinical Study Report Reference	Method Used (reference)*
1200.1	MTD finding trial in cancer patients	[U06-2055]	[U04-1421], [U05-2022]
1200.2	MTD finding trial in cancer patients	[U07-3025]	
1200.3	MTD finding trial in cancer patients including a food effect sub-study	[U08-1023]	
1200.4	MTD finding trial in cancer patients	[U07-3128]	
1200.5	Phase II combination with letrozole in BC	[U10-2018]	[U08-1226]
1200.6	Phase I combination with docetaxel	[U08-3208]	[U05-2022]
1200.10	Phase II monotherapy in BC patients	[U10-1598]	[U08-1226]
1200.11	Phase II monotherapy in BC patients	[U09-2463]	
1200.17	Extension study (1200.1 and 1200.2)	[U07-3059]	[U04-1421], [U05-2022]
1200.20	Phase I combination with docetaxel	[U10-1339]	[U05-2022]
1200.22	Phase II monotherapy in NSCLC patients	[U10-3047]	[U08-1226]
1200.23	Phase II/III monotherapy in NSCLC patients	[U10-3048]	
1200.24	Phase II QT Study in cancer patients	[U11-2519]	
1200.25	Human ADME in healthy volunteers	[U07-1759]	[U07-1311], [U06-2289]#
1200.26	Phase II in EGFR amplified tumors	[U11-3474]	[U08-1226]
1200.28	Phase II in HNSCC patients	[U12-3254]	
1200.32	Phase III in 1st line NSCLC (EGFR mutations)	[U12-1199]	
1200.33	Phase I/II monotherapy in Japanese NSCLC patients	Phase I [U10-2037] Phase II [U11-2226]	
1200.35	Relative BA trial in healthy volunteers	[U09-2233]	[U09-2026]

1200.36	Phase I/II with temozolomide in glioma patients	[U11-2804]	[U08-1226]
1200.37	Phase I combinations with cisplatin, 5-FU, paclitaxel	[U11-1190]	
1200.44	Phase II as neoadjuvans in HER2+ BC patients	[U12-3255]	
1200.68	Phase I combination with trastuzumab	[U12-1338]	
1200.79	DDI trial with ritonavir	[U10-1163]	[U09-2367]
1200.80	Dose proportionality trial in healthy volunteers	[U10-1164]	
1200.86	Hepatic impairment trial	[U12-1171]	[U11-2675], [U12-1021]#
1200.151	DDI trial with ritonavir	[U12-1170]	[U11-2675]
1200.152	DDI trial with rifampicin	[U12-1140]	
1239.1	Phase I combination with nintedanib$	[U10-3263]	[U08-1226]
1239.2	Phase II combination with nintedanib$ in CRC patients	[U08-2248]	
1239.3	Phase II combination with nintedanib$ in HRPC patients	[U10-1013]	

For some studies of long duration more than 1 method was used.
Methods relate to afatinib in human plasma except # (human urine)
Nintedanib (BIBF 1120) is another BI investigational agent

(Source: Table 1.4.1.4:1 on Page 32 of Summary of Biopharmaceutics and Associated Analytical Methods in the NDA)

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

The range of the standard curve for human plasma samples calibration was 0.5 - 250 ng/mL in 4 assays, 0.1 - 20 ng/mL in 3 assays and 0.1 – 50 ng/mL in 1 assay (see Table 20). The range of the standard curve for human urine samples calibration was 0.5 - 250 ng/mL in 1 assay and 5 – 1000 ng/mL in other 2 assays (see Table 21). The C_{max} (CV%) for 50 mg afatinib dosing is 37.1 ng/mL (37%) after a single dose and 77 ng/mL (64%) after repeating doses. The mean trough plasma concentration (C_{trough}) for 40 mg in cancer patients ranged from 14.4 to 27.4 ng/mL in 6 cycles with CV% of 70% in a meta-analysis. The C_{trough} for 20 mg (minimum dose) is most likely to be above 0.1 ng/mL. Therefore the range of the standard curve is suitable to calibrate the plasma concentration of afatinib in cancer patients.

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

The LLOQ for human plasma samples was 0.1 ng/mL in 4 assays and 0.5 ng/mL in other 4 assays (see Table 20). The LLOQ for urine samples analysis was 0.5 ng/mL in 1 assay and 5 ng/mL in other 2 assays (see Table 21).

The ULOQ for human plasma samples was 20 ng/mL in 3 assays, 50 ng/mL in 1 assay and 250 ng/mL in other 4 assays (see Table 20). The ULOQ for urine samples was 250 ng/mL in 1 assay

and 1,000 ng/mL in other 2 assays (see Table 21).

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

The accuracy and precision of 11 assays are within 20% for the LLOQ and 15% for all other concentrations except assay [U11-2821] and [U12-1021] (see Table 20 and Table 21). These two assays used extended (25%) acceptance criteria because the observed adsorption losses from urine during sample collection and handling.

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

Afatinib was stable in human EDTA whole blood for up to 1 hour at 37°C with no more than 15% deviation from initial concentration. The stability data of afatinib in human EDTA plasma and urine are shown in Table 23 and Table 24. In summary, the deviations from initial concentration of afatinib are all within ±15% for both human plasma and urine, for both high range and low range of standard curve, in both early and later urine assay, and in the conditions of room temperature, 3 freeze-thaw cycles, -20°C, and autosampler.

Table 23: Summary of Stability of Afatinib in Human Plasma

	High range (0.500 - 250 ng/mL)			Low range (0.100 - 20.0 ng/mL resp. 0.100 - 50.0 ng/mL)		
Nominal analyte concentration	1.25 or 1.50 ng/mL	200 ng/mL		0.250 or 0.300 ng/mL	16.0 or 40.0 ng/mL	
Stress condition	Determined (relative to nominal concentration)		Report (reference)	Determined (relative to nominal concentration)		Report (reference)
room temperature	91.2 % (12 hours)	95.5 % (12 hours)	[U04-1421]	88.1 % (10 hours)	96.9 % (10 hours)	[U11-2675]
3 freeze-thaw cycles*	97.6 % 104.3 %	99.5 % 108.8 %	[U04-1421] [U11-2675]	92.4 % 110.0 %	87.5 % 112.1 %	[U09-2026] [U11-2675]
freezer at -20°C	87.2 % (538 days)	92.0 % (538 days)	[U04-1421]	98.8 % (301 days)	101.3 % (301 days)	[U09-2026]
Extract stability (on the autosampler)	108.0 % (39 hours)	108.0 % (40 hours)	[U04-1421]	98.4 % (112 hours)	102.5 % (112 hours)	[U09-2026]
	96.0 % (84 hours)	100.0 % (85 hours)	[U05-2022]	104.4 % (87 hours)	107.5 % (87 hours)	[U09-2367]
	101.9 % (5 days)	104.0 % (5 days)	[U11-2675]	95.9 % (5 days)	110.7 % (5 days)	[U11-2675]

* with only short periods at room temperature between complete thawing and re-freezing

(Source: Table 1.4.1.3:1 on Page 30 of Summary of Biopharmaceutics and Associated Analytical Methods in the NDA)

Table 24: Summary of Stability of Afatinib in Human Urine

	Initial assay# (0.500 - 250 ng/mL)			Later assay& (5.00 - 1000 ng/mL)		
Analyte concentration	1.25 ng/mL	200 ng/mL		12.5 or 15.0 ng/mL	750 or 800 ng/mL	
Stress condition	Determined (relative to nominal concentration)		Report (reference)	Determined (relative to nominal concentration)		Report (reference)
room temperature	91.2 % (22 hours)	95.5 % (22 hours)	[U06-2289]	94.4 % (24 hours)	90.6 % (24 hours)	[U11-2821]
3 freeze-thaw cycles	92.8 %	94.0 %	[U06-2289]	90.4 %	92.4 %	[U11-2821]
freezer at -20°C	85.6 % (198 days)	87.5 % (198 days)	[U06-2289]	94.3 % (149 days)	99.0 % (149 days)	[U12-1021]
Extract stability (on the autosampler)	104.0 % (64 hours)	108.0 % (64 hours)	[U06-2289]	93.8 % (3 days)	107.8 % (3 days)	[U12-1021]

urine acidified with 1 % citric acid to prevent adsorption losses
& urine with 1 % Tween 20 to prevent adsorption losses

(Source: Table 1.4.1.3:2 on Page 31 of Summary of Biopharmaceutics and Associated Analytical Methods in the NDA)

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

4 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY PHARMACOMETRICS REVIEW	
NDA Number	201,292 (submitted on November 14, 2012)
Brand Name	Gilotrif®
	Tablets (20, 30, 40, [redacted] (b) (4)
Generic Name	Afatinib
PM Reviewer	Jun Yang, Ph.D.
PM Secondary Reviewer	Kevin Krudys, Ph.D.
Division	Clinical Pharmacology V
Clinical Division	Division of Drug Oncology Product II
Sponsor	Boehringer Ingelheim
Submission Type; Code	NDA (NME)
Proposed Indication	Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s)

4.1 SUMMARY OF FINDINGS

4.1.1 Key Review Questions

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

1. Does the exposure-response for efficacy and safety support titration [redacted] (b) (4)
2. Does the population PK analysis support the label statements?

4.1.1.1 Dose the exposure-response (E-R) relationship for efficacy and safety support titration [redacted] (b) (4)

No, [redacted] (b) (4)
First, we note that clinical experience from the pivotal trial (1200.32) suggests that the 50 mg dose may not provide additional benefit. After the first cycle treatment with a daily (QD) 40 mg dose, 16 patients tolerated the 40 mg dose and had their dose escalated to 50 mg QD. However, 10 of those 16 patients experienced dose reduction at the QD 50 mg regimen. The E-R relationships for efficacy and safety were supportive of this finding.

E-R for Efficacy: The E-R relationship between the primary efficacy endpoint, progression-free survival (PFS) and quartiles of steady state AUC at final titration dose (AUC_f) in patients treated with afatinib in the registration trial was evaluated by a Kaplan-Meier analysis. The results indicate that patients in the highest exposure quartile (Q4) have comparable PFS to the control arm and exhibit shorter PFS than those of other quartiles (Figure 1). EGFR status, smoking

status, ECOG performance, baseline tumor size, gender, body weight, Asian status, and final titration dose were all approximately evenly distributed across different quartiles of AUC_f. Similar results were obtained for PFS and quartile of first cycle afatinib trough concentration on Day 15 (CP_day15) based on a Kaplan-Meier analysis in patients (N=91) who only received the 40 mg daily dose and did not experience a dose reduction (Figure 2), suggesting that patients with higher exposure may not have PFS benefit. Because the dose de-escalation is based on a patient's tolerability, the E-R analysis results indicate that patients who can not tolerate high exposure may be more sensitive to afatinib treatment. These results suggest that titration to a 50 mg dose may not provide additional PFS benefit in NSCLC patients.

Figure 1: E-R Relationship for PFS Stratified by Quartiles of Steady State AUC at Final Dose (AUC_f) in Afatinib Arm.

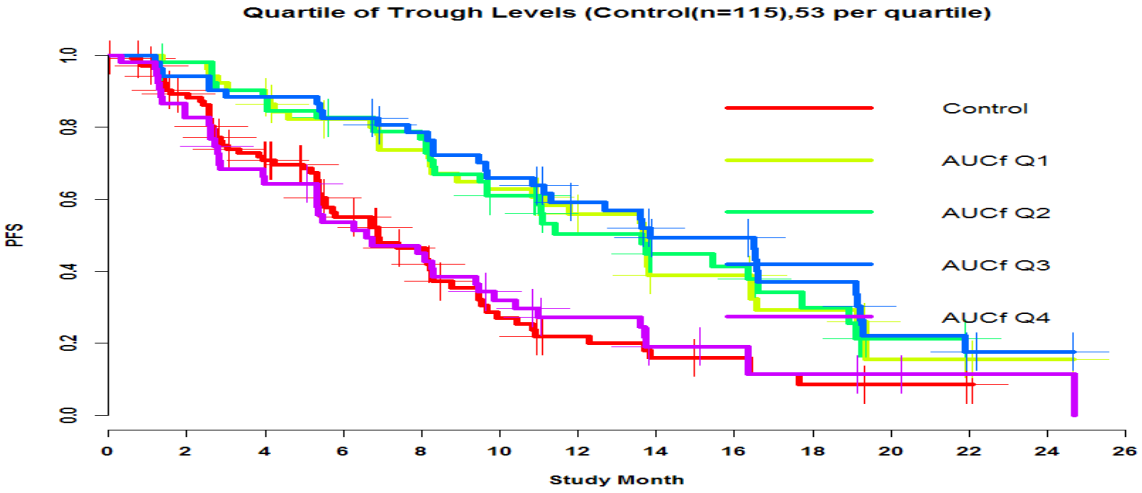
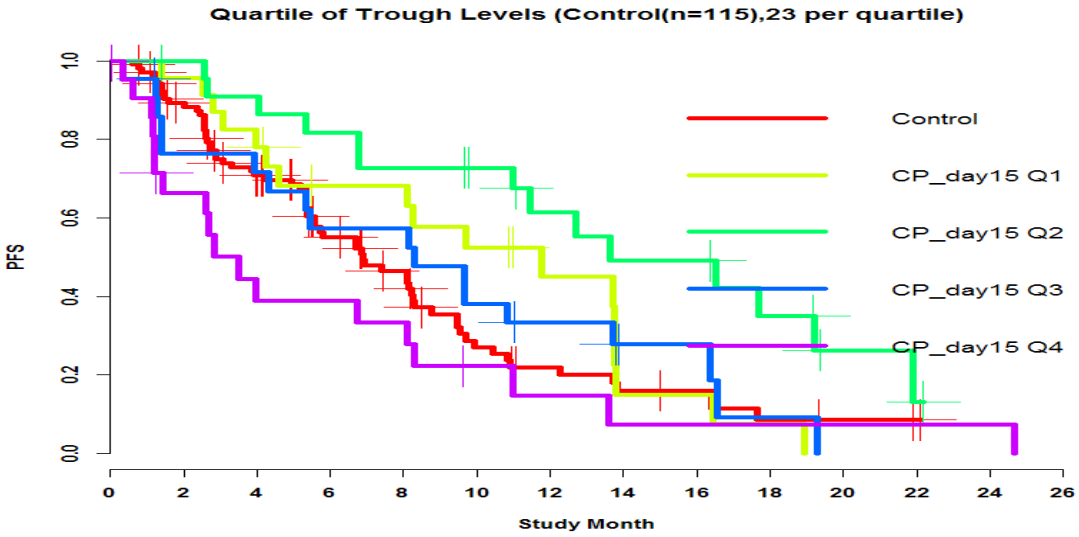


Figure 2: E-R Relationship for PFS Stratified by Quartiles of CP_day15 in patients who only received 40 mg afatinib daily.



<u>*E-R for Safety*</u>: Patients in the afatinib treatment group also experienced higher incidence of adverse events (AEs) with the most frequent AEs leading to dose reduction being diarrhea

(19.7%), rash/acne (19.2%), nail effects (13.5%), and stomatitis (10.0%). In the registration trial 1200.32, 83.5% of patients experienced their first diarrhea episode within 14 days of beginning afatinib treatment at the 40 mg starting dose. Therefore, the observed afatinib trough concentration at day15 (CP_day15) were used for the E-R analyses for Common Terminology Criteria for Adverse Events (CTCAE, grade ≥3) and the two most common AEs, diarrhea and skin rash/acne (grade ≥2). The results of logistic regression analyses suggest that higher exposure of afatinib increases the risk of experiencing CTCAE grade ≥3 toxicity or grade 2 or higher diarrhea event (Figure 3 & 4 Left). There was no E-R relationship between grade 2 and higher rash/acne event and afatinib exposure (Figure 4 Right). The E-R for safety analyses is consistent to the clinical observation that 10 of the 16 patients who were escalated to 50 mg QD dose experienced dose reduction.

Figure 3: Relationship between experiencing CTCAE grades >=3 toxicity and trough afatinib levels in cycle 1 (CP_day15).

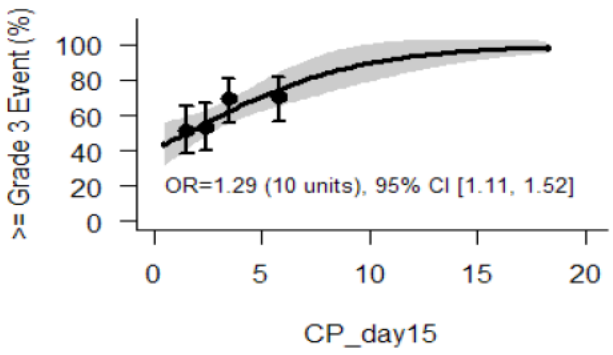
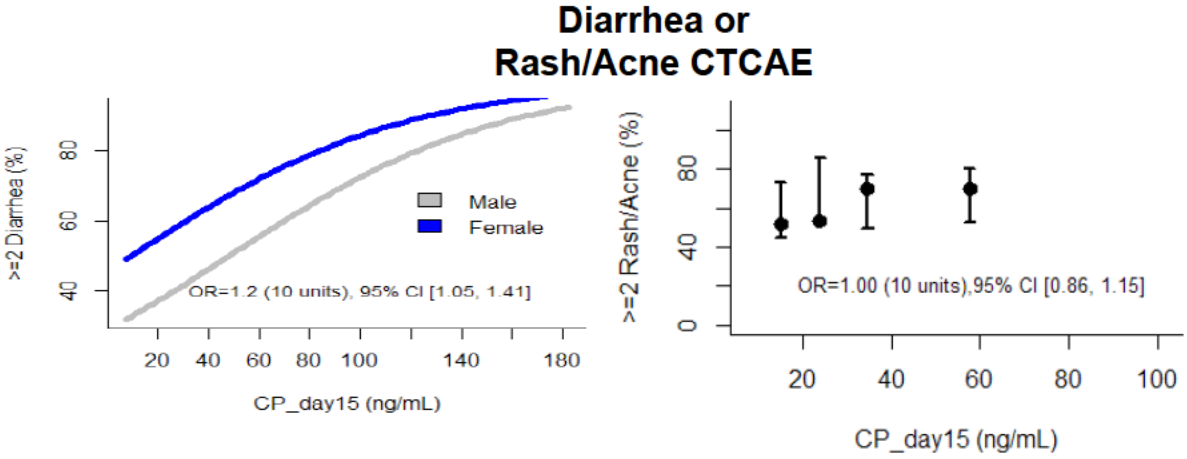


Figure 4: Relationship between experiencing grades >=2 diarrhea or rash/acne and trough afatinib levels in cycle 1 (CP_day15).



In summary, the E-R analyses showed that higher exposure may not provide PFS benefit but is associated with adverse events. The applicant's proposed dose de-escalation scheme based on

patient's tolerability appears reasonable; however, patients in the highest quartile of steady state AUC did not show a PFS benefit, which suggests that the driving force for PFS may not be the afatinib exposure once the exposure has reached certain levels, but the patient's sensitivity to afatinib treatment or other unknown factors.

4.1.1.2 Dose the Population PK Analysis Support the Label Statements?

Approximately 92% (N=1010) of the trough plasma concentration of afatinib at day 15 (CP_day15) were observed and the rest (8%) were missing data and replaced with simulated data based on the final Population PK model. Because the steady state AUC at the starting dose of 40 mg (AUC_{ss}=40mg*F1/posthoc individual CL) is highly correlated to CP_day15 (See reviewer's analysis), the CP_day15 were therefore selected in the Population PK covariate analyses.

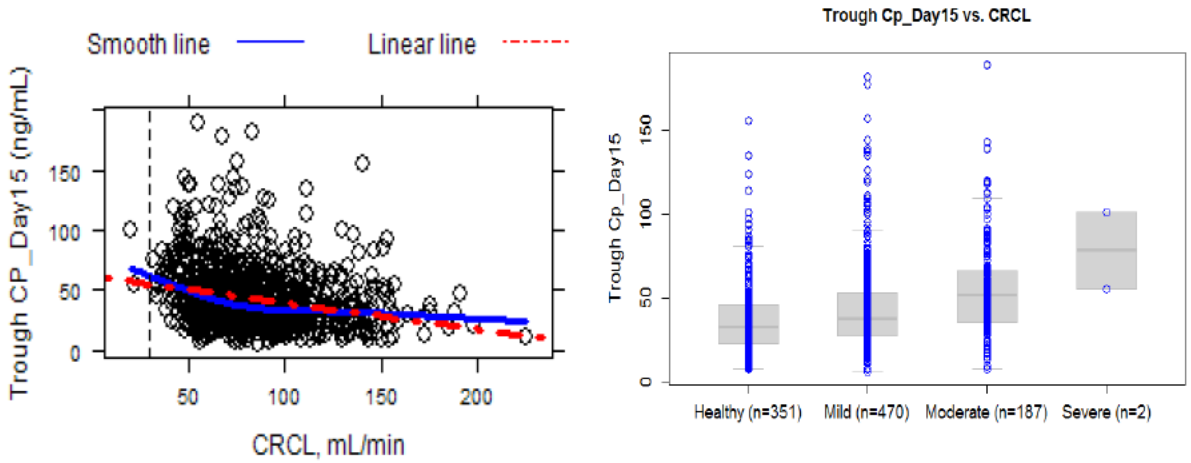
Hepatic Impairment

According to the sponsor's human mass balance study, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of afatinib. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied. Adjustments to the starting dose of afatinib are not recommended in patients with mild or moderate hepatic impairment

Renal Impairment

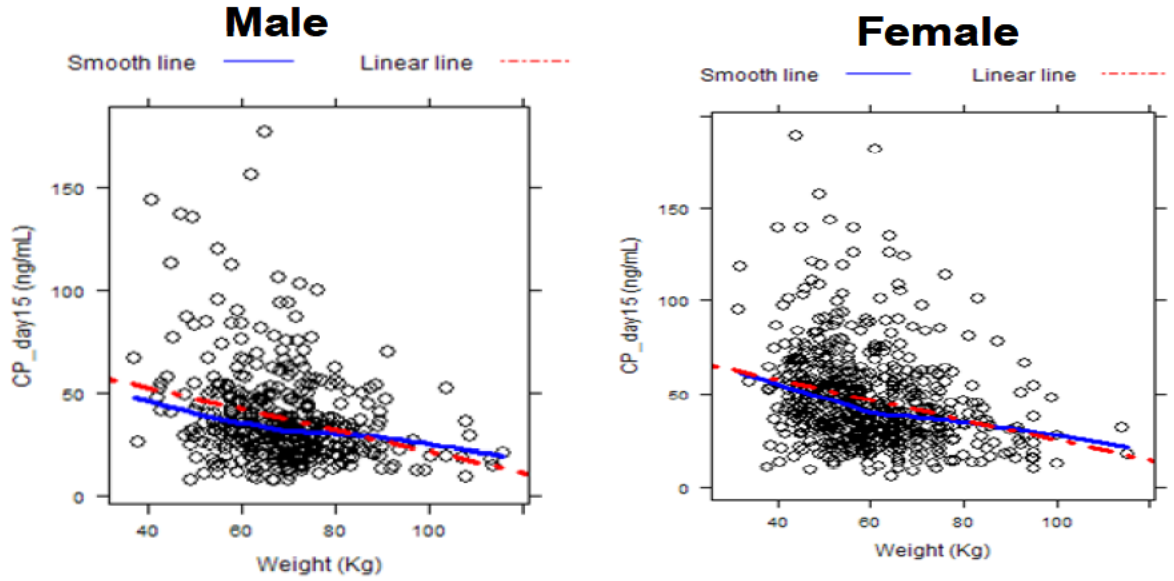
Less than 5% of afatinib is eliminated via renal excretion. However, there is a trend that the exposure of afatinib increases as the CRCL value decreases (Figure 5), where the median trough afatinib levels in patients with mild and moderate renal impairment are 14.5 % and 37.4 % higher than that of healthy subjects. There were only 2 patients with baseline CRCL values less than 30 mL/min. However, the exposure difference due to renal function is not considered clinically relevant in patients with mild or moderate renal impairment and no dose adjustment is recommended. Afatinib treatment in patients with severe renal impairment has not been studied. Adjustments to the starting dose of afatinib are not recommended in patients with mild (CRCL 60-89 mL/min) or moderate (CRCL 30-59 mL/min) renal impairment.

Figure 5. Association between trough afatinib levels and CRCL values.



Body Weight:
The exposure of afatinib in the first cycle (CP_day15, ng/mL) tends to decrease as the body weight increases regardless of the gender (Figure 6). For every 10 kg of body weight increase, the trough level of afatinib in first cycle drops 5.7 ng/mL. However, the exposure difference due to body weight is not clinically relevant and no dose adjustment is recommended.

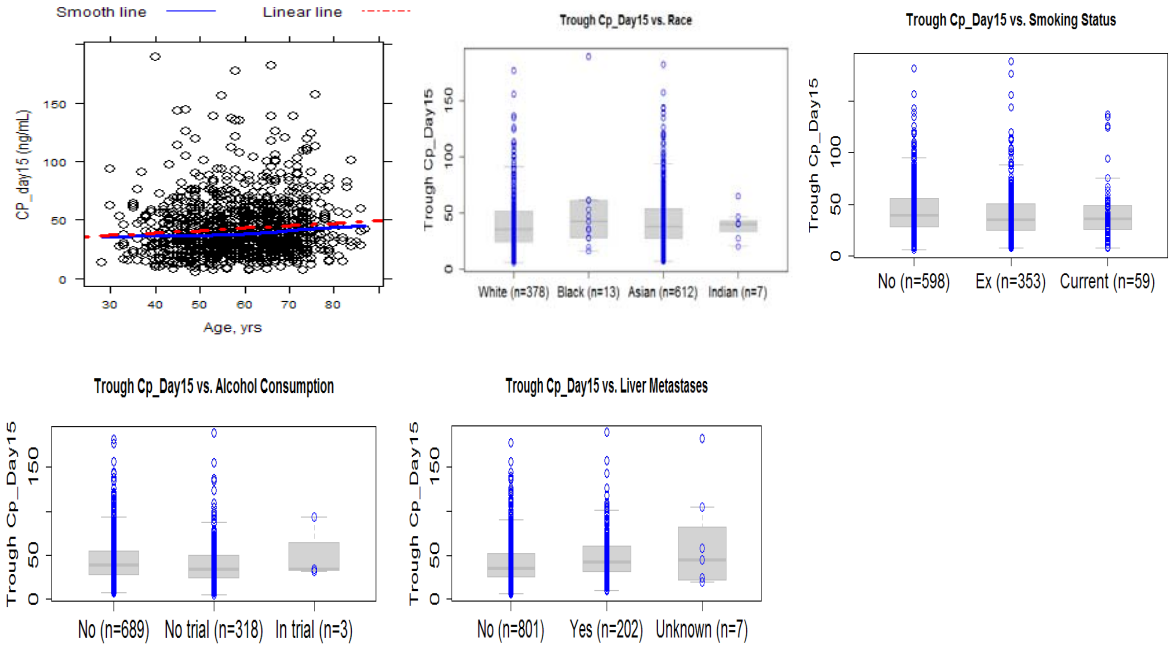
Figure 6. Association between trough afatinib levels and body weight



Gender:
The median trough plasma concentration of afatinib (CP_day15) is approximately 20% higher in females than that of males. According to the sponsor's population PK analysis, the gender is a significant covariate after adjusting for the body size. However, the exposure difference due to gender is not clinical relevant and no dose adjustment is recommended.

Age, Race, and Other Extrinsic/Intrinsic Factors:
Age, race, smoking history, alcohol consumption, or presence of liver metastases had no effect on the exposure of afatinib and no dose adjustment is recommended for these factors (Figure 7).

Figure 7. Association between trough afatinib levels and age, race, smoking status, alcohol consumption, and liver metastases.



4.1.2 Recommendations

Based on the E-R analysis of efficacy and safety and the clinical observation, we recommend

(b) (4)

4.1.3 Label Statements

The ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency. The blue fonts are FDA edits.

SECTION 12.3 Pharmaockinetics

(b) (4)

(b) (4)

Body Weight, Gender, Age, and Race
Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinical important effect on exposure of afatinib.

4.2 PERTINENT REGULATORY BACKGROUND

Afatinib covalently binds to kinase domains of EGFR, HER2 and HER4 and irreversibly inhibits the tyrosine kinase autophosphorylation of ErbB receptor family homo- and heterodimers. Inhibition of ErbB receptor kinase activity results in downregulation of signaling. The applicant seeks an approval of afatinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR mutation(s) as detected by an FDA-approved test. The recommended dose of BRAND is 40 mg orally once daily (QD) for first-line treatment or for patients not previously treated with an EGFR-tyrosine kinase inhibitor (EGFR-TKI naïve patients). The 40-mg daily dose can be reduced to 30 mg and then to 20 mg QD for management of intolerable toxicities. (b) (4)
(b) (4)

4.3 RESULTS OF SPONSOR'S ANALYSIS

4.3.1 Pivotal Trial (1200.32)

A multi-center, randomized (2:1) double-blind trial comparing afatinib (N = 230) with placebo (N = 115) was conducted in patients with EGFR mutation-positive locally advanced or metastatic NSCLC who were naïve to prior systemic TKI treatment. Randomization was stratified according to EGFR mutation status (L858R; Del19; other) and race (Asian; non-Asian). In the pivotal Trial 1200.32, NSCLC patients were dosed with 40 mg afatinib QD, but were dose-escalated to 50 mg QD if the 40 mg dose was tolerated in first 3 weeks. The 40-mg daily dose was reduced to 30 mg QD and then to 20 mg QD in case of non-tolerated adverse events (i.e., diarrhea, skin rash, stomatitis, and/or other drug-related events >CTCAE Grade 1). There was a significant improvement in the median progression free survival (PFS) in patients treated with afatinib compared to patients treated with chemotherapy (11.1 months vs. 6.9 months). Based on investigator review, objective response rate (ORR) was 69.1% vs. 44.3% and

disease control rate (DCR) was 90.0% vs. 82.6% in afatinib-treated patients compared with chemotherapy-treated patients, respectively.

4.3.2 Population Pharmacokinetic (PopPK) Analysis

4.3.2.1 Studies Included in the Analysis

The sponsor included 4 population PK (PopPK) study reports in the current NDA submission:

- PopPK1: Population PK analysis of Trials 1200.1, 1200.2 and 1200.3
- PopPK2: Population PK analysis of Trials 1200.1, 1200.2, 1200.3, 1200.4 and 1200.20
- PopPK3: Population PK analysis of Trials 1200.10, 1200.11, 1200.22 and 1200.23
- PopPK4 (Final PopPK Model): Population PK analysis of Trials 1200.10, 1200.11, 1200.22, 1200.23, 1200.28, 1200.32 and 1200.33

The above PopPK analyses were performed using nonlinear mixed effects modeling techniques as implemented in the software NONMEM (version VI.2.0). Perl-speaks-NONMEM (PsN, version 3.1.0) was used for the bootstrap analyses. R for Windows (version 2.12.1), R for Unix (2.5.1), Xpose (version 4.0) and SAS 9.2 were used for data, graphics and statistical analysis.

4.3.2.1.1 PopPK analysis of Trials 1200.1, 1200.2 and 1200.3 (PopPK1)

Title: Development of A Population PK Model of BIBW2992 Based on Preliminary Data in Patients with Advanced Solid Tumors and Simulation of Different Administration Schedules.

Objective: The primary objective was to support further dosing schedule selection for afatinib in cancer patients using simulations.

Methods: The PK dataset comprised of a total of 109 patients and 1850 plasma concentrations values from 3 Phase 1 studies: 1200.1 (N=38), 1200.2 (N=43), and 1200.3 (N=53) . All three studies were open label, dose escalation studies of continuous once daily (QD) oral treatment with afatinib to determine the MTD in cancer patients. The doses ranged from 10 to 100 mg.

Results: The plasma concentration-time profiles of afatinib were described by a 2-compartment model with a first order absorption (Ka) and elimination process. The estimated typical value of Ka, clearance (CL/F), inter compartmental clearance (Q/F), central volume of distribution (V_2/F) and peripheral volume of distribution (V_3/F) were estimated to be 0.223 h^{-1}, 44.0 L/h, 137 L/h, 441 L, and 1750 L, respectively. The inter-individual variabilities (IIVs) were estimated to be 44 %, 132 % and 58 % on CL, V_2 and F, respectively.

4.3.2.1.2 PopPK analysis of Trials 1200.1, 1200.2, 1200.3, 1200.4 and 1200.20 (PopPK2)

Title: Characterization of the Nonlinear PK Behaviors of Afatinib in a Combined Study of Phase 1 Trials in Patients with Advanced Solid Tumors

Objective: The primary objective is to characterize dose nonlinearity and PK of afatinib in cancer patients after single and multiple administrations.

Methods: The model (PopPK2) was refined from previous PopPK1 (a 2-compartmental model with data from trials 1200.1, 1200.2, and 1200.3) with additional datasets from trials 1200.4 and

1200.20 in patients with various advanced cancer types. Only PK data from the first treatment cycle were used. A total of 2595 valid plasma concentrations obtained from 187 patients after QD oral dosing in a dose range of 10 to 160 mg were used for the analysis.

Results: The plasma concentration-time profiles of afatinib were described by a 2-compartment model with a first order absorption and elimination process. The over dose-proportional increase in exposure was described by a dose-dependent relative bioavailability (F1), where F1 increased with doses up to a maximum dose of 70 mg following a power function with an estimated power of 0.512. F1 was a constant for doses higher than 70 mg. The typical values for Ka, CL/F, Q/F, V_2/F and V_3/F were estimated to be 0.492 h^{-1}, 36 L/h, 104 L/h, 833 L, and 1080 L, respectively. The IIVs were estimated to be 37 %, 54 %, 92%, and 55 % on CL, V_2, Ka, and F, respectively. Residual variability was described by a proportional random effect model (CV=29 %).

Conclusions: The plasma concentration-time profiles of afatinib were described by a two-compartment model with a first-order absorption rate and elimination process. The over-proportional increase in plasma concentration was described by a dose dependent relative bioavailability. The data suggest a linear PK behavior for 70 mg and higher doses.

4.3.2.1.3 Population PK analysis of Trials 1200.10, 1200.11, 1200.22 and 1200.23 (PoPPK3)

Title: Combined Population PK Analysis of BIBW 2992 Monotherapy in Advanced or Metastatic Non-Small-Cell Lung Cancer (NSCLC) and Metastatic Breast Cancer (BC) Patients.

Objective: The objectives of this PopPK analysis were to describe afatinib PK in the target population and to perform a covariate analysis to evaluate the effect of intrinsic and extrinsic factors on the PK of afatinib such as: demographics (age, sex, ethnic origin, body size metrics, alcohol consumption, smoking history); renal and hepatic impairment; disease specific variables: ECOG performance score, presence of liver metastases, cancer type, and race (Asian and Caucasian, Chinese, Korean, Taiwanese, other Asian and non-Asian). Another objective was to provide individual post-hoc exposure estimates to support exploration of exposure-response relationships if requested.

Methods: Data from two Phase 2 trials in metastatic breast cancer patients (1200.10 and 1200.11), one Phase 2 trial in NSCLC patients (1200.22) and one Phase 3 trial in patients with stage IIIB or IV NSCLC (1200.23) were combined. The full PK dataset contained 2994 observations from 570 patients. To explore the effect of intrinsic and extrinsic factors on the PK of afatinib, a stepwise forward inclusion/backward elimination approach was applied. Confidence intervals (CIs) for the parameters estimates of the final model were determined by bootstrap analysis. Simulations were performed to evaluate the impact of covariates on the PK of afatinib.

Results: The afatinib plasma concentration-time profiles were best described by a 2-compartment model with linear elimination, first order absorption and absorption lag time (ALAG). IIV could be implemented in relative bioavailability (F1) and Ka. Inter-occasion variability (IOV) was incorporated for F1 (occasion was defined as a treatment cycle). Transfer rate from central to peripheral compartment (K23) and vice versa (K32) were fixed to the values obtained in the

previous PopPK1 model. A slightly more than dose-proportional increase in exposure was accounted for by implementing actual dose level as covariate on F1. Food intake within 3 h before and less than 1 h after afatinib administration, body weight (WT), ECOG performance score and lactate dehydrogenase levels (LDH) were identified as statistically significant covariates influencing the afatinib exposure by affecting F1. Mild hepatic impairment had no significant impact on PK of afatinib. The available data however did not allow a reasonable assessment of the effect of moderate or severe hepatic impairment. Asian status (Asian vs. non-Asian or Asian subpopulations), age, smoking history, alcohol consumptions, patient population (cancer type) and presence of liver metastasis had no significant impact on the PK of afatinib.

4.3.2.1.4 PopPK analysis of Trials 1200.10, 1200.11, 1200.22, 1200.23, 1200.28, 1200.32 and 1200.33 (Final Model)

Title: Combined Population PK Analysis of Afatinib Monotherapy in Patients Suffering From Various Cancer Types.

Objective: The objectives of this combined PopPK analysis were to describe the PK of afatinib in the target populations and to re-assess the effect of various intrinsic and extrinsic factors on the PK of afatinib.

Methods: The PK data were a combination of the analysis dataset from the PopPK3 model and a Phase 2 trial in head & neck squamous cell carcinoma (HNSCC) patients (1200.28), a Phase 2 trial in Japanese patients with stage IIIB or IV NSCLC (1200.33) and a registrational Phase 3 trial in NSCLC patients (1200.32) (Table 3.1). The PK analysis dataset contained 4460 observations from 927 patients (764 NSCLC, 90 BC and 73 HNSCC patients) which were used for the model development and covariate analysis. A stepwise forward inclusion/backward elimination approach was applied to evaluate the effect of intrinsic and extrinsic factors on the PK of afatinib. The CI for the parameters estimates of the final model were determined by bootstrap analysis. The predictive performance of the final model was assessed using quantitative predictive checks. Simulations were performed to evaluate the impact of covariate effects identified as statistically significant during the analysis on the PK of afatinib.

Table 3.1. Summary of studies included in the population PK analysis

Study	Cycle							ALL
	1	2	3	4	5	6	7	
1200.10	194	135	12	10	2	2	1	356
1200.11	140	118	13	8	7	6	2	294
1200.22	106	381	257	0	0	0	0	744
1200.23	326	820	454	0	0	0	0	1600
1200.28	186	168	25	0	0	0	0	379
1200.32	0	381	186	0	0	0	0	567
1200.33 (Phase I)	274	6	10	8	0	0	0	298
1200.33 (Phase II)	104	118	0	0	0	0	0	222
All studies	1330	2127	957	26	9	8	3	4460
Percentage of total number	29.8	47.7	21.5	0.6	0.2	0.2	0.1	100

Source: 1200_28_32_33-popPK Report, Page 62. Table 9.12.1:5.

Results:

Final PopPK model

The afatinib plasma concentration-time profiles were described by a 2-compartment model with first order absorption and linear elimination. F1 increases with increasing dose following a power function up to a dose of 70 mg; for doses greater than 70 mg F1 stays constant. Food intake, ECOG, LDH and alkaline phosphatase levels (AP) were identified as statistically significant covariates influencing the afatinib exposure by affecting F1. Body weight (WT), creatinine clearance (CRCL), gender and total protein (TPRO) are significant covariates affecting afatinib clearance.

$$F1 = 1\cdot(DOSE/70)^{\theta SLP}\cdot\theta_{Food}\cdot\theta_{ECOG}\cdot(1 + \theta_{LDH}\cdot(LDH-241))\cdot(1 + \theta_{AP}\cdot(AP-251))\cdot\theta_{Indication}\cdot e^{\eta F1}$$

$$V2/F = \theta_{V2}\cdot(WT/62)^{\theta WT}$$

$$CL/F = \theta_{CL}\cdot(WT/62)^{\theta WT}\cdot(1 + \theta_{CRCL}\cdot(CRCL-120))\cdot\theta_{SEX}\cdot(1 + \theta_{TPRO}\cdot(TPRO-72))$$

$$KA = \theta_{KA}\cdot e^{\eta KA}$$

Mild hepatic impairment on the afatinib exposure is minimal. However, the data were too limited to allow the assessment of moderate hepatic impairment. Age, smoking history, alcohol consumption and presence of liver metastases had no significant impact on the PK of afatinib. There was no statistically significant difference in the PK of afatinib between Asian (incl. all tested subpopulations) and Caucasian patients. There was also no obvious difference in the PK for American Indian/Alaska native or Black patients based on the limited data available in these populations. There was a statistically significant difference in the PK of HNSCC patients as compared to BC or NSCLC patients which was accounted for by implementing an increased relative bioavailability (35%) for HNSCC patients. There was no difference in the PK between BC and NSCLC patients; nor between the tested NSCLC subpopulations. The PK parameter estimations from final model are provided in Table 3.2. The shrinkage of these model parameters such as inter-individual variability on F1 and Ka were 6.0% and 39.9%, respectively.

Table 3.2. Population PK parameters from Final model.

FOCE INTERACTION Objective function = 28420.167 [927 subjects, 4460 observations]		NONMEM		95% CI from bootstrap analysis*
		Parameter estimate	Rel. standard error [%]	
Fixed effects				
CL/F [L/h]		42.3	8.53	37.6-47.7
V2/F [L]		456	8.40	387-537
K23 [1/h]		0.170 FIX[a]	NA	NA
K32 [1/h]		0.0685 FIX[a]	NA	NA
KA [1/h]		0.252	8.10	0.214-0.294
F1		1 FIX[b]	NA	NA
SLP_F1:	DOSE > 70 DOSE ≤ 70	0 FIX[b] 0.485	NA 21.0	NA 0.321-0.654
Food_F1:	No food effect Food intake less than 3 h before or less than 1 h after drug administration	1 FIX[b] 0.739	NA 7.28	NA 0.638-0.854
ECOG_F1:	ECOG 0 ECOG 1 ECOG ≥ 2	1 FIX[b] 1.08 1.27	NA 2.76 6.80	NA 1.02-1.14 1.12-1.46
LDH_F1 [L/U]		0.000331	39.3	0.000131-0.000551
AP_F1 [L/U]:	> 251[c] ≤ 251[c]	0 FIX[b] 0.00128	NA 14.5	NA 0.000908-0.00163
Indication_F1:	BC or NSCLC HNSCC	1 FIX[b] 1.35	NA 7.85	NA 1.16-1.56
WT_V2/F		0.899	17.2	0.576-1.18
WT_CL/F		0.595	17.1	0.405-0.783
CRCL_CL/F [mL/min]:	CRCL ≥ 120 CRCL < 120	0 FIX[b] 0.00484	NA 9.09	NA 0.00398-0.00558
SEX_CL/F:	Male Female	1 FIX[b] 0.871	NA 3.87	NA 0.814-0.931
TPRO_CL/F [L/g]		-0.00436	41.5	-0.00793-(-0.000881)

Random effects			
IIV in F1 [CV%]	47.5	6.59[d]	44.4-50.5
IIV in KA [CV%]	77.3	11.1[d]	68.7-85.8
Proportional residual variability (PROP) [CV%]	26.5	2.60	25.1-27.7
Additive residual variability (ADD) [ng/mL]	2.08	17.1	1.38-2.78

Source: 1200_28_32_33-popPK Report, Page 79-80, 90-92.

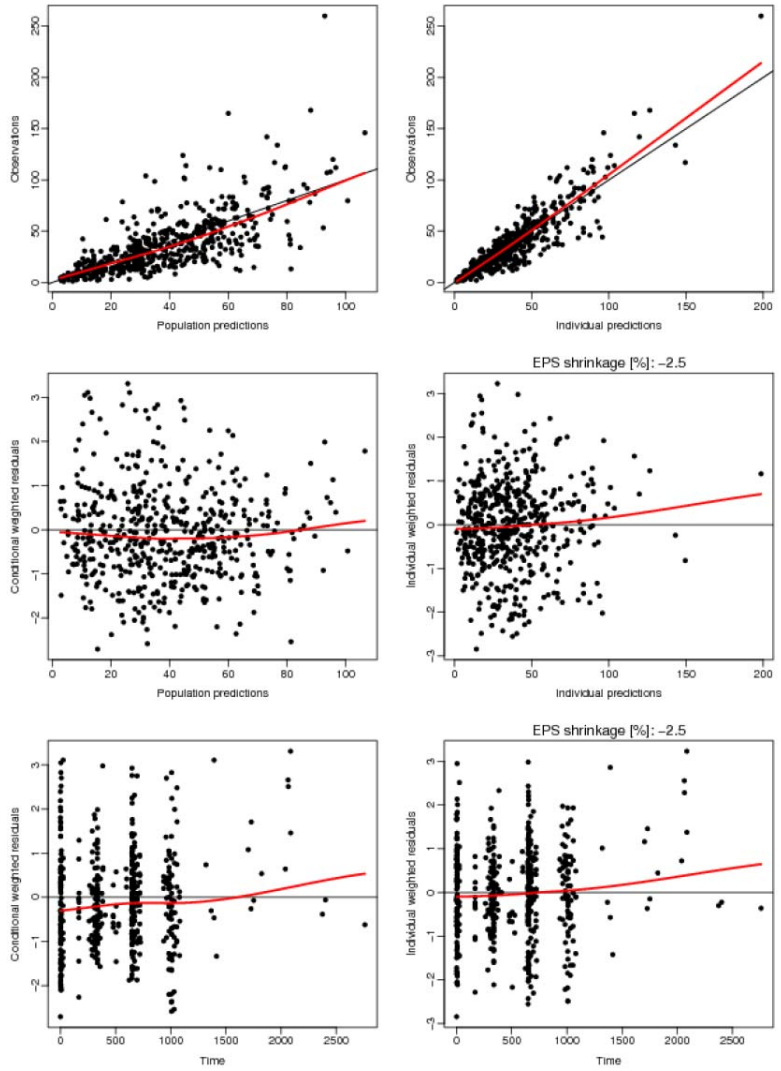
Steady state exposure in NSCLC patients is described as model-predicted population mean (AUCτ,ss, Cmax,ss, tmax,ss, CL/F, Vz/F and terminal half life $t_{1/2}$ (β-phase)) in Table 3.3. The model prediction were based on the typical patient defined by the median/mode of the respective baseline covariate values of all patients from studies 1200.22, 1200.23 and 1200.32 receiving at least one dose of afatinib (female, 62 kg, CRCL of 77 mL/min, ECOG performance score of 1, AP of 104 U/L, LDH of 252 U/L and TPRO of 72 g/L). The standard goodness of fit plots for the final model are shown in Figure 3.1.

Table 3.3. Model predicted population mean values of afatinib PK parameters after multiple dose administration of 20, 30, 40, and 50 mg afatinib from the final PopPK model in NSCLC patients

Afatinib		20 mg	30 mg	40 mg	50 mg
NSCLC patients		Model predicted population mean values[1]			
$AUC_{\tau,ss}$	[ng·h/mL]	329	600	920	1280
$C_{max,ss}$[2]	[ng/mL]	17.7	32.3	49.6	69.0
$t_{max,ss}$[2]	[h]	4.25	4.25	4.25	4.25
$t_{1/2}$	[h]	45.4	45.4	45.4	45.4
CL/F	[mL/min]	1010	833	725	651
V_z/F	[L]	3990	3280	2850	2560

Source: Summary of Clinical Pharmacology Studies, Page 104. Table 3.2.4:1.

Figure 3.1: Goodness of fit plot of the final model For Pivotal Trial 1200.32. The red line represents the linear regression line.



Source: 1200_28_32_33-popPK Report, Pages 288 & 295. Figure 15.2.3:17&24.

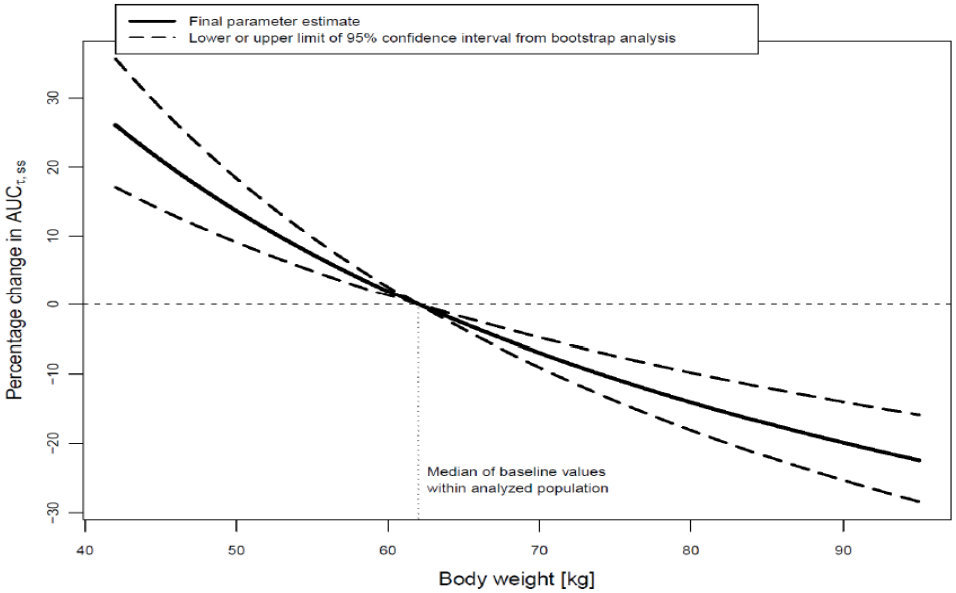
Reviewer's Comments: *The diagnostic plots and shrinkage of model parameters appear reasonable. Overall, the applicant's population PK model reasonably describes the data.*

4.3.2.2 Body Size and Gender

Simulations were performed to evaluate the impact of covariate effects identified as statistically significant during the analysis on the PK of afatinib.

Exploration of the relationship between model predicted AUCτ,ss at 40 mg and body weight is provided in Figure 3.2. Figure 3.2 illustrates the percentage change in AUCτ,ss in relation to body weight. The median of body weight in the NSCLC (target patient population) was 62 kg.

Figure 3.2. Percentage change in AUCτ,ss in dependence of body weight



Source: Summary of Clinical Pharmacology Studies, Page 107. Figure 3.3.1.2:1.

4.3.2.3 Gender

The final parameter estimate for reduction in CL/F in females compared to males was 12.9 % (95 % CI from bootstrap analysis: 6.9 to 18.6 %) (see Table 3.2) when accounting for all other covariate effect, resulting in a 14.8 % higher AUCτ,ss.

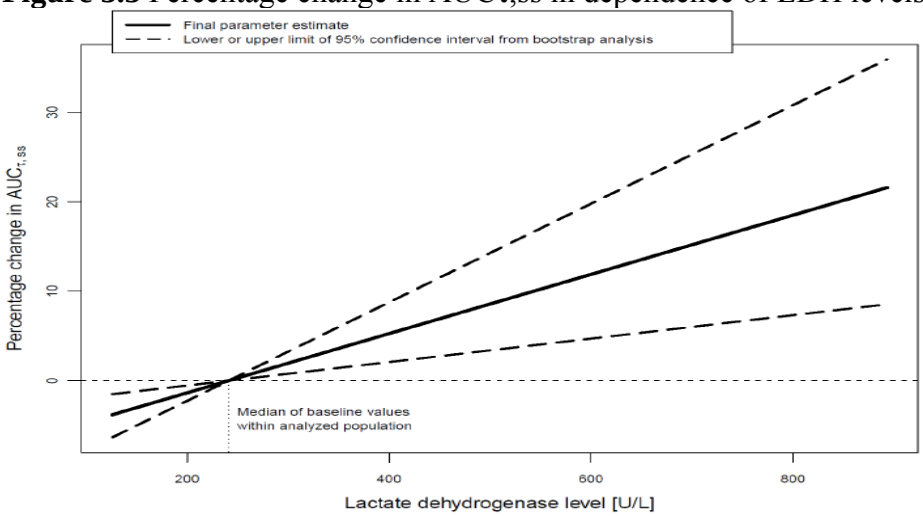
4.3.2.4 ECOG Performance

Patients with an ECOG of 0 had a 7% lower and patients with an ECOG greater than or equal to 2 had a 18% higher AUCτ,ss, respectively, compared to patients with a ECOG of 1 (mode within analyzed population).

4.3.2.5 Lactate Dehydrogenase (LDH) Levels

The change in afatinib exposure was described by a linear function of LDH with a slope of 0.000331, i.e. AUCτ,ss was decreased by 3.81 % for a patient with LDH of 126 U/L (2.5th percentile) and increased by 21.6 % for a patient with LDH of 893 U/L (97.5th percentile) relative to a patient with a LDH of 241 U/L (median within analyzed population) (Figure 3.3).

Figure 3.3 Percentage change in AUCτ,ss in dependence of LDH levels

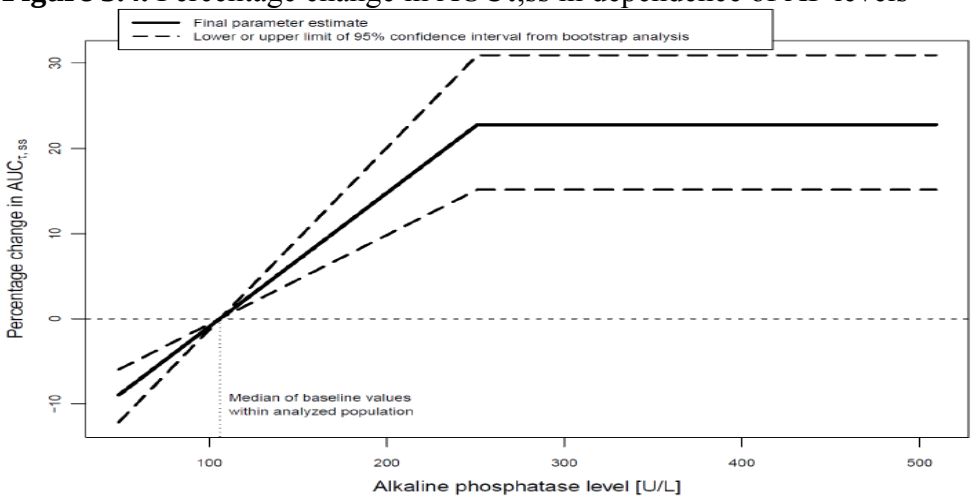


Source: Summary of Clinical Pharmacology Studies, Page 114. Figure 3.3.6.1:1.

4.3.2.6 Alkaline Phosphatase (AP) Levels

For patients with an AP lower than 251 U/L, F1 declined linearly by 0.128 % for one unit decrease in AP, i.e. AUCτ,ss was decreased by 8.96 % for a patient with AP of 49 U/L (2.5th percentile) and increased by 22.8 % for a patient with AP of 509 U/L (97.5th percentile) relative to a patient with a AP of 106 U/L (median within analyzed population) (Figure 3.4).

Figure 3.4. Percentage change in AUCτ,ss in dependence of AP levels

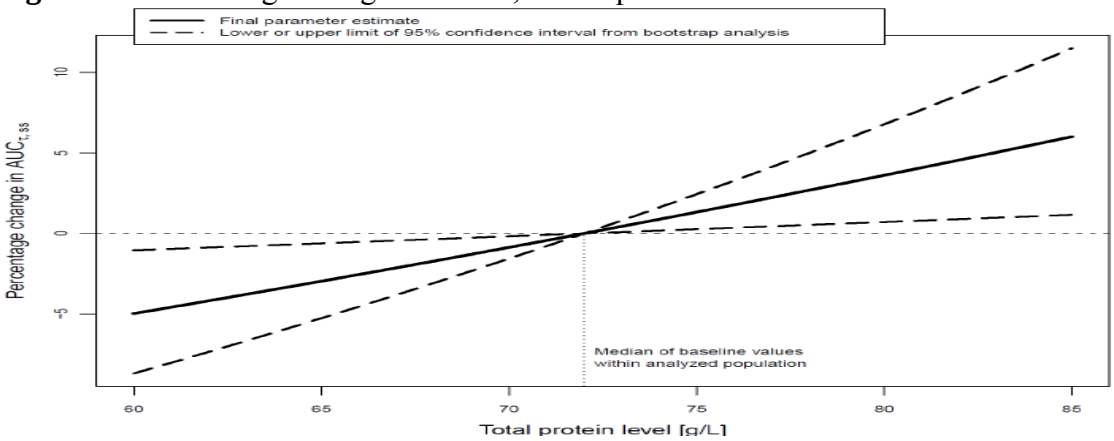


Source: Summary of Clinical Pharmacology Studies, Page 115. Figure 3.3.6.2:1.

4.3.2.7 Total Protein (TPRO) Levels

The change in CL/F was described by a linear function of TPRO with a slope of 0.00436. This translates into a decrease in AUCτ,ss by 4.97 % for a patient with TPRO of 60 g/L (2.5th percentile) and an increase by 6.01 % for a patient with TPRO of 85 g/L (97.5th percentile) relative to a patient with a TPRO of 72 g/L (median within analyzed population) (Figure 3.5).

Figure 3.5. Percentage change in AUCτ,ss in dependence of TPRO levels



Source: Summary of Clinical Pharmacology Studies, Page 115. Figure 3.3.6.2:1.

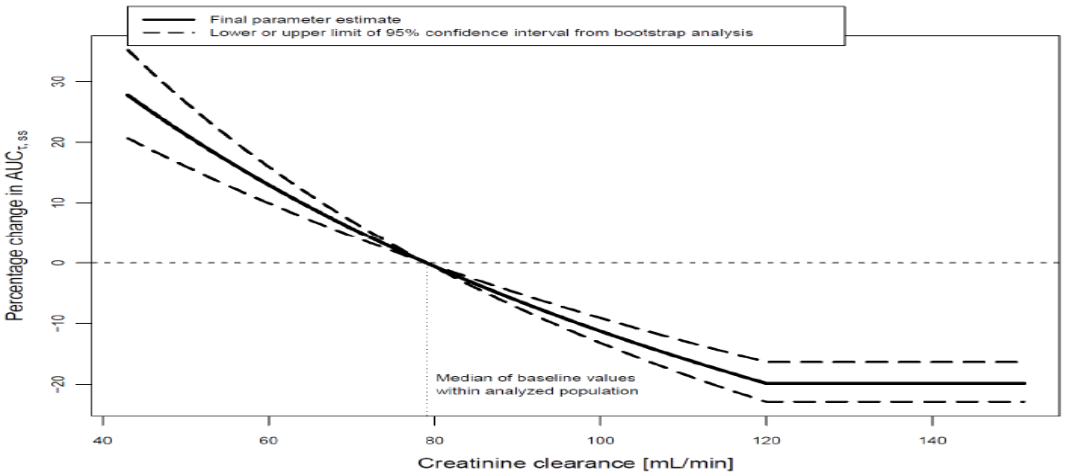
4.3.2.8 Food Effect

Food intake less than 3 h before or less than 1 h after afatinib administration decreased the area under the concentration-time curve within a dosing interval at steady state (AUCτ,ss) by 26.1 %.

4.3.2.9 Renal Impairment

CRCL: For patients with a CRCL lower than 120 mL/min, the CL/F declined linearly by 0.484 % for one unit decrease in CRCL, i.e. for a patient with a CRCL of 60 or 30 mL/min AUCτ,ss increased by 13.0 % and 42.0 %, respectively, and decreased by 6.23 % and 19.8 % for a patient with CRCL of 90 or 120 mL/min compared to a patient with the CRCL of 79 mL/min (median within analyzed population). Figure 3.6 illustrate the percentage change in AUCτ,ss in dependence of CRCL.

Figure 3.6. Percentage change in AUCτ,ss in dependence of CRCL



Source: Summary of Clinical Pharmacology Studies, Page 112. Figure 3.3.4:1.

4.3.2.10 Hepatic Impairment

The influence of hepatic impairment on the PK of afatinib was evaluated by investigating the effect of the surrogate markers ALT, AST and BIL individually as well as composite measure based on an adapted classification system from the NCI Organ Dysfunction Working Group on CL/F and F1. The classification system consisted of five impairment categories (mild 1, mild 2, moderate, severe 1 and severe 2) and was chosen for further evaluation after the univariate analysis. No data were available in severely impaired patients and only 0.8 % of all observations included in the PK analysis dataset were from patients with moderate hepatic impairment. An increased exposure was determined in patients with mild hepatic impairment (both categories) which formally reached the significance level during the backward elimination procedure. However, the effect size (7 % increase in F1) could not be accurately determined (95 % CI as determined by a bootstrap analysis: -1.1 % to 16 %) and no further increase in the effect size (nor a trend) could be detected for the grade of moderate dysfunction.

4.3.2.11 Age, Race, Alcohol Consumption, and Smoking Status

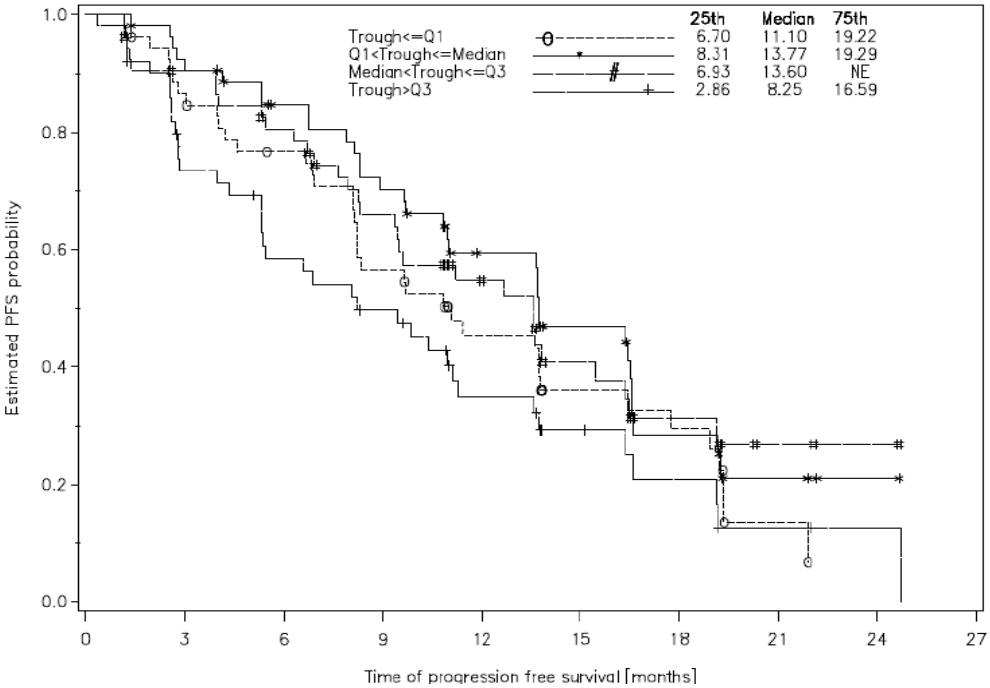
Age, smoking history, alcohol consumption and presence of liver metastases had no significant impact on the PK of afatinib. There was no difference in the PK between BC and NSCLC patients and also not in between NSCLC subpopulations. The PK of afatinib did not exhibit statistically significant differences between Asian (including the tested subpopulations, i.e. Chinese, Japanese, Korean, Southeast Asian, Taiwanese and other Asian) and White patients. Also, no obvious difference in PK for American Indian/ Alaska native or Black patients could be detected based on the limited data available in these populations (6 and 9 of the 927 patients included in PK analysis dataset, respectively).

4.3.3 Exposure-Response (ER) Analysis

4.3.3.1 Exposure-Efficacy Analysis

The exposure-efficacy analyses were only conducted for the pivotal trial, 1200.32. The trough plasma concentrations on Day 42 information was used in the analyses; if the Day 42 value was missing then the trough value taken on Day 29 was used; if the Day 29 value was missing then the trough value taken on Day 21 was used. The primary endpoint, PFS was explored in a Kaplan-Meier analysis stratified by trough plasma concentration quartiles (Figure 3.7). The relationship between quartiles of trough afatinib concentrations and week 6 tumor shrinkage (absolute and percentage change) was also explored (Table 3.4). The sponsor stated that no correlation between afatinib trough plasma concentrations and any efficacy endpoint could be detected. It is noted that patients with the highest quartile of trough afatinib level had the shortest median PFS value of 8.25 months (Figure 3.7).

Figure 3.7. ER Analysis for PFS stratified by quartiles of afatinib trough concentrations.



Source: Summary of Clinical Pharmacology Studies, page 129, Figure 3.6: 1.

Table 3.4: Decrease from baseline to week 6 in the sum of target lesion diameters (independent review) by quartiles of afatinib trough plasma concentrations.

	Quartiles **of afatinib trough plasma concentrations** (N=193)			
	Trough < = Q1	Q1 < Trough < = Median	Median < Trough < = Q3	Trough > Q3
Patients with trough/ tumour measurements [N (%)]	49 (100.0)	48 (100.0)	48 (100.0)	48 (100.0)
Maximum decrease from baseline [mm]				
Mean (SD)	-17.81 (18.48)	-12.60 (13.57)	-17.01 (14.15)	-15.05 (18.43)
Median	-13.00	-8.40	-12.80	-14.65
(Min, Max)	(-86.1, 6.2)	(-43.9, 4.3)	(-50.1, 1.0)	(-64.2, 33.5)
Maximum percentage decrease from baseline [mm]				
Mean (SD)	-26.85 (18.87)	-24.91 (22.49)	-27.45 (15.97)	-23.38 (23.15)
Median	-30.27	-22.66	-30.45	-25.15
(Min, Max)	(-68.5, 11.3)	(-82.2, 17.1)	(-58.7, 7.5)	(-75.5, 37.1)

Source: Summary of Clinical Pharmacology Studies, page 128, Table 3.6: 1.

4.3.3.2 Exposure-Safety Analysis

The safety endpoints diarrhea and skin rash/acne, were explored against the trough afatinib plasma concentration on Day 15 (Course 1), as the onset of these AEs is occurring within the first or second week of afatinib treatment. This analysis was performed in both TKI-naïve NSCLC patients (40 mg starting dose studies 1200.22 and 1200.32) and in TKI-resistant NSCLC patients (50 mg starting dose studies 1200.23 and 1200.33). In addition, pre-dose plasma

concentrations were summarized per CTCAE grade for both NSCLC patient populations (Total: 40 and 50 mg starting dose of studies 1200.22, 1200.23, 1200.32 and 1200.33). Table 5 describes the association between maximum CTCAE grades for diarrhea with trough plasma concentrations of afatinib. Median afatinib trough levels are increased with the severity of diarrhea indicating a correlation between plasma exposure to afatinib and diarrhea. Table 3.5 describes the association between maximum CTCAE grades of diarrhea with trough afatinib plasma concentrations.

Table 3.5. Association between maximum CTCAE grades of diarrhoea with trough (Cpre,ss) afatinib plasma concentrations

	Afatinib trough plasma concentrations ($C_{pre,ss}$) Day 15					
Severity of DIARRHOEA	50 mg starting dose (SAF 4)		40 mg starting dose (SAF 2)		Total	
	N	Median	N	Median	N	Median
0			1	86.4	1	86.4
CTC Grade 1	159	35.6	113	25.2	272	31.3
CTC Grade 2	152	44.1	93	31.6	245	39.6
CTC Grade 3	90	50.1	35	35.8	125	47.5

Source: Summary of Clinical Pharmacology Studies, page 130, Table 3.7: 1.

Table 3.6 describes the association between maximum CTCAE grades for rash/acne with pre-dose plasma concentrations (trough levels) of afatinib. Median afatinib trough levels are increased with the severity of rash/acne indicating a correlation between plasma exposure to afatinib and rash/acne.

Table 3.6. Association between maximum CTCAE grades for rash/acne with trough (Cpre,ss) afatinib levels

	Afatinib trough plasma concentrations ($C_{pre,ss}$) Day 15					
Severity of RASH/ACNE	50 mg starting dose (SAF 4)		40 mg starting dose (SAF 2)		Total	
	N	Median	N	Median	N	Median
CTC Grade 1	125	37.9	77	27.6	202	34.4
CTC Grade 2	164	39.9	111	26.8	275	34.2
CTC Grade 3	73	52.1	39	31.4	112	45.1

Source: Summary of Clinical Pharmacology Studies, page 131, Table 3.7: 2.

4.4 REVIEWER'S ANALYSIS

4.4.1 Introduction

The trough plasma concentration of afatinib at day 15 (CP_day15), and steady state AUC at the final dose (AUC_f) were included in the ER analysis. For CP_day15, 84/1010 (~92%) data were observed and the rest (8%) were missing data and replaced by simulated data. The first cycle steady state AUC (AUCss=40 mg*F1/posthoc individual CL) are highly correlated to CP_day15 (Figure not shown), therefore the observed trough concentrations CP_day15 were used as an exposure marker. Since all patients received the same starting dose 40 mg and the onset of AEs such as diarrhea and skin rash occurred mostly within the first cycle of afatinib treatment, the CP_day15 represents the initial exposure of afatinib and were used for the E-R analysis for safety.

4.4.2 Objectives

The objectives are to evaluate the effect of intrinsic/extrinsic factors on PK of afatinib and to evaluate the ER relationship for efficacy and safety in patients receiving afatinib in the pivotal trial 1200.32.

4.4.3 Methods and Results

4.4.3.1 Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
1200-28-32-33	poppk-data1.xpt	\\cdsesub1\evsprod\NDA201292\0000\m5\datasets\1200-28-32-33\analysis
1200-28-32-33	Poppkp.xpt	\\cdsesub1\evsprod\NDA201292\0007\m5\datasets\1200-iss\analysis
1200.32	Basco.xpt	\\cdsesub1\evsprod\NDA201292\0013\m5\datasets\1200-0032\analysis
1200.32	indsurv.xpt	\\cdsesub1\evsprod\NDA201292\0000\m5\datasets\1200-0032\analysis
1200-28-32-33	aegrp2	\\cdsesub1\evsprod\NDA201292\0000\m5\datasets\1200-iss\analysis

4.4.3.2 Software

R Version 2.14.0 and NONMEM 7.2 were used for the analyses.

4.4.3.3 Evaluation of Intrinsic/Extrinsic Factors on Exposure of Afatinib

Hepatic Impairment

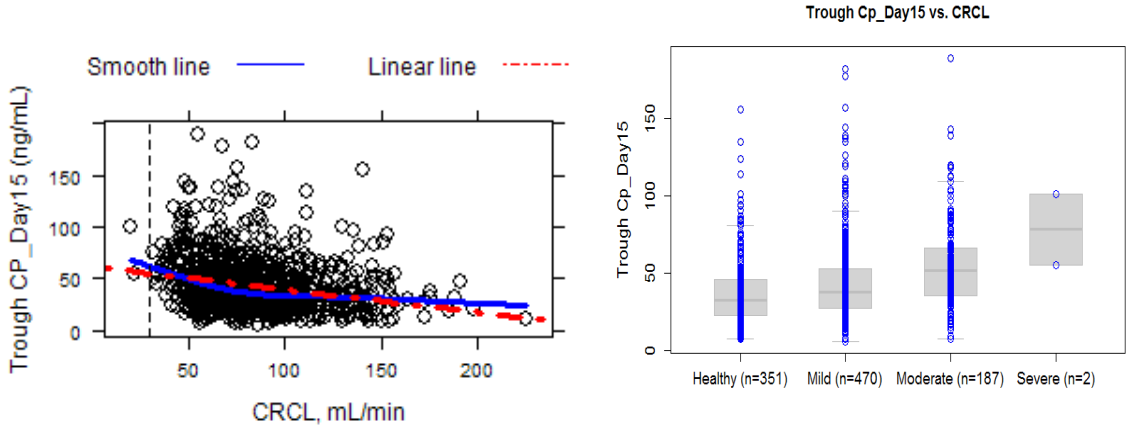
According to the sponsor's human mass balance study, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose. Hepatic impairment study indicated that mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of afatinib. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied. The influence of hepatic impairment

on the PK of afatinib was further evaluated by studying the relationship between CP_day15 and the surrogate liver markers such as billirubin, ALT, AST, lactate dehydrogenase levels (LDH) and alkaline phosphatase levels (AP) and no correlation was identified for these liver markers and the afatinib exposure.

Renal Impairment

Less than 5% of afatinib is eliminated via renal excretion. However, there is a trend that the exposure of afatinib increases as the CRCL value decreases (Figure 4.1), where the median trough afatinib levels in patients with mild and moderate renal impairment are 14.5% and 37.4% higher than that of healthy subjects. There were only 2 patients with baseline CRCL values less than 30 mL/min. However, the exposure difference due to renal function is not considered clinical relevant in patients with mild or moderate renal impairment and no dose adjustment is recommended. Afatinib treatment in patients with severe renal impairment has not been studied. Adjustments to the starting dose of afatinib are not recommended in patients with mild (CRCL 60-89 mL/min) or moderate (CRCL 30-59 mL/min) renal impairment.

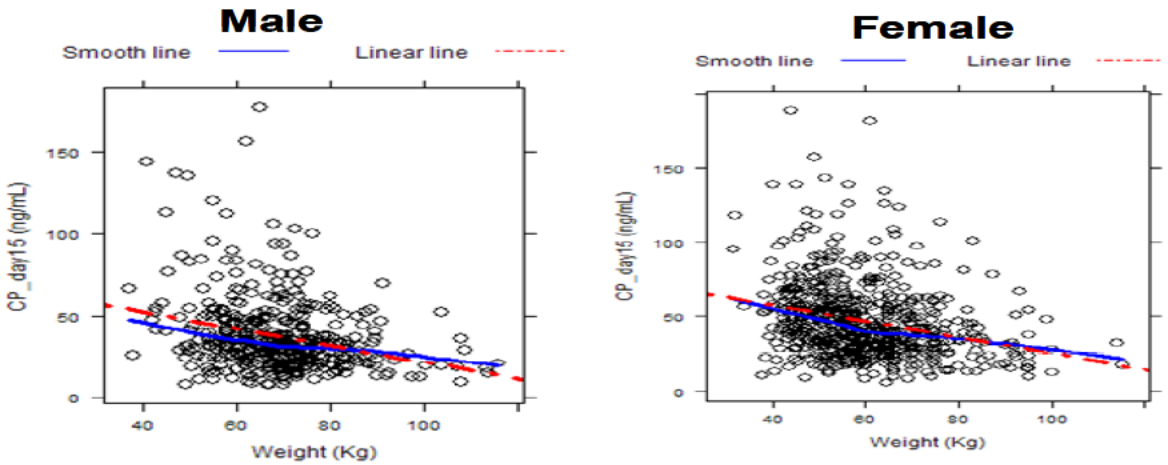
Figure 4.1. Association between trough afatinib levels and CRCL values.



Body Weight

The exposure of afatinib in the first cycle (CP_day15, ng/mL) tends to decrease as the body weight increases regardless of the gender (Figure 4.2). For every 10 kg of body weight increase, the trough level of afatinib in first cycle drops 5.7 ng/mL. However, the exposure difference due to body weight is not clinical relevant and no dose adjustment is recommended.

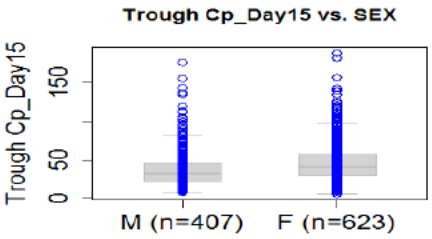
Figure 4.2. Association between trough afatinib levels and body weight



Gender

The median trough levels of afatinib (CP_day15) is approximately 20% higher in females than that of males (Figure 4.3). According to the sponsor's population PK model, the gender is a significant covariate after adjusting for the body size. However, the exposure difference due to gender is not clinical relevant and no dose adjustment is recommended. It is noted that the chances of experiencing grade 2 or higher diarrhea are significantly higher in females than that of males after adjusting for the exposure of afatinib (See reviewer's analysis 4.3.5).

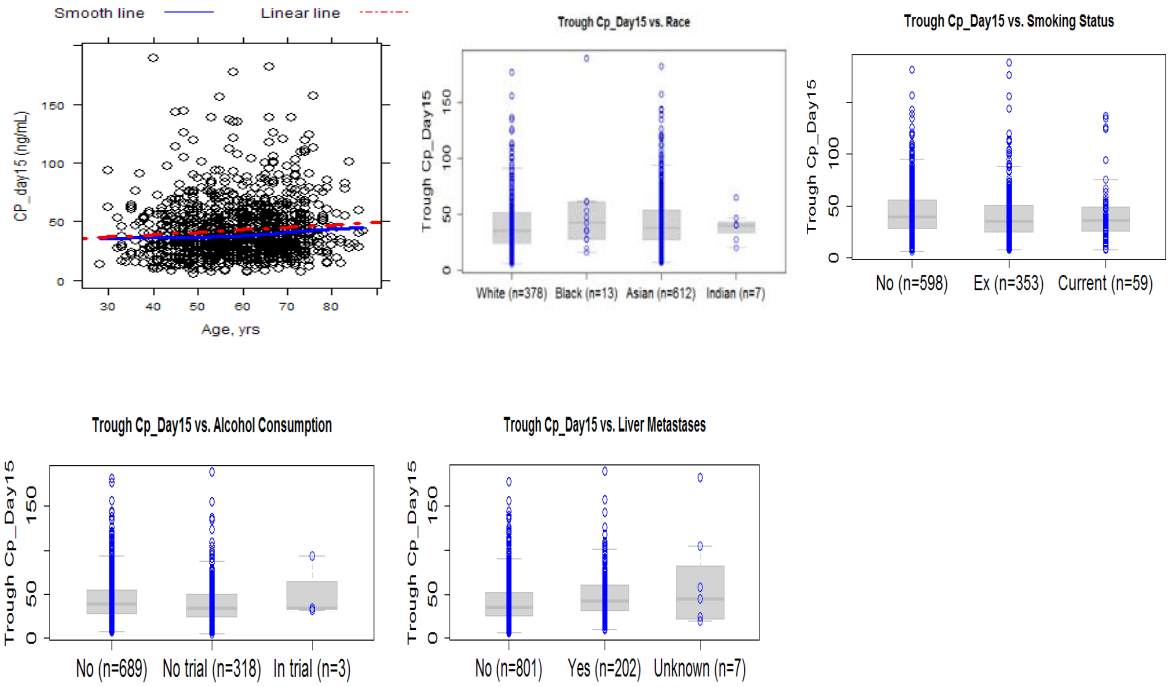
Figure 4.3. Association between trough afatinib levels and gender.



Age, Race, and Other Extrinsic/Intrinsic Factors

Age, race, smoking history, alcohol consumption, or presence of liver metastases had no effect on the exposure of afatinib (Figure 4.4).

Figure 4.4. Association between trough afatinib levels and age, race, smoking status, alcohol consumption, and liver metastases.



4.4.3.4 Exposure-Response (E-R) Relationship for Efficacy and Safety

E-R for Efficacy: In the pivotal trial (1200.32), the primary endpoint, progression-free survival (PFS) was tested as stratified by quartiles of steady state at final titration dose (AUC_f), steady state dose level and quartiles of first cycle trough plasma concentrations at day 15 (CP_day15) using Kaplan-Meier analysis. The results indicated that patients in the highest exposure quartile (Q4) have comparable PFS to the control arm and exhibit shorter PFS than those of other quartiles (4.5, Left). The covariates such as smoking status, EGFR status, baseline tumor size, age, gender, weight, race, hepatic function (billirubin levels), and ECOG performance were approximately equally distributed within each quartile of AUC_f (Figure 4.6). A similar trend was observed when the PFS was stratified by quartile of first cycle trough afatinib level (CP_day15) in the pivotal trial (Figure 4.5, Right). A Cox proportional hazard model has identified AUCf as a significant predictor of PFS with HR of 1.81 (HR 95% CI: 1.26, 2.60) in patients treated with afatinib the pivotal trial. The Cox model was adjusted by several covariates such as smoking status ($p<0.05$), EGFR status ($p<0.05$), baseline tumor size ($p<0.05$), age, gender, weight, race, hepatic function (bililubin levels), ECOG performance, renal creatinine clearance (CRCL) (Table 4.1).

Figure 4.5. E-R Relationship for PFS Stratified by Quartiles of Quartiles of Steady State AUC at Final Dose (AUC_f) (Left) and Quartiles of First Cycle Trough Levels (CP_day15) (Right) in Pivotal Trial 1200.32.

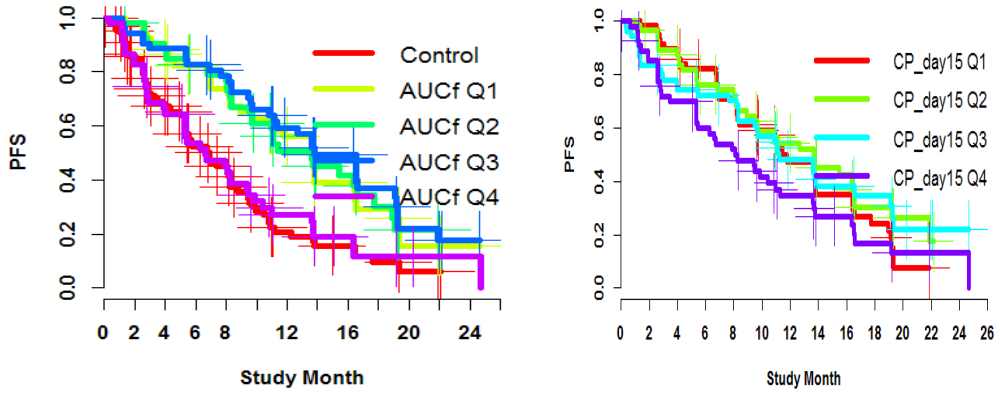
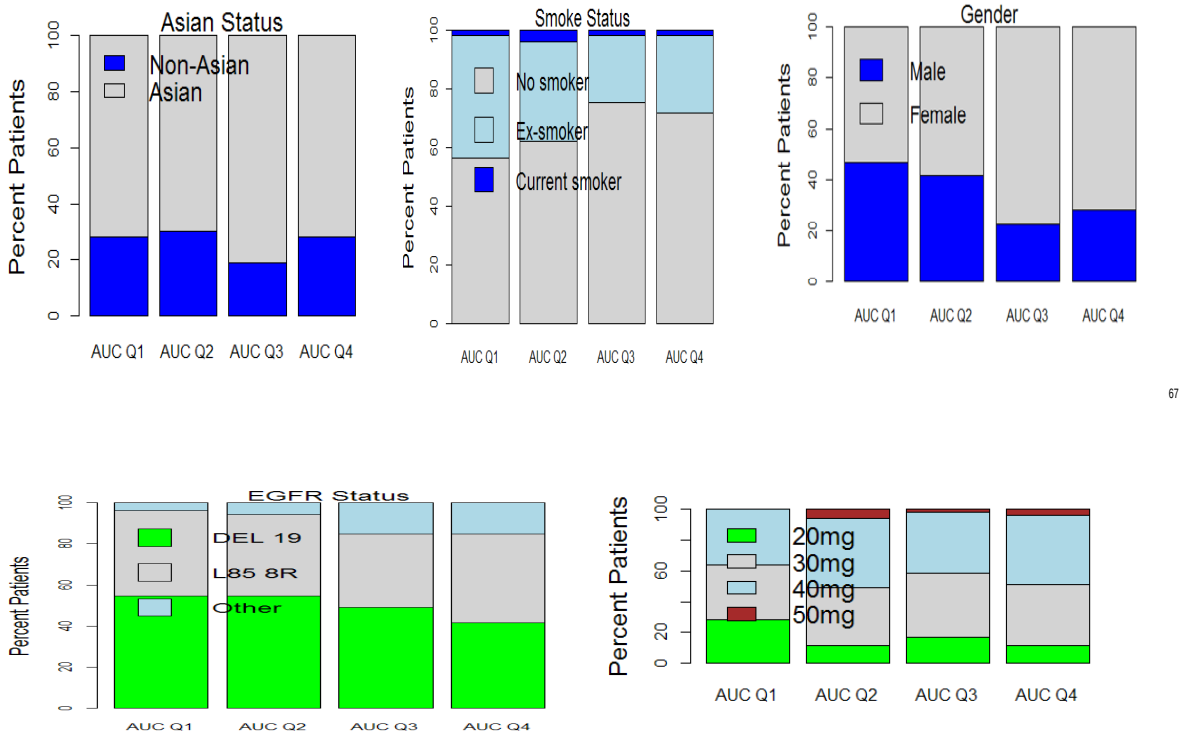


Figure 4.6: Covariate distribution with each Quartile of Steady State AUC at Final Dose (AUC_f) in Pivotal Trial 1200.32.



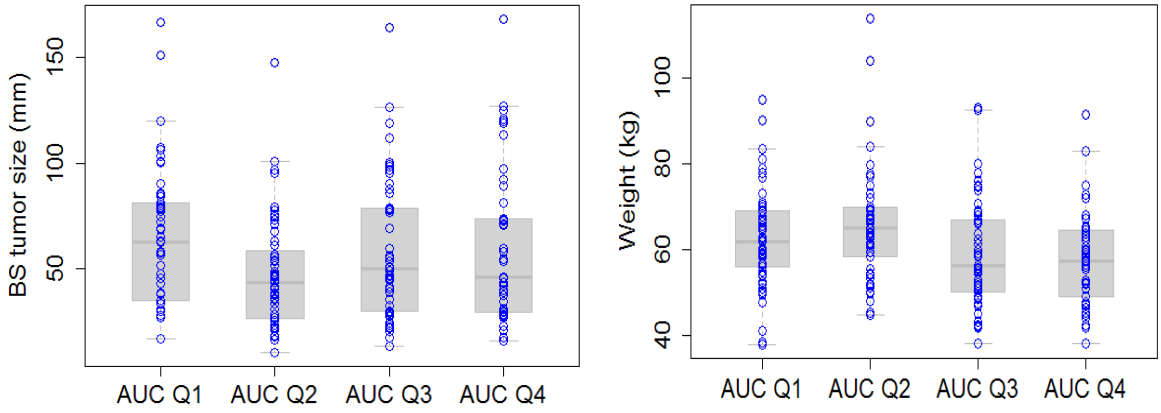
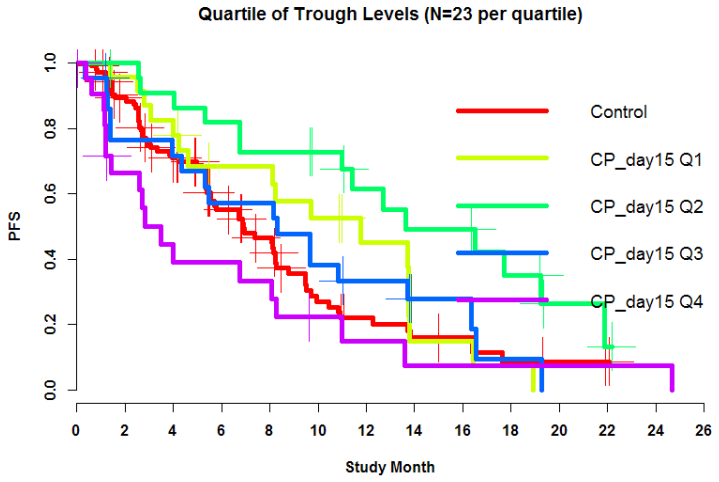


Table 4.1. Covariates identified by Cox model for predicting PFS in the afatinib arm (1200.32)

Covariate	HR	95% CI
AUCf	1.81	1.26-2.60
Smoking (Ex-smoker)	2.21	1.34-3.63
EGFR (Other)	3.00	1.67-5.41
Baseline tumor size (mm)	1.01	1.01-1.02

To reduce possible confounding effects due to dose modification or interruption, the relationship between PFS and quartile of first cycle trough concentration of afatinib on Day 15 (CP_day15) in patients (N=91) who only received 40 mg daily dose (not dose reduction or escalation) in the pivotal trial was evaluated using a Kaplan-Meier analysis. The result suggests that patients with the highest exposure do not have PFS benefit (Figure 4.7). Because the dose de-escalation is based on a patient's tolerability, the E-R analysis results indicate that patient who can not tolerate high exposure may be more sensitive to afatinib treatment. These results suggested that titration to a 50 mg dose may not provide additional benefit in terms of PFS in NSCLC patients.

Figure 4.7. E-R Relationship for PFS Stratified by Quartiles of CP_day15 in patients who only received 40 mg afatinib daily.



E-R for Safety: Patients in the afatinib treatment group also experienced a higher incidence of adverse events leading to dose reduction, with the most frequent adverse events (AEs) being diarrhea (19.7%), rash/acne (19.2%), nail effects (13.5%), and stomatitis (10.0%). In the pivotal trial 1200.32, 83.5% of patients experienced their first diarrhea episode within 14 days of beginning afatinib treatment at 40 mg starting dose. Therefore, the observed trough concentration at day15 (CP_day15) were used for E-R analyses for Common Terminology Criteria for Adverse Events (CTCAE, grade ≥3) and two most common AEs, diarrhea and skin rash/acne (grade ≥2). The results of logistic regression analyses suggest that higher exposure of afatinib increases the risk of experiencing CTCAE grade ≥3 toxicity or grade 2 or higher diarrhea event (Figure 4.8 & 4.9 Left). There was no E-R relationship between grade 2 or higher rash/acne event and afatinib exposure (Figure 4.9, Right). The E-R for safety analyses is consistent to the clinical observation that 10 of the 16 patients who were escalated to 50 mg QD dose experienced dose reduction.

Figure 4.8. Relationship between experiencing CTCAE grade >=3 toxicity and trough afatinib levels in cycle 1 (CP day15).

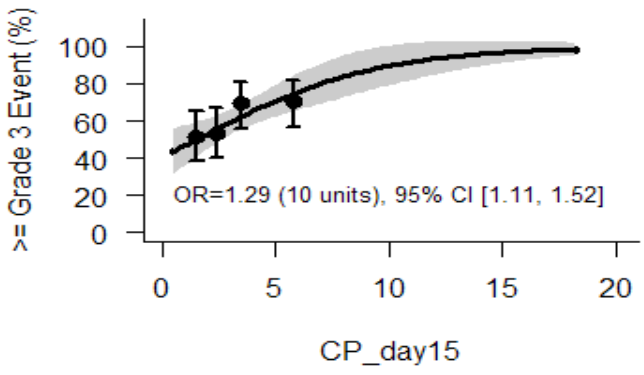
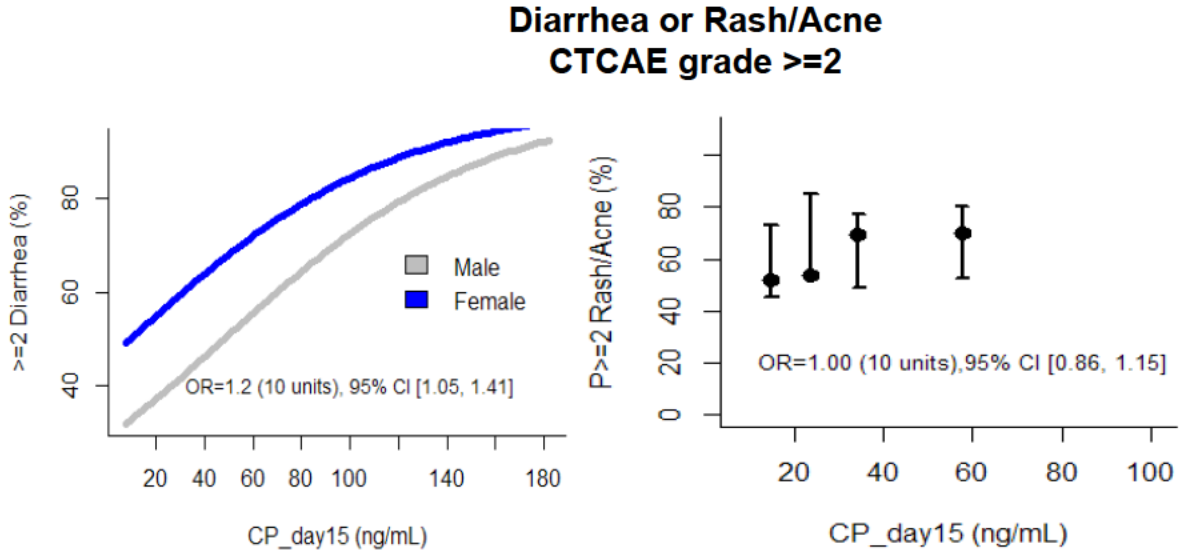


Figure 4.9. Relationship between experiencing grade >=2 diarrhea or rash/acne and trough afatinib levels in cycle 1 (CP_day15).



In summary, the E-R analyses showed that higher exposure may not provide PFS benefit but is associated with adverse events. The applicant's proposed dose de-escalation scheme based on patient's tolerability appears reasonable; however, patients in the highest quartile of steady state AUC did not show a PFS benefit, which suggests that the driving force for PFS may not be the afatinib exposure once the exposure has reached certain levels, but the patient's sensitivity to afatinib treatment or other unknown factors.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER_afatinib.R	ER Analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Afatinib NDA201292 JY

5 GENOMICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA Number	201292
Submission Date	November 14, 2012
Applicant Name	Boehringer Ingelheim
Generic Name	Afatinib
Proposed Indication	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test
Genomics Reviewer	Rosane Charlab Orbach, Ph.D.
Associate Director for Genomics	Michael Pacanowski, Pharm.D., M.P.H.

EXECUTIVE SUMMARY

Afatinib is an ErbB1 (EGFR), ErbB2 and ErbB4 tyrosine kinase inhibitor (TKI) proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. EGFR mutations are considered the strongest predictor of response to treatment with EGFR TKIs in metastatic NSCLC. The best characterized mutations associated with EGFR TKI sensitivity are the deletions in exon 19 and the L858R substitution in exon 21, which account for approximately 90% of all reported EGFR mutations. Some other EGFR mutations (e.g., exon 20 insertions, T790M) are associated with lower sensitivity to clinically achievable doses of EGFR TKIs. Patients with tumors harboring different types of EGFR mutations were enrolled in the afatinib pivotal trial 1200.32. The EGFR mutations were identified with the use of a PCR-based diagnostic test designed to detect 19 deletions in exon 19 (Del 19), L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. The purpose of this review is to assess outcomes in patients according to the EGFR mutation and determine whether the indication should be limited based on the type of EGFR mutation. Randomization was stratified by EGFR mutation status (L858R, Del 19, other). The majority of enrolled patients (89.3%) had Del 19 or L858R positive-tumors. Uncommon or "other" mutations (i.e. EGFR mutations other than Del 19 and L858R alone) were detected in only 37 patients (26 in afatinib and 11 in the chemotherapy arm) and represented a small and genetically heterogeneous group, in which a total of 10 different subtypes of EGFR mutations were identified. Patients with exon 19 deletions or exon 21 L858R showed PFS improvement. This effect was more pronounced in the subset with exon 19 deletions. Conversely, subgroup analysis in patients with "other" EGFR mutations suggested a detrimental effect on both PFS [HR 1.89; (95% CI 0.84, 4.28)] and OS [HR 3.08; (95% CI 1.04, 9.15)] for afatinib-treated patients compared with chemotherapy. The results of the pivotal trial suggest that afatinib may be detrimental to NSCLC patients with some of the uncommon mutation subtypes in the "other" category subset. However, there is limited data to adequately establish efficacy within the subset. We therefore recommend that the afatinib treatment should

be indicated to patients with EGFR exon 19 deletion or L858R substitution mutations.

5.1 BACKGROUND

Afatinib is an irreversible EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4) TKI proposed for the treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation(s) as detected by an FDA-approved test. EGFR is part of the ErbB family of cell surface receptor tyrosine kinases, which are involved in essential signaling pathways that regulate proliferation and apoptosis. In recent years, somatic EGFR mutations have been identified in a subset of NSCLC tumors. These mutations occur in EGFR exons 18 to 21, which encode part of the kinase domain, and thus have the potential to modify EGFR activity and influence sensitivity to TKIs. EGFR mutations are more common in NSCLC tumors from East Asians (30% vs.15 % in Western Europeans), and in tumors with adenocarcinoma histology, from women, and never-smokers (PMID: 21764376). In the metastatic setting, EGFR mutations are considered the strongest predictor of response to erlotinib and gefitinib (herein referred to as EGFR TKI(s)). EGFR-mutated tumors are also associated with a better prognosis than EGFR wild-type tumors (PMID: 20966921). The most well documented mutations associated with increased EGFR TKI sensitivity are exon 19 deletions and L858R in exon 21. These two hotspot mutations constitute about 90% of reported EGFR mutations in NSCLC. A multitude of other less common mutations comprises the remaining 10% to 15% of EGFR mutations (PMID: 23403632). Some of these less common mutations are associated with either increased sensitivity or resistance to EGFR TKIs. However, because of the low prevalence and large heterogeneity of this subset, the clinical significance of these less common mutations is not clear. The purpose of this review is to assess outcomes in patients according to the EGFR mutation and determine whether the indication should be limited based on the type of EGFR mutation.

5.2 SUBMISSION CONTENTS RELATED TO GENOMICS

NONCLINICAL STUDIES

The results of the following nonclinical studies were used to assess the IC50s of afatinib in different mutations.

- Study No: 07-06: Completed to evaluate afatinib (BIBW 2992) inhibitory activity on L858R and L858R/T790M-EGFR mutants.
- Study No. bircv02-13: Completed to evaluate the inhibition of EGFR mutant protein autophosphorylation by afatinib and erlotinib in cellular assays.

CLINICAL STUDIES

To support the NDA the applicant has submitted clinical data from a **pivotal (1200.32)** and 3 supportive trials (1200.22, 1200.23, and 1200.42) as indicated below.

Pivotal:

- **1200.32:** A randomized (2:1), open-label, phase III study of afatinib versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harboring an EGFR-activating mutation (LUX-Lung 3).

Supportive studies:

- 1200.22: A Phase II single-arm trial of BIBW 2992 in non-small cell lung cancer patients with EGFR activating mutations (LUX-Lung 2)
- 1200.23: Phase IIb/III randomized double-blind trial of BIBW 2992 plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients failing erlotinib or gefitinib (LUX-Lung 1). – *Failed primary endpoint*
- 1200.42: Phase III randomized trial of afatinib plus weekly paclitaxel versus Investigator's choice of chemotherapy following afatinib monotherapy in non-small cell lung cancer patients failing previous erlotinib or gefitinib treatment (LUX-Lung 5) – *Stopped early at the Data and Safety Monitoring Board (DSMB) recommendation because of toxicity*

This review will consider only the results of the pivotal trial **1200.32** (LUX-Lung 3) supporting an indication for first-line treatment (refer to Clinical review for details). The 1200.32 trial evaluated afatinib 40 mg (n=230) to pemetrexed/cisplatin chemotherapy (n=115) in EGFR-mutation positive patients. Patients were enrolled in North and South America, Asia, and Europe.

The presence of EGFR mutations was determined by central testing of tumor biopsy samples using a quantitative real-time polymerase chain reaction (PCR) protocol with fluorescence detection (TheraScreen: EGFR29 Mutation Kit, [DxS Product Code EG-51; Qiagen Manchester Ltd, Manchester, UK]). The test was designed to detect 29 EGFR mutations against a background of wild-type genomic DNA, i.e. 19 deletions in exon 19 (Del 19), L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. In support of the US registration, experiments were submitted to demonstrate equivalence between the clinical trial assay and a newly developed TheraScreen EGFR RGQ PCR Kit (Qiagen Manchester Ltd, Manchester, UK), for which US Pre-market Approval (PMA) is sought. For details regarding the companion diagnostic submitted in parallel with this NDA, refer to the CDRH review of the assay.

Randomization was stratified by EGFR mutation status (L858R, Del 19, other) and race (Asian, non-Asian). If both L858R and a deletion in exon 19 were detected in the same sample, the patient was to be allocated to the "L858R" stratification category (no cases with this genotype were detected though). In any other case of double mutations, the patient was allocated to the "other" stratification category. Results were reported as "Negative" if no mutations were detected (patient recorded as screen failure). For inconclusive EGFR mutation tests, the investigator was allowed to send further tumor samples.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by central independent review according to RECIST version 1.1. The key secondary endpoints were objective response (complete response [CR], or partial response [PR]), disease control (objective

response or stable disease [SD]) and overall survival (OS). The data cut-off for the primary analysis of trial 1200.32 was performed on 9 February 2012.

5.3 KEY QUESTIONS AND SUMMARY OF FINDINGS

5.3.1 Should the indication be limited based on the type of EGFR mutation?

Yes. Limited data are available to adequately establish efficacy of afatinib in patients with EGFR mutations categorized (b) (4) *We therefore recommend that the proposed indication be revised to indicate afatinib for patients whose tumors have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations.*

PUBLISHED CLINICAL AND NONCLINICAL LITERATURE:

The characteristics of mutations relevant to this review are summarized below. Of note, the frequencies reported in this section may not reflect geographic and ethnic variations related to EGFR-mutated NSCLC, and/or differences in assays used to detect mutations in various studies. Furthermore, EGFR mutations can occur alone or in combination increasing the degree of complexity of tumor genotypes and potentially leading to differential sensitivity to EGFR TKIs (PMID: 20966921; 21531810). The correlation between tumor genotypes and sensitivity to EGFR TKIs is not well established for the most part for less prevalent mutations.

***Table 1**: Location and frequency of EGFR mutations of interest*

Mutation type	Location within EGFR tyrosine kinase domain	*Estimated frequency in EGFR-mutated NSCLC**	*Sensitivity to erlotinib/gefitinib EGFR TKIs **
Exon 19 deletions	*Exon 19*	*48%*	*increased*
L858R	*Exon 21*	*43%*	*increased*
T790M	*Exon 20*	*<5% naive/ 50% resistant*	*decreased*
Exon 20 insertions	*Exon 20*	*4%*	*decreased*
G719X	*Exon 18*	*3%*	*increased*
S768I	*Exon 20*	*2%*	*mixed-response*
L861Q	*Exon 21*	*2%*	*increased*

**http://www.mycancergenome.org/content/disease/lung-cancer/egfr/1; PMID: 15886310; 23485129*

Classic or "common" EGFR mutations:

- **Exon 19 deletions:** Several different in-frame exon 19 deletion mutations have been identified, and the most common ones all lead to amino acid substitutions of residue L747 (PMID: 22317760). Although known as EGFR TKI sensitizing mutations, it has been suggested that a subset of exon 19 deletions is less likely to respond to EGFR TKI treatment (PMID: 23403632).

- **L858R substitution:** Exon 19 deletions and L858R are the best characterized mutations associated to EGFR TKI sensitivity, however NSCLC patients with exon 19 deletion

positive tumors are more likely to respond to EGFR TKIs that those with exon 21 L858R (PMID:23384674).

Uncommon or "other" mutations

- **G719X (G719A, G719C, G719 S) substitutions:** Associated with some sensitivity to erlotinib and gefitinib EGFR TKIs (PMID: 21531810). In addition, three of 4 patients with EGFR G719X mutation had partial responses to the irreversible pan-ErbB TKI neratinib in a phase II trial in advanced NSCLC and the fourth had stable disease lasting 40 weeks. The EGFR G719X mutations were identified in combination with a second substitution mutation of unknown clinical significance. Of note, neratinib had low activity in most patients including those with T790M or exon 20 insertion mutations as referred below (PMID: 20479403).

- **S768I substitution:** This mutation is reported as mixed-response. It appears that differential sensitivity is influenced by mutations that coexist with S7681.

- **L861Q substitution:** Associated with some sensitivity to EGFR TKIs (PMID: 21531810).

- **Exon 20 insertions:** Account for 4% to 9% of EGFR mutations, and are associated with primary resistance to EGFR TKIs. Exon 20 insertions can rarely be found in combination with other EGFR mutations (PMID: 22722783). Several exon 20 insertions have been identified making this a highly heterogeneous EGFR mutation subgroup. Preclinical and clinical data suggest that the most prevalent EGFR exon 20 insertion proteins are resistant to clinically achievable doses of reversible (e.g, erlotinib) and irreversible (e.g., afatinib) EGFR TKIs. However, it has been suggested that response of these insertion mutations to EGFR TKI differs based on insertion location. In a phase II trial of neratinib, no responses were observed for the three patients with exon 20-mutated NSCLC (S768 D770dupSVD, H773 V774dupHV, delN771insGF). In a phase I trial of dacomitinib (also a panErbB inhibitor), 1(out of six) patient with EGFR exon 20 insertions (with delA770insGY) had a response. In a phase II trial of afatinib, one patient (out of 11 enrolled) had a partial response, but progression-free survival for these patients was short (PMID: 23485129; 20479403; 21764376).

- **T790M:** Associated with resistance to EGFR TKIs. The T790M mutation is detected in <5% of untreated EGFR mutated tumors using conventional methods, and is frequently identified in conjunction with an EGFR TKI sensitizing mutation. It can be present as a germline or somatic mutation. The T790M mutation is also detected in more than 50% of EGFR-mutated NSCLC with acquired resistance to EGFR TKIs (as a "second-site resistance mutation"). The coexistence of T790M with a second mutation may confer a "mixed response" pattern. Patients with known T790M did not respond to neratinib (PMID: 20479403). However partial responses to gefitinib were reported in patients positive for a T790M coexisting with exon 19 deletion mutation prior to TKI therapy (PMID: 21670455; Supplementary Appendix). Of note, responses were seen also in the chemotherapy arm for patients with T790M coexisting with a sensitizing mutation. Some

of the T790M tumor genotypes however were not confirmed when different assays were used.

NONCLINICAL STUDIES SUBMITTED BY THE APPLICANT

Nonclinical results reported by the applicant suggest some EGFR mutations such as T790M and exon 20 insertions (associated with therapeutic resistance to EGFR TKIs) are less sensitive to afatinib when compared to the EGFR TKI sensitizing exon 19 deletion or L858R mutations. Please refer to the Pharmacology/Toxicology review for details on these studies; the following synopses are based on results provided by the applicant.

Study No. 07-06:

- In molecular kinase assays afatinib inhibited the kinase activity of the wild-type EGFR, the L858R mutant and the L858R/T790M double mutant with IC50 values of 0.99 nM, 0.43 nM and 10 nM, respectively (erlotinib 1520 nM for L858R/T790M double mutant).

- In EGF-induced EGFR phosphorylation assays using NSCLC cell lines with different EGFR mutant isoforms, afatinib inhibited (a) H1666 cells (wild-type EGFR) with an IC50 of 7 nM, (b) H3255 cells (L858R mutant) with an IC50 of 6 nM and (c) NCI-H1975 cells (L858R/T790 double mutant) with an IC50 of 93 nM (erlotinib > 4000 nM).

- In anchorage-independent proliferation assays also using NSCLC cell lines, afatinib was inhibitory to (a) H1666 cells (wild-type EGFR) with an EC50 of 60 nM, (b) H3255 cells (L858R mutant) with an EC50 of 0.7 nM, and (c) NCI-H1975 cells (L858R/T790 double mutant) with an EC50 of 99 nM (erlotinib> 4000 nM).

Study No. bircv02-13

- Afatinib inhibited autophosphorylation of EGFR mutant (expressed in a cellular context) L861Q at a concentration of 1nM, of G719S at ≥ 10 nM, of T790M at ≥ 100 nM and of exon 20 insertions (WASVins770, D770_N771insNPG, P772_H773insV, WHins774) at concentrations ranging from ≥ 100 nM to ≥ 1000 nM.

Comment: It is possible that clinically achievable doses of afatinib are lower than required to inhibit tumors positive for T790M or exon 20 insertion mutations based on observed PK data and the potential for dose reductions consequent to toxicity.

CLINICAL STUDIES SUBMITTED BY THE APPLICANT

Pivotal trial 1200.32

- EGFR Mutation Distribution in trial 1200.32:

The majority of patients (308 [89.3%]) had EGFR Del 19 or L858R mutation positive tumors.

Uncommon, or "other", mutations (i.e. EGFR mutations other than Del 19 or L858R alone) were detected in only 37 [10.7%] patients, 26 on the afatinib arm and 11 on the chemotherapy arm (Table 2).

Table 2: EGFR mutation status at baseline in trial 1200.32 / RS

	Afatinib 40 mg		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Patients	230	(100.0)	115	(100.0)	345	(100.0)
EGFR mutation category						
L858R	91	(39.6)	47	(40.9)	138	(40.0)
Del 19 only	113	(49.1)	57	(49.6)	170	(49.3)
Other	26	(11.3)	11	(9.6)	37	(10.7)

Data as recorded on the CRF

Source: Applicant's table 3.1.2.1: 3 - Summary of Clinical Efficacy; RS-randomized set

The EGFR mutation category "other" corresponded to a small and heterogeneous subset encompassing a total of 10 different genetic subtypes of uncommon EGFR mutations that were not balanced between treatment arms, representing a large degree of complexity (Table 3). Out of ten genotypes, nine were represented in the afatinib arm and five in the chemotherapy arm. Eleven patients (out of 26) in the afatinib arm had a T790M mutation at baseline, nine coexisting with other mutations; only two patients had T790M in the chemotherapy arm (coexisting with L858R). Exon 20 insertions were the second most common EGFR mutation type. The remaining mutations were represented by 0-3 patients per treatment arm.

Table 3: Patients with uncommon EGFR mutations in trial 1200.32 / RS

	EGFR mutation	Afatinib 40 mg N (%)		Chemotherapy N (%)		Total N (%)	
Patients		230	(100.0)	115	(100.0)	345	(100.0)
T790M	T790M only	2	(0.9)	0	(0.0)	2	(0.6)
	Del 19 + T790M	3	(1.3)	0	(0.0)	3	(0.9)
	L858R + T790M	5	(2.2)	2	(1.7)	7	(2.0)
	G719S, G719A, and G719C + T790M	1	(0.4)	0	(0.0)	1	(0.3)
Exon 20 insertions	Exon 20 insertion only	6	(2.6)	3	(2.6)	9	(2.6)
S768I	S768I only	1	(0.4)	0	(0.0)	1	(0.3)
	L858R + S768I	2	(0.9)	0	(0.0)	2	(0.6)
G719X[1]	G719S, G719A, and G719C only	3	(1.3)	1	(0.9)	4	(1.2)
	G719S, G719A, and G719C + S768I	0	(0.0)	2	(1.7)	2	(0.6)
L861Q	L861Q only	3	(1.3)	3	(2.6)	6	(1.7)

Source: Applicant's Table 3.1.2.1: 4: Summary of Clinical Efficacy; RS-randomized set

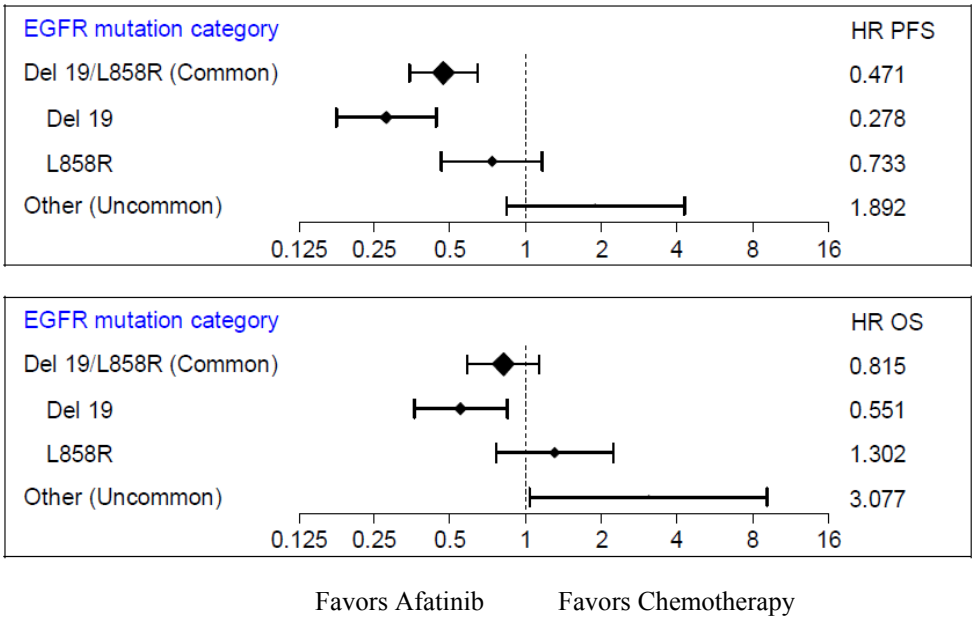
Comment: Of note, the EGFR genotype is limited by the type of mutations the assay is designed to detect. For example patients classified as having T790M only may actually have a coexisting EGFR mutation not interrogated by the trial assay. Also, it is not clear whether the T790M mutations detected in the trial correspond to germline or somatic mutations.

- PFS , OS

The median PFS was 11.14 months for the afatinib arm and 6.90 months for the chemotherapy arm (HR 0.577; 95% CI 0.425, 0.784; p = 0.0004), as reported by the applicant. Within the pre-specified "common" EGFR mutation subgroup (Del 19 + L858R), median PFS was 13.60 months for the afatinib arm and 6.90 months for the chemotherapy arm (HR 0.471; 95% CI 0.344, 0.646; p<0.0001). The effect was more pronounced in the Del 19 subset (median PFS 13.70 months vs. 5.55 months; HR 0.278; 95% CI 0.176, 0.441; p <0.0001; Figure 1).

As of January 21, 2013, deaths had been reported for approximately half of the randomized patients. Median OS was estimated to be approximately 28 months for both treatments (HR 0.907; 95% CI 0.660, 1.246; p=0.5457). Within the pre-specified "common" EGFR mutation subgroup (Del 19 + L858R), median OS was 30.26 months for afatinib and 26.22 months for chemotherapy (HR=0.815; 95% CI 0.585, 1.135; p=0.2244). As for PFS, the benefit seems to be driven by the Del 19 deletion subgroup (Figure 1). Conversely, subgroup analysis in patients with "other" EGFR mutations suggested a detrimental effect on both PFS [HR 1.89; (95% CI 0.84, 4.28)] and OS [HR 3.08; (95% CI 1.04, 9.15)] for afatinib-treated patients compared with chemotherapy (Figure 1).

Figure 1: Forest plot of PFS based on central independent review (top) and OS (bottom) for EGFR mutation category / RS



Source: Applicant's figure, modified from figures 3.3.1: 1 (Summary of Clinical Efficacy) and 15.2.3.3: 17 (overall survival data; January 2013 update). Number of patients: Del 19/L858R (common) n=308, Del 19 n=170, L858R n=138, Other (Uncommon) n= 37; RS-randomized set

- Tumor responses:

As reported by the applicant, the percentage of afatinib-treated patients with an objective response was 56.1% vs. 22.6% in the chemotherapy arm; 1 afatinib-treated patient had a

complete response. The percentage of afatinib-treated patients with "common" mutations with an objective response was 60.8% vs. 22.1% in the chemotherapy arm. Objective response rates were lower for afatinib-treated patients in the "other category" compared to chemotherapy-treated patients with "other" mutations, as well as afatinib-treated patients with Del 19 or L858R. Details are depicted in table 4.

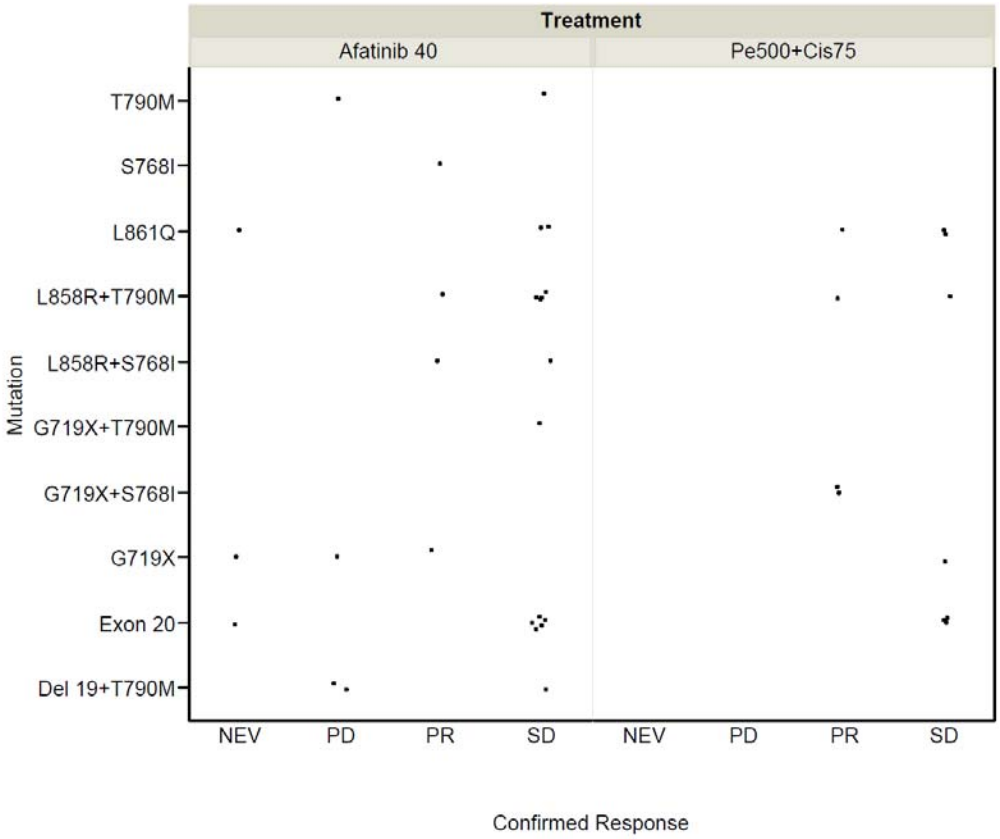
Table 4: Objective response rates by EGFR mutation category

Mutation category	Objective Response N (%)	
	Afatinib	Chemotherapy
Common EGFR mutations	124 (60.8)	23 (22.1)
Del 19	73 (64.6)	13 (22.8)
L858R	51 (56.0)	10 (21.3)
Other EGFR mutations	**5 (19.2)**	**3 (27.3)**

(Based on central independent review / randomized set).
Source: Applicant's Table 11.4.1.2.1: 4-1200.32 report.

Of the 37 patients with "other" mutations (Tables 2 and 3), 26 received afatinib and 3/26 were not evaluable. For the 11 afatinib-treated patients with a T790M (alone or coexisting with another mutation), the best overall response was PR in 1 patient with a coexisting L858R, SD in 7 patients, and PD in 3 patients (chemotherapy: 1 patient with PR, 1 patient with SD). For all evaluable patients with exon 20 insertions in both arms, the best overall response was SD. Four afatinib-treated patients had confirmed PRs from the following EGFR mutation subtypes (one of each): S768I, G719X, L858R/S768I and L858R/T790M. Four patients in the chemotherapy also attained confirmed PRs (2 G719X/S768I, 1 L658R/T790M and 1 L861Q (Figure 2).

Figure 2: Individual patient responses* to afatinib or chemotherapy in the category "other" (investigator assessments)



*Confirmed response (*source data: Applicant's listing 96.1*); Response = Complete response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Non-evaluable (NEV); Exon 20 = exon 20 insertions

5.4 SUMMARY AND CONCLUSIONS

Afatinib is a kinase inhibitor proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test.

Randomization was stratified by EGFR mutation status (L858R, Del 19, other) in the pivotal trial 1200.32. Afatinib showed PFS improvement in the overall population, however different EGFR mutations appear to have demonstrated different sensitivities to afatinib inhibition in clinical trial 1200.32. Tumors positive for exon 19 deletion mutations appear more likely to respond to afatinib than those with L858R mutations. Similar results were reported in the published literature for reversible EGFR TKIs.

The applicant pooled several different mutations associated to either increased sensitivity or therapeutic resistance to EGFR TKIs in the category "other". Exploratory analyses showed lower objective response rates and a worse estimate of PFS and OS for afatinib compared with chemotherapy for the uncommon mutation subset.

Despite a possible detrimental effect of afatinib in the "other" EGFR mutation category, some of

the individual responses from afatinib-treated patients with “other” EGFR mutations suggested evidence for activity of afatinib, in a manner that was generally consistent with in vitro assessments. However, because of the small sample size, numeric imbalances and biological heterogeneity, this subset is not adequately powered to draw firm conclusions.

Various other emerging uncommon EGFR mutations (PMID: 23485129) were not evaluated in this NDA.

5.5 RECOMMENDATIONS

The early studies in EGFR-mutated NSCLC were dichotomized in wild-type and mutant for simplicity. It is now clear that many tumor genotypes occur and may confer differential sensitivity to treatment (PMID: 23485129). The high variability identified in these mutations may translate into distinct functional consequences. The mechanisms that underlie differential responses to EGFR tyrosine kinase inhibitors need to be better elucidated before uncommon mutations can be categorized into “responsive” or “resistant”. The therapeutic decision-making in EGFR-mutated NSCLC patients seems to be contingent on the type of mutation present and, therefore, strategies to understand these mutations in the clinical setting are needed. Specific labeling recommendations are provided below.

5.5.1 Labeling

Afatinib is a kinase inhibitor indicated for the first line treatment of patients with 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.**

Furthermore, we recommend that the labeling (1) include in Section 14 outcomes for the subgroup of patients with “other”, less common mutations to reflect the potential for poorer PFS compared to chemotherapy, and also the potential for anti-tumor activity in some of the genotypes, and (2) include in Section 12.1 the sensitivity of different mutations to afatinib inhibition in nonclinical models.

5.5.2 Post-marketing studies

None.

6 NDA FILLING FORM

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	201,292/0	Brand Name	Thundrion
OCP Division (I, II, III, IV, V)	V	Generic Name	Afatinib
Medical Division	DDOP2	Drug Class	Small Molecular Drug
OCP Reviewer	Runyan Jin, Ph.D. Jun Yang, Ph.D.	Indication(s)	Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s)
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Oral tablets (20, 30,40, (b) (4)
Pharmacometrics Reviewer	Jun Yang, Ph.D.	Dosing Regimen	40 mg Orally Daily
Date of Submission	11/14/12	Route of Administration	Oral
Estimated Due Date of OCP Review	4/22/13	Sponsor	Boehringer Ingelheim
Medical Division Due Date	7/5/13	Priority Classification	Priority
PDUFA Due Date	7/15/13		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology	x			
Mass balance:	x	1		
Isozyme characterization:				
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -	x	17		
Healthy Volunteers-				
single dose:	x	6		
multiple dose:	x	6		
Patients-				
single dose:				
multiple dose:	x	14		
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	3		
In-vitro:	x	10		
Subpopulation studies -				

ethnicity:	x	1		
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	x	1		
PD -				
Phase 2:	x	10		
Phase 3:	x	2		
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	x	2		
Population Analyses -				
Data rich:				
Data sparse:	x	4		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		31		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			No absolute BA. Relative BA to solution determined
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	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			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	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			ER for efficacy was conducted. Further analysis may be evaluated
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		Waiver requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			According to sponsor, no ER relationship for efficacy and safety
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

Reviewer's Comments

- Relative BA to oral solution instead of absolution BA has been determined.
-Meal reduces exposure by 26%
-Slightly more than proportional increase in exposure with dose increases
-PK trial for hepatic impairment (mild and moderate) was conducted; no renal impairment study was conducted as the liver mainly contributes to the elimination of afatinib.
-No CYP-enzymes were involved in the metabolism of afatinib.
-Substrates and inhibitors of BCRP in vitro, in vivo study not conducted.
-QT-IRT consult has been requested.

-Based on the applicant analyses, no ER relationship has been identified between steady state trough concentration and efficacy endpoint (tumor size and PFS).
-PK data were obtained from 17 Phase I, 2 Phase I/II, 10 Phase II, and 2 Phase III trials. Four popPK studies were submitted. A popPK analysis containing all PK data was not conducted; however, this model is sufficient for us to assess the ER relationship. The F in HNSCC pts (phase II 1200.28) is 35% higher though with similar PK parameters to those of BC and NSCLC pts.
-Further ER for efficacy and safety may be evaluated during the review.
-All datasets used for exposure-response analyses will be requested.

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.

Reviewing Clinical Pharmacologist	Date
Team Leader/Supervisor	Date

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

/s/

RUNYAN JIN
04/22/2013

JUN YANG
04/22/2013

ROSANE CHARLAB ORBACH
04/22/2013

NITIN MEHROTRA
04/22/2013
Kevin Krudys was the secondary Pharmacometrics reviewer for Afatinib NDA

NAM ATIQUR RAHMAN
04/22/2013

HONG ZHAO
04/22/2013
I concur.

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 201292	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	November 15, 2012		
Division:	Division of Oncology Products 2	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	November 19, 2012
Generic Name:	(BIBW 2992 MA2) Afatinib dimaleate Tablets	**Date of Review:**	April 22, 2013
Indication:	Treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor inhibitor (EGFR) mutation(s)	**Type of Submission:** 505(b)(1) Priority Original New Drug Application	
Dosage form/ strengths	Tablet/ 20, 30, 40 (b) (4) (b) (4) tablet		
Route of Administration	Oral		

SUMMARY

Submission: This 505(b)(1) New Drug Application is for an immediate release film coated afatinib dimaleate tablet indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor inhibitor (EGFR) mutation(s).

Review: The Biopharmaceutics review for this NDA is being focused on the evaluation and acceptability of: 1) the proposed dissolution methodology, 2) dissolution acceptance criterion, and 3) the comparative dissolution profiles between the final formulation (FF) drug product used in the pivotal trials and the proposed commercial FF drug product.

RECOMMENDATION:

The dissolution method and acceptance criteria as summarized below are acceptable.

- Dissolution method:
  USP Apparatus II (paddle)
  Temperature: 37 °C
  Rotation speed: 75 rpm
  Medium: 900 mL McIlvaine buffer pH 4.0

- Dissolution acceptance criterion:
  Q= (b) (4) at 15 minutes

- Comparative dissolution profiles:
  The Applicant has provided comparative dissolution profiles to show that the final formulation (FF) drug product used in the Phase III clinical trials has a similar dissolution profile as the commercial FF drug product.

From the Biopharmaceutics perspective, NDA 201292 for afatinib dimaleate Tablets (20, 30, 40 and (b) (4) /tablet) is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

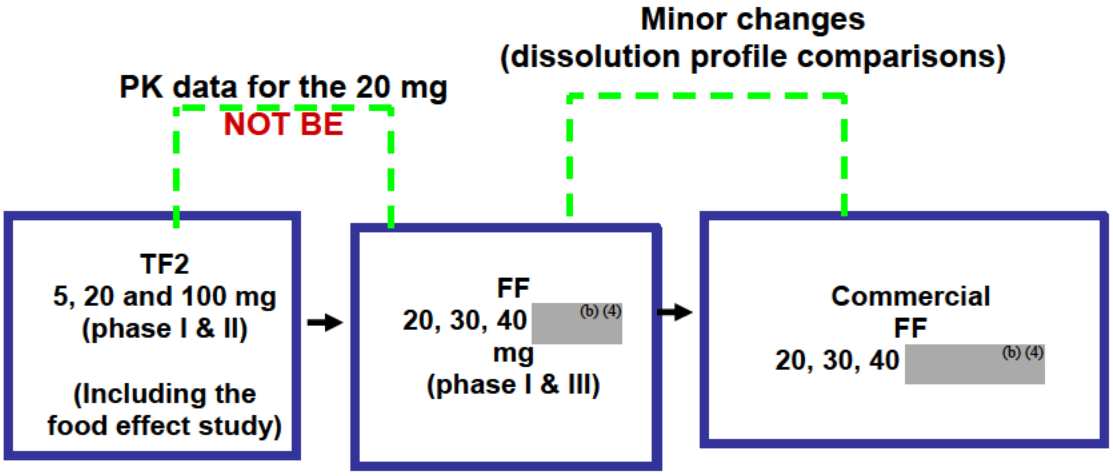
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

This 505(b)(1) New Drug Application is for an immediate release film coated afatinib dimaleate tablet indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor inhibitor (EGFR) mutation(s). Afatinib belongs to the pharmacotherapeutic group of "other antineoplastic agents – protein kinase inhibitors". Afatinib is a potent and selective, irreversible blocker of the ErbB family of receptor tyrosine kinases. Afatinib covalently binds to and irreversibly blocks signaling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER 2 (ErbB2), ErbB3 and ErbB4.

Afitinib is highly soluble in aqueous media throughout the pH 1 to 6 range (BCS class 1 or 3). [redacted] (b) (4) The CMC Reviewer agrees with the Applicant that the final drug product specifications do not need to contain a test for polymorphism. During the drug product development, a formulation change from the test formulation (TF2) to the final formulation (FF) occurred, followed by a minor change to FF [redacted] (b) (4), resulting in the commercial FF. The following schematic overview depicts the tablet formulation development:



The formulation of the 20 mg TF2 tablets differs [redacted] (b) (4) from the 20 mg FF tablets.

REVIEW:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of
1) the proposed dissolution methodology,
2) dissolution acceptance criterion, and
3) the comparative dissolution profiles between the FF drug product used in the pivotal Phase III trials and the proposed commercial FF drug product.

BIOPHARMACEUTICS INFORMATION:

Composition of the proposed tablets:

Dosage strength		20 mg	30 mg	40 mg	(b) (4)	
Part of tablet	Ingredient	[mg/coated tablet]				Function
Core	BIBW 2992 MA2 (BIBW 2992 free base)	29.5600 (20.0000)	44.3400 (30.0000)	59.1200 (40.0000)		Active
	Lactose monohydrate	(b) (4)				(b) (4)
	Microcrystalline cellulose					
	Colloidal silicon dioxide					
	Crospovidone					
	Magnesium stearate					
Film-coat	Hypromellose (b) (4)					
	Polyethylene glycol (b) (4)					
	Titanium dioxide					
	Talc					
	FD&C Blue No. 2 (b) (4) (b) (4)					
	Polysorbate 80					
	(b) (4)					
	Total mass	**185.00**	**277.00**	**368.00**		

(b) (4)

The tablet cores for all strengths are manufactured from a common blend. (b) (4) All (b) (4) dosage strengths consistently dissolved more than (b) (4) after 15 minutes in dissolution media pH 1.0, pH 4.0, and pH 6.8.

DISSOLUTION METHOD:

The proposed dissolution method is:
USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 75 rpm
Medium: 900 mL McIlvaine buffer pH 4.0
Sampling time: 15 minutes
Sample analysis: HPLC-UV

The dissolution method development report describes the selection of the dissolution test conditions as follows:

Selection of apparatus and rotation speed:

The paddle apparatus (Apparatus 2; USP) which is generally preferred for dissolution testing of fast disintegrating and rapidly dissolving immediate release tablet formulations was selected. Paddle rotation speeds of 50 rpm and 75 rpm were used to generate the following dissolution profiles (test conditions: paddle 75 and 50 rpm, 900mL, pH 4.0):

(b) (4)

FF = final formulation
TF2 = test formulation 2

Additional dissolution experiments showed that coning occurs at 50 rpm. By increasing the paddle speed to 75 rpm, coning could be avoided. Therefore, a rotation speed of 75 rpm was selected.

Selection of dissolution medium:

The properties impacting the selection of the dissolution medium are pH-dependency of drug substance solubility and solution state stability as a function of pH. The tablet dissolution profiles at various pH were evaluated in order to select the appropriate medium that provides suitable discriminatory power for the dissolution test. The high solubility of afatinib dimaleate of ≥ 0.3 mg/mL in the pH range from 1 to 7.5 ensures sink conditions for all developed dosage strengths and is therefore not a rate limiting factor for the dissolution of the drug product.

Afatinib dimaleate drug substance solubility at various pH:

(b) (4)

The following dissolution profiles in the pH range of 1-6.8 were generated to select the most suitable dissolution medium:

(b) (4)

For all (b) (4) dosage strengths (20, 30, 40, (b) (4) /tablet) and different formulations (TF2 and FF), the dissolved amount of afatinib dimaleate was not less than (b) (4) within 15 minutes in all three dissolution media. These results demonstrate that afatinib dimaleate film-coated tablets show rapid dissolution throughout the physiological pH range.

A pH 6.8 dissolution medium was not selected because decomposition of the drug substance is observed at pH 6.8. Instead, McIlvaine buffer pH 4.0 was selected to cover the upper value of the normal acidic pH range in the stomach where the dissolution of this rapidly dissolving formulation probably takes place *in vivo*.

Discriminatory power of the method:

The discriminatory power of the proposed dissolution method depends on the method's ability to detect differences and changes in the drug product's composition and/or in its manufacturing process. The following variables that might affect tablet dissolution were selected to investigate the discriminatory power of the proposed method: different quantities of excipients, different compression forces/ tablet hardness.

(b) (4)

Dissolution method validation:

The analytical method used for the dissolution test of the 20, 30, 40, (b) (4) tablets has been validated in accordance with ICH Q2(R1) with respect to specificity, linearity, accuracy, repeatability, intermediate precision, and robustness. The results demonstrate that the analytical procedures are suitable for the intended purpose.

Reviewer's Overall Assessment of the dissolution method and the dissolution method validation: Acceptable

The Applicant has justified the selected dissolution apparatus, rotation speed, and medium pH. The discriminatory power of the dissolution method is limited, due to the fast dissolving nature of the proposed drug product; nevertheless, the method is capable of showing the influence of tablet hardness on dissolution at the early time points of the dissolution profile. The proposed dissolution method is found acceptable. Also, based on the provided validation report, the dissolution method has been appropriately validated.

DISSOLUTION ACCEPTANCE CRITERION:

Dissolution profile comparison of 20 mg, 30 mg, 40 mg (b) (4) afatinib film-coated tablets, final formulation (FF) used in clinical trials (test conditions: paddle 75 rpm, 900 mL, pH 4.0, n = 12):

(b) (4)

The proposed dissolution acceptance criterion is:

Q = (b) (4) in 15 minutes (stage 1,2,3, according to USP requirements)

The Applicant states that the proposed acceptance criterion is based on results from clinical batches and primary stability batches. The Applicant notes that the stability studies indicate that for the test formulation 2 (TF2) and as well as for the final formulation (FF), nearly no change of the test parameter "dissolution" was observed for all stability storage conditions and stability time points.

Reviewer's Assessment of the proposed dissolution acceptance criterion:

The proposed acceptance criterion is not acceptable. The Applicant has stated that for all four dosage strengths, the dissolved amount of afatinib dimaleate was not less than (b) (4) in 15 minutes and that nearly no change of the test parameter "dissolution" was observed for all stability storage conditions and stability time points.

The following information request was sent to the Applicant in order to better understand the dissolution profiles of the clinical batches used in the relative BA study:

Information request dated 2/20/13: *Provide dissolution profiles using the proposed dissolution method, for the clinical batches used in the relative BA study 1200.35 (see table below).*

Clinical protocol (description)	Dosage form	Strength [mg]	Drug product bulk batch number	Drug product batch size	Drug product manufacturing date	Drug product manufacturing site	Drug substance batch number	Formulation code (TF used)
1200.35 open label Phase I	Film-coated tablet	20	B071002217	(b) (4)	27.06.07	BIP GmbH&CoKG Biberach	06217	HU00134 (FF)
	Film-coated tablet	20	B071003953		06.11.07	BIP GmbH&CoKG Biberach	07137	HU00175 (FF)
	Film-coated tablet	20	B081002939		22.07.08	BIP GmbH&CoKG Biberach	07135	TAF 99 2A 1B (TF II)
	Film-coated tablet	20	808920		15.09.08	BIP GmbH&CoKG Ingelheim	2	70108 (FF)

Applicant's response dated 3/4/13:

The bulk batches of film-coated tablets selected and used for the relative BA study 1200.35 were B081002939 (TF II) and B071003953 (FF). These primary packaged drug products received a new batch number code that differed from the batch number code used for the bulk samples as follows:

Dosage form (TF used)	Strength [mg]	Drug product bulk batch number[1]	Batch number of the primary packaged drug product[2]
Film-coated tablet (FF)	20	B071003953	B081004319
Film-coated tablet (TF II)	20	B081002939	B081003866

1 Batch number cited in Module 2, Section 2.7.1, Summary of Biopharmaceutics and Associated Analytical Methods (U12-1482-01)

2 Batch number cited in Module 3, Section P.5.6, Justification of Dissolution Specification (U09-2422-02)

Therefore, the dissolution profiles using the proposed method (using 75 rpm) for these batches are shown in the following figure:

(b) (4)

The TF2 and FF 20 mg tablets were found to be not bioequivalent (not BE). The proposed dissolution method is capable of showing a difference in the early time points of the dissolution profiles of these two formulations, indicating the discriminatory power of the dissolution method at the early time points. However, the acceptance criterion can not be set at 10 minutes, because the FF shows only around [redacted] (b) (4) *. Therefore, the recommended acceptance criterion for the dissolution test is* [redacted] (b) (4) *at 15 minutes. It should be noted that the recommended acceptance criterion will pass both the TF2 and the FF formulation, even though these are not BE. Based on the provided information on the clinical batches, the following information request was sent to the Applicant:*

Information request dated on 4/8/13:
Revise the dissolution acceptance criterion from Q= [redacted] (b) (4) *at 15 minutes to Q=* [redacted] (b) (4) *at 15 minutes. Submit a revised drug product specification table.*

Applicant's response dated 4/11/13:
The Applicant responded that they will revise the acceptance criteria from Q= [redacted] (b) (4) *at 15 minutes to Q* [redacted] (b) (4) *at 15 minutes. The revised specification documents for the 20 mg, 30 mg, 40 mg,* [redacted] (b) (4) [redacted] (b) (4) *dosage strengths will be provided to the NDA via an amendment by May 3, 2013.*

Reviewer's Assessment of the response: Acceptable.

COMPARATIVE DISSOLUTION PROFILES:
The pivotal phase III clinical study has been performed with tablets of the final formulation (FF) in the dosage strengths 20 mg, 30 mg, 40 mg [redacted] (b) (4) . While tablets of the strengths 30 mg, 40 mg [redacted] (b) (4) differed in debossing only from tablets of these strengths intended for market (commercial FF), tablets of the 20 mg strength differed in debossing and color compared with the commercial FF.

A dissolution profile comparison of 20 mg tablet cores, 20 mg light blue film-coated tablets used in clinical trials during development and 20 mg white film-coated tablets intended for market supply is shown below:

The 20 mg, 30 mg, 40 mg [redacted] (b) (4) film-coated tablets used for the pivotal Phase III study were debossed on one side only with the Boehringer Ingelheim company symbol. Film-coated tablets for market supply (commercial FF), however, are debossed on both sides to include the Boehringer Ingelheim company symbol debossing on one side and the dosage strength related

code ("T20" (20 mg), "T30" (30 mg), "T40" (40 mg), [redacted] (b) (4) on the other side. Dissolution profiles of one-sided debossed vs. two-sided debossed film-coated tablets of all dosage strengths are provided. As examples, the comparative dissolution profiles for the one-sided debossed vs. two-sided debossed 30 mg [redacted] (b) (4) tablets are copied below:

[redacted] (b) (4)

Time [min] Time [min]

A clinical trial was conducted to evaluate the relative bioavailability (BA) of the film-coated tablet formulation tested in Phase I/II trials (TF2) and the FF film-coated tablet at the dose strength of 20 mg. TF2 and FF (20 mg) were found to be NOT bioequivalent. Dissolution test results for drug product batches used in this study were used to select and evaluate the dissolution method and acceptance criterion as discussed above. Dose proportionality of the different FF dosage strengths has been investigated in the open-label, single rising dose, trial 1200.80. Detailed information about the relative bioavailability study as well as the food effect and the dose proportionality study will be reviewed by the Clinical Pharmacology Reviewer from the Office of Clinical Pharmacology (OCP).

The drug product manufacturing process was developed initially at R&D site Boehringer Ingelheim, Biberach, Germany, and then transferred to the intended commercial manufacturing site in Boehringer Ingelheim, Ingelheim, Germany. The initial clinical drug product batches were manufactured at the Biberach R&D site and the pivotal clinical batches, the primary drug product stability batches and further batches for clinical trial supply were manufactured at the intended commercial manufacturing site Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim. The following comparative dissolution profiles were provided to support the drug product manufacturing site change for all four strengths:

[redacted] (b) (4)

(b) (4)

Reviewer's Assessment of the comparative dissolution data:

The provided dissolution data for the 20 mg light blue film-coated tablets used in clinical trials during development and for the 20 mg white film-coated tablets intended for market supply, indicate that the change in film-coat composition of the 20 mg tablet does not affect dissolution of the 20 mg tablets.

The difference in tablet debossing (one-sided debossed for the pivitol Phase III drug product vs. two-sided debossed for the to-be marketed commercial drug product) did not affect the dissolution behavior of the film-coated tablets for all four dosage strengths.

Dissolution profile comparisons between the initial clinical drug product batches that were manufactured at the Biberach R&D site and the pivotal clinical batches that were manufactured at the intended commercial manufacturing site in Ingelheim appear to show that drug product dissolution at 5 and 10 minutes is different between batches from the two manufacturing sites. Therefore, the following information request was sent to the Applicant:

Information request dated 4/8/13:

Provide an explanation for the observed difference at the early time points between the dissolution profiles of the 20 mg and 30 mg drug product batches manufactured in Biberbach and Ingleheim. (Figures 30 and 31, section 3.2.P.2 Pharmaceutical Development). Indicate if there are any differences between the two manufacturing sites that could have caused the observed difference in the initial phase of the dissolution profiles of the drug products made at each site.

Applicant's response dated 4/11/13:

The (b) (4) *dissolution rate of the film-coated tablets batches B071003953 (20 mg) and B071003954 (30 mg) at the 5 min and 10 min time points is attributable to* (b) (4) *the core tablets and film-coated tablets, correspondingly. The following two tables show hardness and disintegration time data of 20 mg and 30 mg core tablets and film-coated tablets for comparison.*

(b) (4)

(b) (4)

<u>Reviewer's Assessment of the response: Acceptable</u>

The Applicant has provided an acceptable explanation of the observed difference at the early time points between the dissolution profiles of the 20 mg and 30 mg drug product batches manufactured in Biberbach and Ingleheim.

RECOMMENDATION:

- The dissolution methodology, as summarized below is acceptable:
  USP Apparatus II (paddle)
  Temperature: 37 °C
  Rotation speed: 75 rpm
  Medium: 900 mL McIlvaine buffer pH 4.0

- Dissolution acceptance criterion:
  Based on the dissolution data provided, the following dissolution acceptance criterion is acceptable: Q= (b) (4) at 15 minutes

- Comparative dissolution profiles:
  The Applicant has provided comparative dissolution profiles to show that the final formulation (FF) drug product used in the Phase III clinical trials has a similar dissolution profile as the commercial FF drug product.

From the Biopharmaceutics perspective, NDA 201292 for afatinib dimaleate Tablets (20, 30, 40 (b) (4) /tablet) is recommended for **APPROVAL**.

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

/s/

ELSBETH G CHIKHALE
04/22/2013

ANGELICA DORANTES
04/22/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**201,292/0**	**Brand Name**	Thundrion
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	Afatinib
Medical Division	**DDOP2**	**Drug Class**	**Small Molecular Drug**
OCP Reviewer	**Runyan Jin, Ph.D. Jun Yang, Ph.D.**	**Indication(s)**	Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s)
OCP Team Leader	**Hong Zhao, Ph.D.**	**Dosage Form**	Oral tablets (20, 30,40 (b) (4)
Pharmacometrics Reviewer	**Jun Yang, Ph.D.**	**Dosing Regimen**	40 mg Orally Daily
Date of Submission	**11/14/12**	**Route of Administration**	Oral
Estimated Due Date of OCP Review	**4/22/13**	**Sponsor**	Boehringer Ingelheim
Medical Division Due Date	**7/5/13**	**Priority Classification**	**Priority**
PDUFA Due Date	**7/15/13**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology	**x**			
Mass balance:	**x**	**1**		
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**	**17**		
Healthy Volunteers-				
single dose:	**x**	**6**		
multiple dose:	**x**	**6**		
Patients-				
single dose:				
multiple dose:	**x**	**14**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**3**		
In-vivo effects of primary drug:	**X**	**3**		
In-vitro:	**x**	**10**		
Subpopulation studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:	x	1		
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	x	1		
PD -				
Phase 2:	x	10		
Phase 3:	x	2		
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	x	2		
Population Analyses -				
Data rich:				
Data sparse:	x	4		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		31		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			No absolute BA. Relative BA to solution determined
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	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			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	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			ER for efficacy was conducted. Further analysis may be evaluated
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		Waiver requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			According to sponsor, no ER relationship for efficacy and safety
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

Reviewer's Comments

- Relative BA to oral solution instead of absolution BA has been determined.
-Meal reduces exposure by 26%
-Slightly more than proportional increase in exposure with dose increases
-PK trial for hepatic impairment (mild and moderate) was conducted; no renal impairment study was conducted as the liver mainly contributes to the elimination of afatinib.
-No CYP-enzymes were involved in the metabolism of afatinib.
-Substrates and inhibitors of BCRP in vitro, in vivo study not conducted.
-QT-IRT consult has been requested.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

-Based on the applicant analyses, no ER relationship has been identified between steady state trough concentration and efficacy endpoint (tumor size and PFS).
-PK data were obtained from 17 Phase I, 2 Phase I/II, 10 Phase II, and 2 Phase III trials. Four popPK studies were submitted. A popPK analysis containing all PK data was not conducted; however, this model is sufficient for us to assess the ER relationship. The F in HNSCC pts (phase II 1200.28) is 35% higher though with similar PK parameters to those of BC and NSCLC pts.
-Further ER for efficacy and safety may be evaluated during the review.
-All datasets used for exposure-response analyses will be requested.

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.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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/s/

RUNYAN JIN
12/19/2012

HONG ZHAO
12/19/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	201292
Submission Date	11/15/12
Product name, generic name of the active	Afatinib Tablets
Dosage form and strength	Tablets – 20, 30, 40, (b) (4) /tablets
Route of Administration	Oral
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Division	Division of Oncology Products 2
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Proposed dissolution method: Apparatus 2 (paddles), 900 mL of McIlvaine buffer pH 4.0 at 37 °C, at 75 rpm Proposed acceptance criterion: Q= (b) (4) at 15 minutes
3.	Does the application contain data to support the proposed dissolution acceptance criteria		x	Dissolution data to justify the proposed dissolution acceptance criterion need to be requested.
4.	Does the application contain the dissolution method development report?		x	The dissolution method development report needs to be requested
5.	Does the application contain data on the discriminating ability of the dissolution method		x	Data to show the discriminating ability of the dissolution method need to be requested as part of the dissolution method development report.
6.	Is there a validation package for the analytical method and dissolution methodology?	x		Section 3.2.P.5.3
7.	Does the application include a biowaiver request?		x	Not needed
8.	Does the application include an IVIVC model?		x	Not applicable
9.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable

10.	Is information on mixing the product with foods or liquids included?	x		To support administration of the drug product by dispersing a tablet in 100 mL of water, the Applicant has performed a relative BA study. The study will be reviewed by OCP.
11.	Is there any in *vivo* BA or BE information in the submission?	x		The Applicant has performed a dose proportionality PK study using 20, 30, 40 and 50 mg tablets. The study will be reviewed by OCP.
12.	Does the application include in *vitro* alcohol interaction studies?		x	Not needed

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
16.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		Additional information/data are needed for the review of the NDA. See Biopharmaceutics comments in the information request below sent to the Applicant on 12/13/12

Biopharmaceutics Information Request sent to the Applicant on 12/13/12:

1. Provide the composition of the McIlvaine buffer pH 4.0.
2. Provide the dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of the dissolution characteristics of Afatinib tablets.

   The dissolution method development report should include the following information:
   a. Solubility data for each drug substance covering the pH range;

b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;

c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*). 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*); and

d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

For the setting of the dissolution acceptance criterion of your product, the following points should be considered:

e. The dissolution profile data (*i.e., 10, 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product.

f. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

g. The selection of the specification time point should be where Q = (b) (4) dissolution occurs.

h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

3. The dissolution data that you collect during your stability study should cover the complete dissolution profile (*i.e., 10, 15, 20, 30, 45, & 60 minutes*). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data for the remaining stability time points and submit to the NDA.

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{See appended electronic signature page}

Elsbeth Chikhale, Ph.D. 12/13/12
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

John Duan, Ph.D. 12/13/12
Acting Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
12/13/2012

JOHN Z DUAN
12/13/2012