CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application number	201292
Priority or Standard	Priority
Submit Date(s)	November 15th, 2012
Received Date(s)	November 15th, 2012
PDUFA Goal Date	July 15, 2013
Division / Office	OHOP/DOP2
Reviewer Name(s)	Shakun Malik, M.D.
Review Completion Date	April 22nd, 2013
Established Name	Afatinib (BIBW 2992)
(Proposed) Trade Name	Gilotrif
Therapeutic Class	EGFR-tyrosine kinase inhibitor (EGFR-TKI)
Applicant	Boehringer Ingelheim
Formulation(s)	Oral (PO)
Dosing Regimen	40 mg orally once daily.
Indication(s)	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 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test for this use Limitation of Use: Safety and efficacy of BRAND have not been established in patients whose tumors have other EGFR mutations
Intended Population(s)	Adult patients with metastatic NSCLC harboring exon 19 deletions or exon 21 (L858R) substitution EGFR mutations.

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A. I recommend approval of Afatinib for the first line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with exon 19 deletions or exon 21 (L858R) substitution epidermal growth factor receptor (EGFR) mutation(s) as detected by FDA-approved test (TheraScreen®) at 40mg po per day dose.

My recommendation is based on the review of Study1200.32.

Study1200.32: In the study, patients (n=345) with EGFR mutation-positive, metastatic non-squamous, NSCLC were randomized (2:1) to receive Afatinib 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (Exon 19 deletion versus Exon 21 L858R versus other) and race (Asian versus non-Asian).

The study met its primary endpoint of PFS showing a statistically significant and clinically meaningful 4.2 month improvement in the median PFS between patients treated with Afatinib as compared to patients treated with chemotherapy [11.1 months vs. 6.9 months [HR 0.58; 95% CI 0.43, 0.78; p-value 0.0003 (log-rank test)]. At the interim updated analysis of survival (based on ~50% of OS events) median OS was estimated to be approximately 28 months for both treatments, with the observed hazard ratio of 0.907 favoring afatinib.

The majority of the patients enrolled had a tumor sample with an EGFR mutation categorized as either Exon 19 deletion [170/345(49%)] or Exon 21 (L858R) [138/345(40%)] while a small number [37/345(11%)] were of the "Other" mutation category. This small cohort of 10 different genetic subtypes were distributed in an unbalanced distribution in the afatinib (N=26) and chemotherapy (N=11) treatment groups.

On exploratory efficacy analyses in the study by EGFR mutation within the pre-specified subgroup of patients with 'common' EGFR mutations [i.e., Exon 19 deletion or Exon 21 (L858R) mutation], the benefit seems to be driven by Exon 19 deletion subgroup while in patients with "Other" mutation category there seems to be a possible detrimental effect on PFS and OS.

- Afatinib-treated patients (N=113) as compared to chemotherapy-treated patients (N=57 with Exon 19 deletion mutation showed a PFS of 13.7 vs. 5.6 months (HR 0.28 95% CI 0.18, 0.44)
- Afatinib-treated patients (N=91) as compared to chemotherapy-treated patients (N=47) with Exon 21 (L858R) mutation showed a PFS of 10.8 vs. 8.1 months (HR 0.73 95% CI 0.46, 1.16)

- Afatinib-treated patients (N=26) as compared to chemotherapy-treated patients (N=11) with "Other" mutations showed a PFS of 2.8 vs. 9.9 months (HR 1.89; 95% CI 0.84, 4.28).

The pattern among strata for overall survival paralleled that of PFS, with patients classified into "Other" categories showing a worse estimate of overall survival for afatinib compared with chemotherapy with HR of 3.077.

Although small in numbers, this exploratory analysis did not establish the benefit of Afatinib in these patients with "uncommon mutations" and showed a possible detrimental effect on PFS and OS in these patients.

(b) (4)

My recommendation is based on my review of the data from Study 1200.32 and Supportive Study 1200.22

Study1200.32: In the study, Afatinib was given as 40 mg once daily (q.d.) dose with possible dose escalation to 50 mg q.d. according to the protocol-defined dose escalation schema. Each treatment courses consisted of 21 days. Patients with pre-specified AEs during course 1, i.e., diarrhea or skin-related AEs or mucositis of any CTCAE Grade, or any drug-related AE of CTCAE Grade ≥2 were to continue afatinib at 40 mg once daily unless dose reduction was necessary. Patients with limited side effects during course 1 (i.e., none of the above events occurred) were to increase the afatinib dose to 50 mg once daily from course 2 onwards. The afatinib dose for these patients was 50 mg once daily for subsequent courses unless dose reduction was necessary.

In the study, the patients treated with afatinib with a starting dose of 40 mg po per day:

- 16/230 patients were dose escalated to 50 mg.
- Of the 16 patients, 13 received afatinib 50 mg for 21 days or more, 10/16 patients needed at least one dose reduction and 5/10 needed 2 dose reductions.

Study 1200.22: was an open-label, single-arm trial, in which the efficacy and safety of Afatinib in EGFR-TKI naïve patients with locally advanced or metastatic lung adenocarcinoma with EGFR mutations was assessed. Patients were enrolled in the first-line (n=61) or second-line setting (n=68) after failure of first-line chemotherapy. The trial enrolled 129 patients who received either 40 mg (n=30) or 50 mg (n=99) of Afatinib orally once daily.

In the study the 2 starting doses of 40 mg and 50 mg showed similar efficacy, with a better tolerability seen for the 40 mg starting dose.

(b) (4)

My recommendation is based on my review of the data from Study 1200.23

Study 1200.23: was a Phase IIb/III randomized double-blind trial of Afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients who had failed erlotinib or gefitinib and had previously received 1 or 2 lines of chemotherapy.

The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg BRAND orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195).

The trial population was clinically enriched for EGFR mutations by requiring patients to have treatment with prior EGFR-TKI therapy for at least 12 weeks. Tissue confirmation for EGFR mutations was not required.

The study failed its primary endpoint of OS with the median OS for placebo of 12.0 months and afatinib of 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35). The secondary endpoint of PFS, based on independent review, showed a median PFS time of 3.3 months for the afatinib group and 1.1 months for the placebo group (HR=0.38, p <0.0001).

Although the selection of the patient population was based on phenotype, the mutation status was tested only if archival tissue was available. In the study, 186/585(32%) of the patients had tissue available for testing at either the local lab or central lab. Of the patients tested, 96 were positive for EGFR mutation, with the most common deletions being Del 19 and L858R. There was a high degree of imbalance between the two arms on this retrospective analysis of EGFR mutation status and a high degree of discrepancy was noted between the types of EGFR mutations reported by the central lab verses the local lab.

Reviewer's comment: The basis for my recommendation (b) (4) (b) (4)

1.2 Risk Benefit Assessment

Study1200.32 met its primary endpoint, showing a statistically significant and clinically meaningful 4.2 month median improvement in PFS between patients treated with Afatinib as compared to patients treated with chemotherapy, with a median PFS of 11.1 months vs. 6.9 months [HR 0.58; 95% CI 0.43, 0.78; p-value 0.0003 (log-rank test)].

At the interim updated analysis of survival (based on ~50% of OS events) median OS was estimated to be approximately 28 months for both treatments, with the observed hazard ratio of 0.907 favoring afatinib.

Within the pre-specified subgroup of patients with NSCLC with 'Common' EGFR mutations (i.e., L858R or Del 19), median PFS was 13.6 months for the afatinib arm and 6.9 months for the chemotherapy arm (HR 0.471; 95% CI 0.344, 0.65). PFS of the patients with "Other Mutation"

was 2.8 months for the afatinib arm and 9.9 months for the chemotherapy arm (HR 1.89; 95% CI 0.84, 4.28). Patients classified into "Other" categories showed a worse estimate of overall survival for afatinib compared with chemotherapy with HR of 3.077.

The evaluation of clinical safety of this NDA is based on the treated set (TS) of patients, i.e. all patients who received at least 1 dose of study medication (over 3800 patients). For analyses of some of the important identified and potential risks, grouped MedDRA PTs of adverse events and standardized MedDRA queries (SMQs) were created.

Diarrhea and Rash were reported in over 90% of the patients. Other Adverse events reported in more than 10% of the patients in pivotal trial 1200.32 were stomatitis, cheilitis, paronychia, cystitis, epistaxis, rhinorrhea, pyrexia and conjunctivitis.

Some of the less frequent but serious side effects reported in 3865 patients who received afatinib across clinical trials include:

- Interstitial Lung disease (1.5%) characterized by lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) that resulted in deaths (0.4%) of patients.
- Hepatic Toxicity was reported in 10.1% indicative of hepatic impairment of which 7 (0.18%) were fatal.
- Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in (0.8%).
- Cardiomyopathy, indicative of heart failure or LVEF decrease was noted in 1.4%.

Over all most of the side effects reported were similar to side effect associated with EGFR inhibitors and EGFR TKIs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of updated analysis for Overall Survival (OS) from the pivotal trial that is basis for this NDA (study 1200.32), the data was not mature. This interim updated analysis of survival was based on ~50% of prespecified OS events .The applicant predicts that the data will be mature by the end of 2013. The following will be a Postmarket Commitment (PMC):

PMC (clinical): *Submit the data from the final Overall Survival (OS) analysis from Study 1200.32 in order to further characterize the OS effect of afatinib treatment*.
Final Submission Date: 3/31/2014

2 Introduction and Regulatory Background

Lung cancer remains the leading cause of cancer deaths in United States (1) and the World (2). The 5 year survival rate for patients with lung cancer remains dismal, around 15% (3). Tobacco smoke exposure is known causes of this cancer in most of the cases, however 10 -15 % of the patients are never/light smokers defined as less than 100 cigarettes in their lifetime. NSCLC histology comprises about 85% of the lung cancer cases. Although surgery remains the only curative modality for this disease, most of these patients (70%) present at advanced stage and thus are not surgical candidates.
Despite multiple subtypes of NSCLC per WHO Criteria (4), until recently first-line treatment for advanced disease was platinum-based doublet chemotherapy. With the discovery of molecular targets and targeted therapies, new treatment options are evolving.

Bevacizumab a monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A) is approved, with carboplatin and paclitaxel, for first line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer.
On May 2003, Gefitinib (Iressa) as monotherapy was the first tyrosine kinase (TK) inhibitor that received accelerated approval under (21 CFR 314, subpart H and 21 CFR 601, subpart E) by the FDA for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. On March 2005, labeling revisions by FDA restricted gefitinib use to patients already receiving and benefiting from the drug when the drug failed the primary endpoint of overall survival in a randomized, placebo-controlled multicenter study. On April 25, 2012 approval of this application was withdrawn.

Erlotinib, an Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor, has been approved for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen and for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

On August 26, 2011, crizotinib received accelerated approval for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer. This drug approval was in tandem with the approval of a test kit that detects the gene rearrangement in a patient's tumor that encodes ALK tyrosine kinase.

Although Bevacizumab and Erlotinib use do not require demonstration of specific molecular abnormalities in the patient's tumor tissue, there is an increasing awareness of the importance of identifying specific NSCLC molecular drivers to appropriately direct targeted agents to patient populations.

The literature review demonstrates that in clinical trials, when compared to chemotherapy, EGFR tyrosine kinase inhibitors are associated with a high response rate (70-80%) in NSCLC patients whose tumor harbor's EGFR favorable mutations [either Exon deletion 19 or Exon 21 (L858R)

substitution mutation] that is associated with improved PFS (5,6), however; no overall survival advantage has been demonstrated.

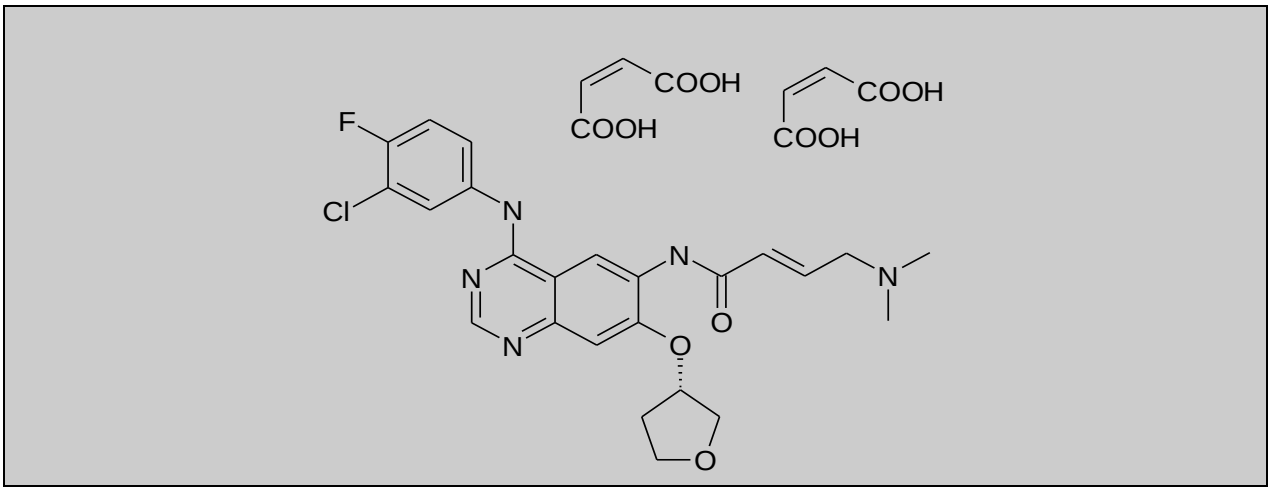
Despite initially promising responses, most patients treated with currently available EGFRTKI therapies will eventually develop disease progression. An apparent drug resistance occurs with a median time of 12 months after the initiation of EGFR-TKI therapy. Retrospective molecular analyses of relapsed NSCLC samples from this group of patients revealed an EGFR mutation in exon 20 rendering the tumor cells resistant to EGFR-TKI therapy (7-10). This specific gene mutation causes an amino acid alteration (T790M) in the EGFR protein, changing the EGFR conformation, thought to sterically hinder the access of TKIs (8).

Afatinib is irreversible EGFR TKI. The Applicant hypothesizes that the irreversible EGFR TKIs may prevent the emergence of secondary resistance mutations (11), thus improving the therapeutic efficacy in patients with NSCLC with EGFR mutations.

2.1 Product Information

Afatinib is a tyrosine kinase inhibitor which is a 4-anilinoquinazoline.
Afatinib is presented as the dimaleate salt, with the chemical name 2 butenamide, N-[4-[(3-chloro-4-luorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2E)-, (2Z)-2-butenedioate (1:2).

FIGURE 1: AFATINIB STRUCTURAL FORMULA



Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of C32H33ClFN5O11, and a molecular weight of 718.1 g/mol.

2.2 Tables of Currently Available Treatments for Proposed Indications

TABLE 1: AVAILABLE THERAPIES FOR METASTATIN NSCLC

Drug	Indication
Bevacizumab Non-squamous NSCLC	Initial treatment, in combination with carboplatin and paclitaxel
Docetaxel	After platinum therapy failure
	Initial treatment, in combination with cisplatin
Erlotinib	Maintenance treatment for patients whose disease has not progressed after four cycles of platinum based first-line chemotherapy
	After failure of at least 1 prior chemotherapy regimen
Gemcitabine	Initial treatment, in combination with cisplatin
Paclitaxel	Initial treatment, in combination with cisplatin
Pemetrexed Non-squamous NSCLC	Initial treatment in combination with cisplatin
	Maintenance treatment for patients whose disease has not progressed after four cycles of platinum based first-line chemotherapy
	After prior chemotherapy as a single agent
Vinorelbine	single agent or in combination with cisplatin for the first-line treatment of ambulatory patients
Crizotinib	for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer

2.3 Availability of Proposed Active Ingredient in the United States

Afatinib is a new molecular entity and is not currently marketed in the United States

2.4 Important Safety Issues with Consideration to Related Drugs

Afatinib is a potent and selective, irreversible ErbB family blocker. It 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.

The most common adverse reactions with EGFR-TKI noted have been rash-like events and diarrhea. Infrequent but significant toxicities of concern with these agents have been Interstitial Lung Disease (ILD), cardiomyopathy, hepatic failure and pancreatitis. In addition the concern with afatinib will be of Her 2 inhibition that may result in cardiomyopathy.

Other toxicities noted with this class of drugs are anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting.

TABLE 2: CLASS EFFECTS OF EGFR AND/OR HER2 INHIBITORS

Risk	Frequency in clinical trials of afatinib	Tarceva (erlotinib) 25, 100, 125 mg	Iressa (gefitinib) 250 mg	Tyverb (lapatinib) (in combination with capecitabine) 250 mg qd	Erbitux (cetuximab) 400 mg/m^2 infusion qd	Herceptin (trastuzumab) infusion 4 mg/m^2 (loading) 2 mg/m^2 (weekly after loading dose)
Diarrhoea	Very common	Very common	Very common	Very common	Common	Very common
Rash/acne	Very common	Very common	Very common	Very common	Very common	Very common (rashes); common (acne)
ILD	Uncommon	Uncommon	Common	Uncommon	Uncommon	Rare (pneumonitis)
Keratitis	Uncommon	Common	--	--	Uncommon	--
Decreased LVEF/heart failure[1]	Uncommon	--	--	Common	--	Very common
Hepatic failure[1]	Rare	Rare	--	Rare	--	Not known
Pancreatitis[1]	Uncommon	--	Uncommon	--	--	Common

[1] Potential risks, not considered ADRs for afatinib.
qd = once daily
Very common (>1/10); common (>1/100, <1/10); uncommon; (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000) including isolated reports.
Data source: afatinib safety data; current SmPCs (accessed of EMA webpage on 18 Jun 2012) of Tarceva (erlotinib), Iressa (gefitinib), Tyverb (lapatinib), Erbitux (cetuximab), and Herceptin (trastuzumab).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

July 31, 2007: EOP1 meeting: T-con to discuss proposed Phase 2/3 study and clinical development plan for Study 1200.23.

February 20, 2009: request for a special protocol assessment (SPA) the protocol titled, "A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harboring an EGFR activating mutation".

FDA had the following concerns that were communicated to the sponsor in a SPA Non-Agreement Letter

- Whether PFS is acceptable as the primary endpoint will be a review issue. In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk/benefit profile may be considered for regulatory decision making. At the time approvals of all products in the first-line setting of NSCLC were based on overall survival as the primary endpoint. Therefore the acceptability of PFS to support approval in the first-line setting will likely require discussion by the Oncologic Drugs Advisory Committee.

- The study design may be adequate provided the patient population selection is made using an analytically validated device.
- For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform. FDA recommended a comparison of the number of censored patients between arms and sensitivity analysis.
- Patient discontinuation will be based upon investigator-assessed progression in this open label study while the primary endpoint will be based on independent review (IRC). FDA was concerned that a substantial number of patients will be censored for Investigator assessed progression prior to IRC assessed progression and recommended that a number of be sensitivity analysis be performed.
- At the time of SPA, office of "In Vitro" Diagnostics and Radiological Health (CDRH) had no information concerning the analytical performance characteristics of the test for EGFR activating mutations. CDRH had concern that the study design, in which only "marker positive" patients will be accrued to the pivotal trial, and will carry implications for the claims that might be approved ultimately for both the device and the drug. CDRH also recommend that the sponsor archive all samples for patients screened, including screened negative subjects who were not enrolled in the trial.

December 15, 2009 and December 9th 2011: Pre-NDA meeting between the FDA and the Sponsor to discuss planning strategies for the NDA submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

- Submission contains all components of e-CTD.

- Information in the datasets was compared to information contained in about 20% of the case report forms and was found to be acceptable. Electronic case report forms were used and all case report forms were submitted.

- Three clinical sites, chosen on the basis of patient number enrolled at each site were inspected for this NDA. Because this is a new molecular entity, the sponsor and a CRO (Independent Review Committee [IRC] for progression free survival [PFS] determination) were also inspected. Based on the review of preliminary inspectional findings for clinical investigators, Drs. Yang, Geater and Schuler, the study sponsor, Boehringer Ingelheim Pharmaceuticals, Inc., and CRO (b) (4) the study data collected appear reliable.

3.2 Compliance with Good Clinical Practices

The sponsor states that the trial was carried out in compliance with the Clinical Trial Protocol, in accordance with the principles of the Declaration of Helsinki, in accordance with ICH-GCP, and in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs).

Prior to the initiation of any study-related procedure, all patients were informed about the trial verbally and in writing by the investigator. Each patient (or the patient's legally accepted representative) signed and personally dated an informed consent form according to the local regulatory and legal requirements. A separate, additional informed consent for the patient's agreement with epidermal growth factor receptor (EGFR) mutation testing was used.

3.3 Financial Disclosures

TABLE 3: ALL PRINCIPAL INVESTIGATORS/SUB-INVESTIGATORS REQUIRING DISCLOSURE

Study Number	Country	Staff Name	Staff Role	Study Site Code	Range or Reason
1200.22	United States of America			(b) (4), (b) (6)	Pending Patent on EGFR
1200.22	United States of America				Pending Patent on EGFR / Post Marketing Royalties
1200.22	United States of America	Seigel, Leonard	PI	1200.22.19	Greater than $50K
1200.23	Canada			(b) (4), (b) (6)	Greater than $50k
1200.24	Great Britain				Advisory Board
1200.32	Germany				Advisory Role
1200.32	Japan	Yoshioka, Hiroshige	PI	1200.32.3214	Greater than $50k

1) (b) (6) has a patent on EGFR testing. (b) (6) did not indicate any financial disclosure at the study completion time point collection. The Inc/Exc criteria for this study require patients to test positive for an EGFR mutation. MGH enrolled four patients in the study. Testing was performed locally at the site and documentation provided in site source documentation, which is allowed per protocol.
2) (b) (6) Patent on EGFR testing. (b) (6) also receives post-marketing royalties for EGFR mutation testing. The Inc/Exc criteria for this study require patients to test positive for an EGFR mutation. MGH enrolled four patients in the study. Testing was performed locally at the site and documentation provided in site source documentation, which is allowed per protocol. Enrollment to the study closed in 2009.As per the applicant since the 1200.22 study requires EGFR testing by central lab (b) (4) or documentation of testing from local lab. Local EGFR testing has been done for patients at MGH/Partners sites enrolled into the study, however documentation of testing is to be provided to (b) (4) for verification of eligibility requirement for EGFR mutation.
3) Leonard Seigel (PI): Celgene Stock, $52,000. The site screened 12 patients for 1200.22 but treated no patients. The site was closed in 2009, and the disclosure should have no impact on this study

4) [redacted] Grant for genetic profiling of lung cancer to [redacted] $500,000.00 paid out November 2010; $1,000,000.00 paid out November 2011. The initial payment of the grant was paid out to [redacted] after the recruitment period and after the primary endpoint of the study. Therefore no steps to be taken are required to minimize the potential for bias inthis case.
5) [redacted] The Investigator discloses that he was paid for advisory boards and to support conduct the studies. As per the applicant although he was considered part of the trial team, the principal investigator, [redacted] confirmed that [redacted] involvement in the trial was minimal, that he was not directly involved in consenting patients, nor was he involved in patient assessments [redacted] role was in patient referral for the study from his clinics at the [redacted]. Boehringer Ingelheim Ltd had complete oversight of the trial and performed 100% source data verification to ensure the quality of the data produced. All patients were reviewed for eligibility and to ensure no bias had taken place.
6) [redacted] Paid for Advisory role (amount not disclosed) As per the Applicant the investigator has resigned from his advisory role, at time-point "interim" and that BI response form is no longer required
7) Hiroshige Yoshioka (PI): Payment: 5,000,000 yen (about $62,730)
The number of patients at this site was limited to 8 patients according to the clinical contract. As per the applicant .Prof Yoshioka [redacted] and the money was not provided to himself but as an endowment for research [redacted]. Therefore, this donation cannot be used for personal purposes

Reviewer's Comments: The number of subjects enrolled by these investigators is small and thus these financial disclosures do not raise questions about data integrity in the Study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG was inspected by the FDA from November 5, 2012 through November 12, 2012. This site is listed as the site of drug substance and drug product manufacturing. At the conclusion of this inspection, the FDA field investigator conveyed deficiencies to the representative of the facility. The review of the Sponsor's responses received between November 2012 and February 28, 2013, to the FDA form 483 issued at the close of this inspection are ongoing. At this time, a final compliance status has not been determined. FDA, per 21 U.S.C. 505 (d)(3), grounds will deny approval of a pending application include finding 'the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity.'
CDER/OC/OMPQ/Division of International Drug Quality will communicate the final status of its review of the Sponsor's response when determined.

Reviewer's comments: This issue will have to be resolved prior to the approval of the NDA application

4.2 Clinical Microbiology

No issues noted

4.3 Preclinical Pharmacology/Toxicology

Based on its mechanism of action, BRAND can cause fetal harm when administered to a pregnant woman. This information with advice to the patients has been incorporated in the package Insert.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR, HER2 and HER4 and irreversibly inhibits the tyrosine kinase auto-phosphorylation of the EGFR receptor family with down-regulation of signaling.

Afatinib demonstrated inhibition of auto-phosphorylation 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 over expressing tumors.

4.4.2 Pharmacokinetics/ Pharmacodynamics

Absorption and Distribution
Following oral administration of BRAND tablets, time to peak afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Mean maximum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The mean relative bioavailability of 20 mg BRAND tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%.
A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition.

Metabolism and Elimination
Covalent adducts to proteins are the major circulating metabolites of afatinib, and enzymatic metabolism of afatinib is minimal.
In humans, 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.

The elimination half-life is 29-33 hours after a single dose BRAND administration and 45 hours after repeat dosing. Steady-state plasma concentrations are achieved within 8 days of repeat dosing of BRAND resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max}.

Specific Populations
Renal Impairment: Less than 5% of a single dose of afatinib is excreted by the kidneys. BRAND has not been studied in patients with severely impaired renal function (CLcr <30 mL/min)

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of BRAND. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied.

For further details, refer to full clinical Pharmacology review

5 Sources of Clinical Data

TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA

Type of Study[a]	Study No. [Report No.]	Location of Study Report[b]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen[c]; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	1200-0080 [U10-1164-01]	5.3.1.1	Dose proportionality	Open-label, randomised, single dose	Tablets, 20 mg, single dose, oral Tablets, 30 mg, single dose, oral Tablets, 40 mg, single dose, oral Tablets, 50 mg, single dose, oral	12 12 12 12 **48 Total**	Healthy male subjects	Single dose	Complete; Full
BA (BA/BE)	1200-0035 [U09-2233-02]	5.3.1.1 (5.3.1.2)	Relative BA tablet vs. solution	Open-label, randomised, single dose, three-way crossover	Tablets, 20 mg single dose (trial form 2), oral Drinking solution, 20 mg single dose, oral Tablets, 20 mg (final formulation) single dose, oral	21 22 20 **63 Total**	Healthy male subjects	Single dose	Complete; Full
PK	1200-0025 [U07-1759]	5.3.3.1	ADME	Open-label, single dose	Solution, 15 mg single dose, oral	8	Healthy male subjects	Single dose	Complete; Full

TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA (CONTINUED)

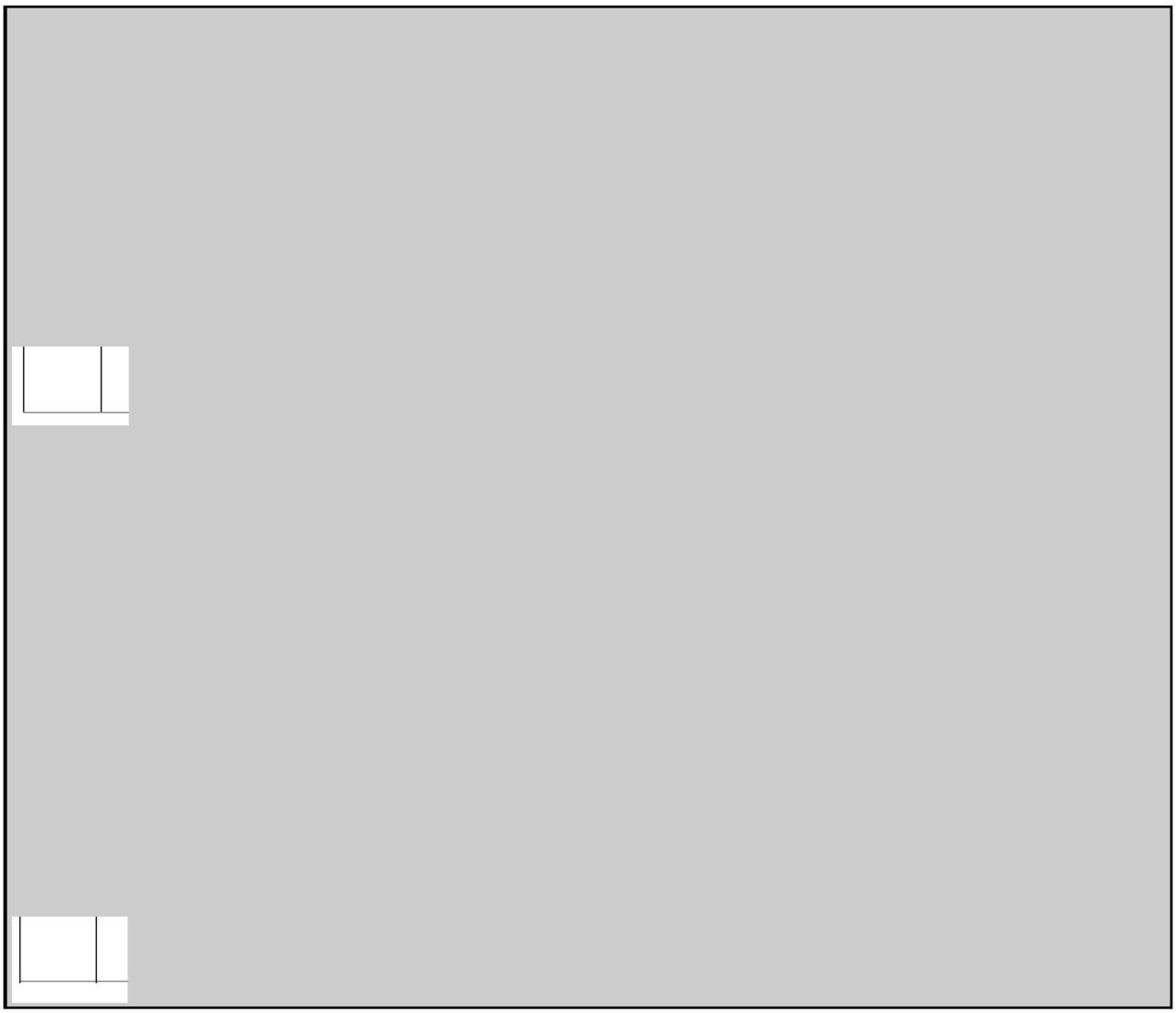
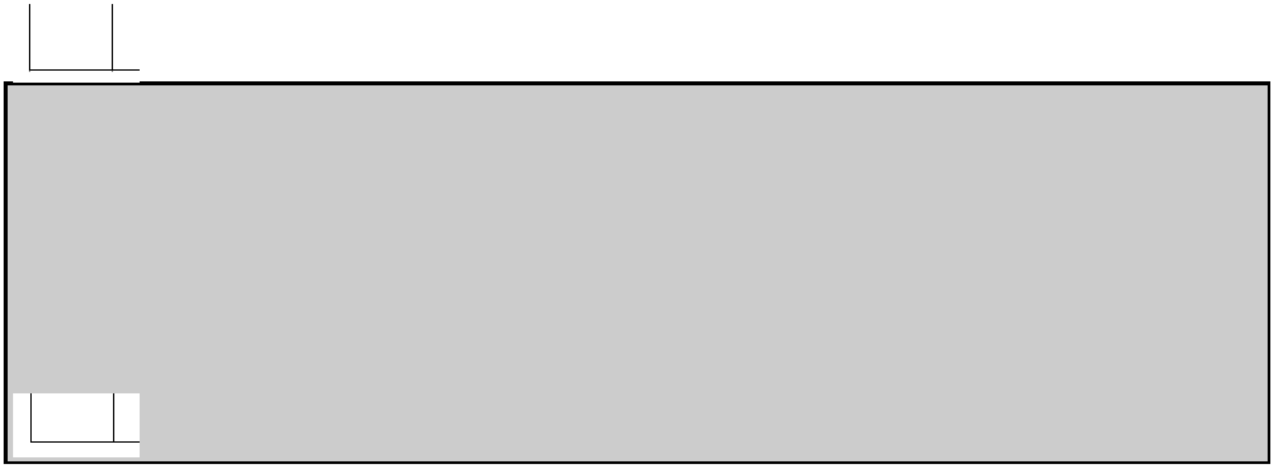


TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA (CONTINUED)



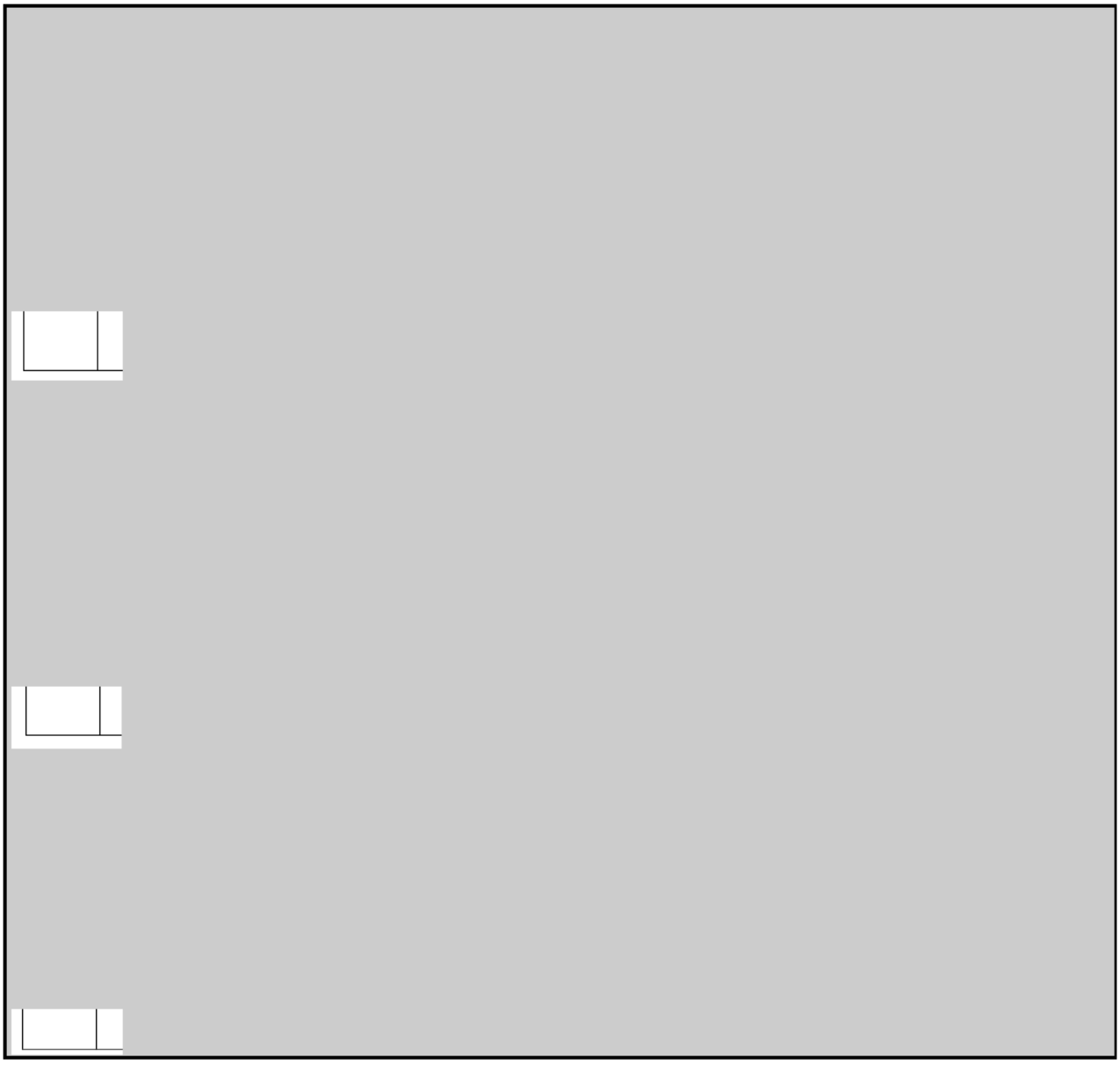


TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA (CONTINUED)

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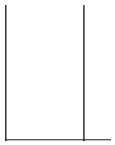


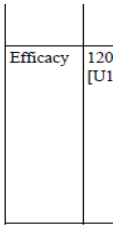


TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA (CONTINUED)

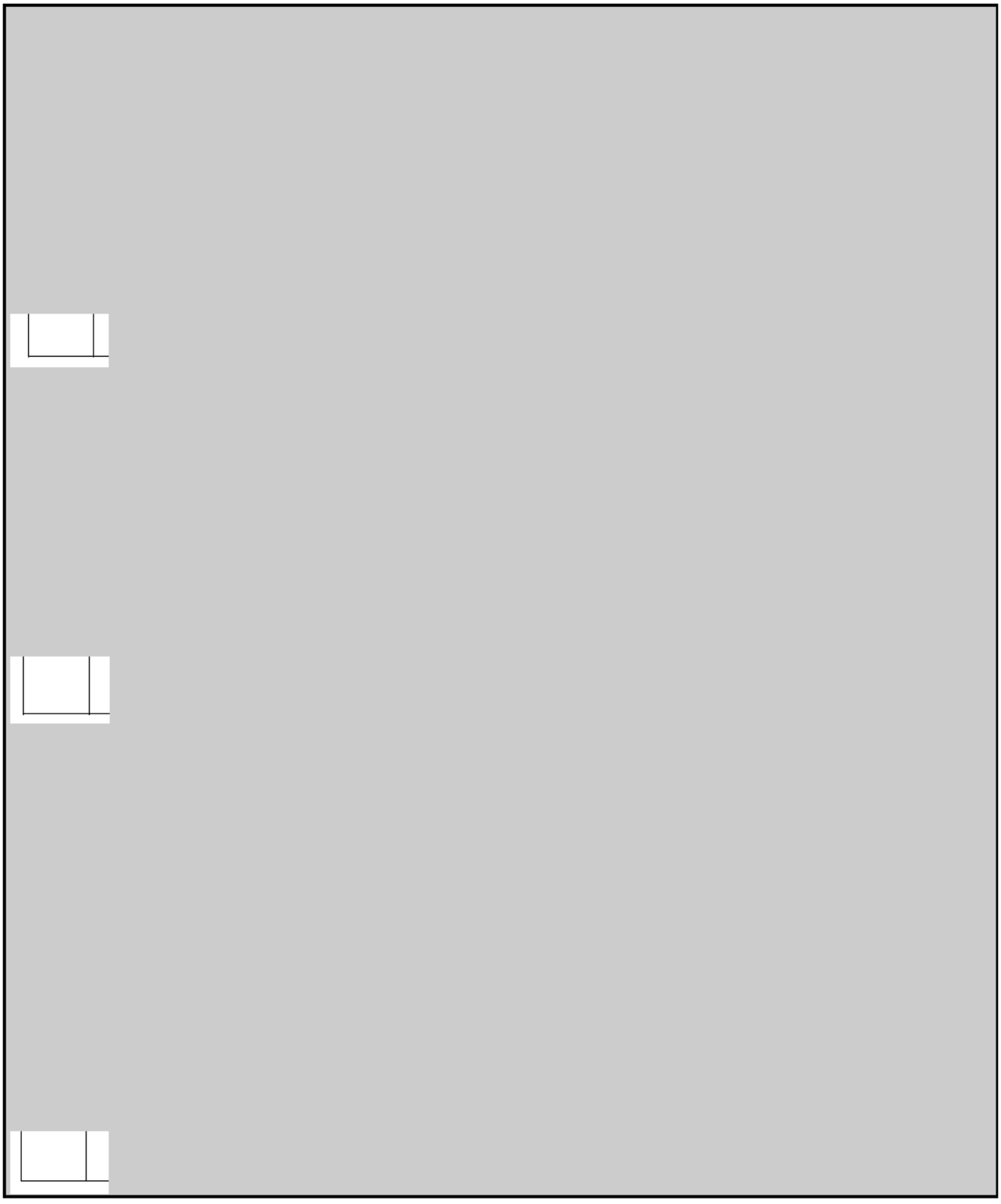


TABLE 4: SUMMARIZED SPONSOR SUBMITTED CLINICAL STUDIES IN SUPPORT OF THIS NDA (CONTINUED)

table 5: summarizes afatinib completed and/or ongoing NSCLC trials Trial number	Trial description	Trial design	Prior treatment		Primary analysis included in submission	Number of patients [1]
			EGFR TKI	Chemo		
A. Trials in EGFR TKI-naïve patients with NSCLC with EGFR mutations						
1200.22	Phase II trial with afatinib monotherapy	Non-randomised, open-label, uncontrolled	No	No or 1 line [2]	Yes	129
1200.32	**Phase III trial with afatinib monotherapy vs. chemotherapy (pemetrexed/cisplatin)**	**Randomised, open-label, active-controlled**	**No**	**No**	**Yes**	**345**
1200.34	Phase III trial with afatinib monotherapy vs. chemotherapy (gemcitabine/cisplatin)	Randomised, open-label, active-controlled	No	No	No (Recruitment complete)	364
1200.123	Phase IIb trial with afatinib monotherapy vs. gefitinib	Randomised, open-label, active-controlled	No	No	No (Recruiting)	264
B. Trials in EGFR TKI pretreated patients with NSCLC with clinical enrichment for EGFR mutations						
1200.23	Phase IIb/III trial with afatinib monotherapy	Randomised, double-blind, placebo-controlled	Yes	1 or 2 lines	Yes	585
1200.33	Phase I/II trial with afatinib monotherapy [3]	Non-randomised, open-label, uncontrolled	Yes	1 or 2 lines	Yes	74
1200.42	Phase III trial with afatinib monotherapy followed by afatinib plus weekly paclitaxel vs. chemotherapy [4]	(Non-)Randomised, open-label, uncontrolled/ active-controlled [4]	Yes	No or at least 1 line [5]	Yes (for trial Part A)	1154
1200.70	Phase Ib dose escalation trial with afatinib plus sirolimus	Non-randomised, open-label, uncontrolled	Yes	1 or more conventional treatment lines	No (Recruiting)	up to 42
1200.71	Phase Ib dose escalation trial with afatinib plus cetuximab	Non-randomised, open-label, uncontrolled	Yes	Any	No (Recruiting)	240
C. Other trials in patients with NSCLC						
1200.40	Phase II trial with afatinib monotherapy in EGFR FISH positive patients	Non-randomised, open-label, uncontrolled	No	No or 1 line	No (Recruitment complete)	70
1200.41	Phase II trial with afatinib monotherapy in EGFR FISH positive patients or patients with EGFR- or HER2-mutation	Non-randomised, open-label, uncontrolled	Yes or no [6]	Up to 3 lines [6]	No (Recruitment complete)	41
1200.72	Phase IIa trial with afatinib monotherapy in patients without EGFR mutation	Non-randomised, open-label, uncontrolled	No	1 or 2 lines	Yes	43

5.1 Review Strategy

Clinical review is was based on Clinical Study reports of the Pivotal study 1200.32, and 3 supportive studies 1200.22, 1200.23 and 1200.42 (Part A), efficacy and toxicity data sets (including Integrated Safety) submitted by the sponsor for the studies, CRF's, sponsor's presentation slides and literature review.

5.2 Discussion of Individual Studies/Clinical Trials

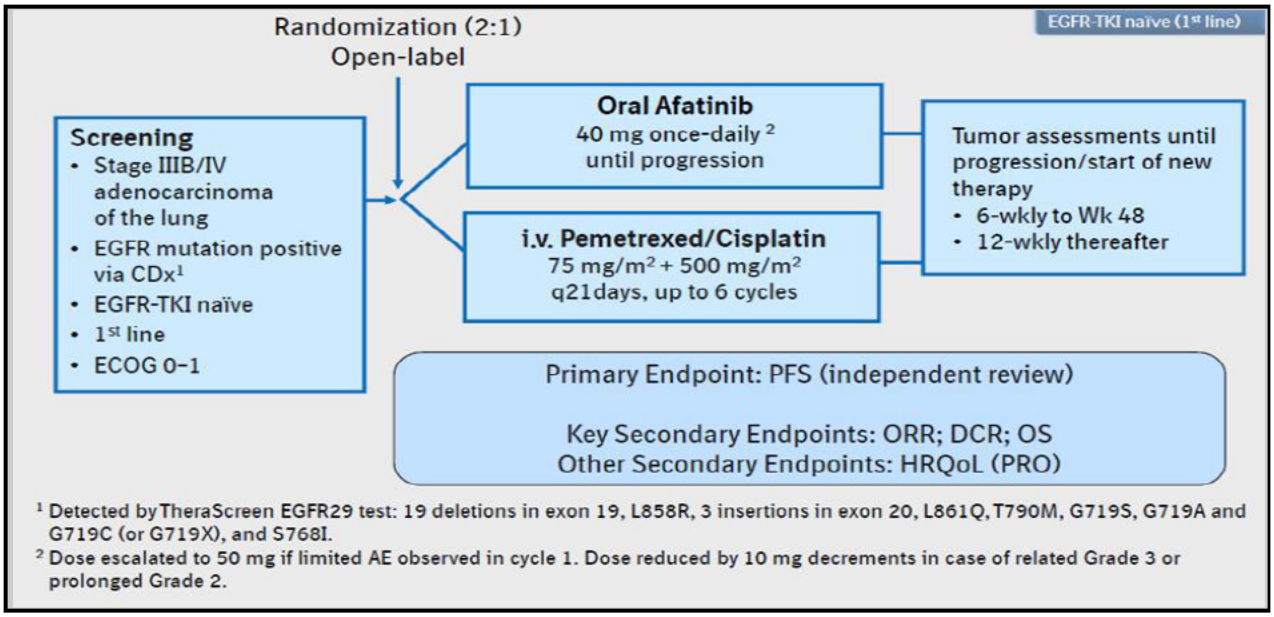
The Applicant has submitted clinical data from:
Pivotal trial: 1200.32 [LUX-Lung 3]; A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harboring an EGFR-activating mutation

3 supportive trials:

- (1200.22 [LUX-Lung 2],: A Phase II single arm trial of BIBW 2992 in non-small cell lung cancer patients with EGFR activating mutations
- 1200.23 [LUX-Lung 1] 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)
- 1200.42 (Part A) [LUX-Lung 5]). Phase III randomized trial of BIBW 2992 plus weekly paclitaxel versus investigator's choice of chemotherapy following BIBW 2992 monotherapy in non-small cell lung cancer patients failing previous erlotinib or gefitinib treatment (LUX Lung 5)

Study 1200.32 [LUX-Lung 3]
This multi-national, multi-center trial was conducted in 133 sites in 25 countries in Asia, Australia, Europe, North America, and South America.
This randomized, open-label, active-controlled, parallel-group phase III trial was designed to compare the efficacy and safety of afatinib monotherapy with pemetrexed / cisplatin chemotherapy as first-line treatment in EGFR TKI-naïve patients with Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or IV adenocarcinoma of the lung harboring an EGFR mutation.

FIGURE 2: Pivotal 1200.32 (LUX-Lung 3) Study Design



EGFR Status Testing: All patients who had signed an informed consent were required to provide a tumor sample biopsy at screening and were tested for their EGFR mutation status. Testing was performed centrally using the TheraScreen®: EGFR29 Mutation Kit (QIAGEN Manchester Ltd, Manchester, UK). It was planned to screen approximately 2200 patients to find 330 eligible patients. Eligible patients who had signed a second informed consent were randomly assigned in a 2:1 ratio to therapy with afatinib or pemetrexed / cisplatin chemotherapy.
The presence of an EGFR mutation, detected by central laboratory analysis, was mandatory for study enrolment. EGFR mutation analysis was to be performed at screening visit 1. Tumor material was to be submitted to the central laboratory as at least five (5), but preferably seven (7), 10 µm unstained sections mounted on non-charged microscopic slides.
It was recommended that the sections should contain at least 20% tumor pathology.
Tumor tissue could be paraffin-embedded material obtained from initial diagnostic surgery for NSCLC.

The following somatic EGFR mutations are detected;

- 19 deletions in exon 19
- L858R
- insertions in exon 20
- L861Q
- G719S, G719A and G719C
- T790M
- S768I

Samples testing positive for one of these mutations was to be reported as 'Positive' and the patient was eligible for Screening Visit 2. If a mutation is not detected, the result will be reported as 'Negative' and the patient will be recorded as a Screen Failure. In the event that the EGFR mutation test is inconclusive the investigator is allowed to send further material for testing if desired.

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. In any other case where more than one mutation was detected, the patient was to be allocated to the 'other mutation' stratification category

Stratification was done according to EGFR mutation category (L858R vs. Del 19 vs. "Other") and race (Asian vs. Non-Asian).

In the afatinib arm, patients were to receive continuous daily treatment with afatinib at a starting dose of 40 mg once daily. Afatinib was administered in treatment courses of 21 days.
Patients with pre-specified AEs during Course 1, i.e., diarrhea or skin-related AEs or mucositis of any CTCAE Grade, or any drug-related AE of CTCAE Grade ≥2 were to continue afatinib at 40 mg once daily unless dose reduction was necessary.
Patients with limited side effects during Course 1 (i.e., none of the above events occurred) were to increase the afatinib dose to 50 mg once daily from Course 2 onwards. The afatinib dose for these patients was 50 mg once daily for subsequent courses unless dose reduction was necessary.
In the pemetrexed / cisplatin chemotherapy arm, patients were to receive pemetrexed (500 mg/m^2) followed by cisplatin (75 mg/m^2) on Day 1 of each 21-day treatment course.
Patients were to receive 6 treatment courses unless they experienced unacceptable side effects or progressive disease.

Visits were scheduled for Days 1 and 8 of Courses 1 and 2, and for Day 1 of all subsequent treatment courses. An assessment of tumor response was to be performed at baseline and then every 6 weeks after the start of study medication. After Week 48, assessment of response was to be performed every 12 weeks until confirmed progression or withdrawal for another reason. End-of-treatment (EOT) procedures were to be performed after the patient had stopped the study medication, i.e., afatinib or pemetrexed / cisplatin. After the permanent discontinuation of the study medication, patients were to be followed every 3 weeks until progression or start of subsequent anti-cancer treatment. In the subsequent observation period, patients were to be followed until death.

Patients were to receive continuous daily treatment with afatinib at a starting dose of 40 mg once daily with each course of 21 days.

PRIMARY ENDPOINTS
The primary endpoint was PFS as assessed by central independent review according to RECIST version 1.1

SECONDARY ENDPOINTS
- Objective response (defined as complete response [CR], or partial response [PR]) according to RECIST version 1.1 (time to objective response, duration of objective response)
- Disease control (defined as a patient with objective response or stable disease [SD]) according to RECIST version 1.1 (duration of disease control)
- Overall survival (OS)

Other secondary endpoints were

- Tumor shrinkage (as specified in the trial statistical analysis plan [TSAP])
- Change from baseline in body weight (as specified in the TSAP)
- Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status
- Health-Related Quality of Life (HRQOL
- Pharmacokinetics of afatinib
- Safety of afatinib as indicated by the incidence and severity of adverse events

KEY Inclusion criteria;

1. Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. Patients with mixed histology were eligible if adenocarcinoma was the predominant histology.
2. EGFR mutation detected by central laboratory analysis of tumor biopsy material.
3. Measurable disease according to RECIST version 1.1
4. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1

KEY Exclusion criteria

1. Prior chemotherapy for relapsed or metastatic NSCLC. Neo-adjuvant or adjuvant chemotherapy was permitted if at least 12 months had elapsed between the end of chemotherapy and randomization.
2. Prior treatment with EGFR-targeting small molecules or antibodies.
3. Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization.
4. Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease).
5. Known pre-existing interstitial lung disease.
6. Significant or recent acute gastrointestinal disorders with diarrhea as a major symptom
7. History or presence of clinically relevant cardiovascular abnormalities or Cardiac left ventricular dysfunction with resting ejection fraction of less than 50%.
8. Inadequate Bone Marrow with normal renal and liver function.

Schedule of Assessment

Physical examination, performance score

A physical examination was to be performed at screening and at the time points specified. A full physical exam served as a clinical tumor assessment and included a cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status.

ECG

A 12-lead resting ECG was to be performed at the time points specified in the Flow Chart.

Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or MUGA scan was to be assessed at time points specified in the Flow Chart. The same method of measurement had to be used throughout the study

CALANDER OF SCHEDULE OF PROCEDURES: ARM A (AFATINIB)

	Screening*		Treatment Courses 1 - 2***		Treatment Course 3 and subsequent courses***	End of Treatment	Follow-up	Observation period
Visit abbreviation	**SV1**	**SV2****	**CxV1[a]**	**CxV2[a]**	**CxV1[a]**	**EOT**	**FUx[b]**	**OP**
Days	**Up to 6 weeks before treatment**	**Up to 28 days before treatment**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**0-14 days after permanent discontinuation of BIBW 2992 ******	**Every 21 days after EOT visit (± 7 days)*******	**Every 60 days after last follow-up visit (± 15 days)**
Informed Consent 1	X (1)							
Informed Consent 2		X (2)						
Demographics	X							
Medical History		X						
Review of In-/Exclusion criteria		X						
Randomisation		X (3)						
Complete physical examination (4)		X				X		
Limited physical examination (4)			X		X		X	
Vital Signs		X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	
HRQOL and caregiver support assessment			X		X	X	X	
12 Lead Digital ECG (5)		X		X (5)	X (5)	X (5)		
ECHO or MUGA (6)		X			X (6)	X (6)		
Safety lab (7)		X	X		X	X	X	
Pregnancy test		X						
Tumour biopsy for EGFR mutation analysis (8)	X						X (8)	
Blood sample for EGFR mutation analysis (9)			X (9)				X (9)	
Blood sample for DNA banking (10)			X (10)					
Blood sample for pharmacokinetic analysis (11)			X (11)	X (11)	X (11)			
Tumour assessment (12)		X	See schedule below (12)					
Concomitant medications		X	X	X	X	X	X	
Compliance Check			X	X	X	X		
Adverse events and healthcare usage		X	X	X	X	X	X	
Dispense Trial drugs			X		X			
BIBW 2992 treatment			Continuous					
Termination of trial medication						X		
Trial Completion							X	
Collection of vital status information (13)								X

* The screening visits are identical for all patients but have been included on both flow charts for clarity.

** EGFR mutation analysis will be performed at Screening visit 1. Only patients who test positive for an EGFR activating mutation should proceed to Screening visit 2. Procedures which are performed as part of routine clinical care prior to receiving the EGFR mutation test result do not need to be repeated at Screening visit 2 if they are within the allowed time window (within 28 days prior to treatment).

*** All courses are 3 weeks in duration (21 days). Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met

**** If the decision to permanently discontinue BIBW 2992 is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

***** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment.

a x is the number of the treatment course

b x is the number of the follow-up visit

1 Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

2 Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.

3 Treatment must commence as soon as possible after randomisation, but within 2 days at the latest.

4 Includes height (at screening only) and weight.

5 A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening, on Day 8 of Course 1, and then on Day 1 of every third course (Day 1 of Course 4, 7, 10 etc.), and at EOT (if not performed in the previous 8 weeks).

6 ECHO or MUGA will be performed at Screening, on Day 1 of Course 4 and then at every third course (Course 7, 10, 13 etc.), and at EOT (if not performed in the previous 8 weeks).

7 Includes haematology, serum biochemistry, and urinalysis.

8 Tumour biopsy to be collected at screening visit 1 for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Tumour biopsy at follow-up (at the time of PD) is optional.

9 A single blood sample for EGFR mutation testing is mandatory at start of treatment and should be taken on Day 1 of Course 1. A single blood sample at follow-up (at the time of PD) for EGFR mutation testing is optional.

10 The blood sample for DNA banking is optional. Separate consent must be obtained. The sample may be taken any time after randomisation, but preferably on Course1Day1.

11 Pharmacokinetic sampling will take place at C2V1, C2V2 and C3V1. For detailed PK sampling time schedule, refer to

12 Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment Assessment will be performed at the following timepoints until progression or start of further treatment for disease;

Screening visit 2
During week 6 (35-42 days after randomisation)
During week 12 (77-84 days after randomisation)
During week 18 (119-126 days after randomisation)
During week 24 (161-168 days after randomisation)
During week 30 (203-210 days after randomisation)
Every 6 weeks thereafter until progression/ start of further treatment. After week 48, assessments will be performed every 12 weeks.

In the event of early discontinuation or an interruption/delay to treatment the tumour assessment schedule should not be changed.

13 Collection of information on progression, further treatment and death. Information should be collected from the patient notes or by telephone contact with the patient. A formal study visit is not required.

CALANDER OF SCHEDULE OF PROCEDURES: ARM B (PEMETREXED/CISPLATIN)

	Screening*		Treatment Courses 1 - 2***		Treatment Courses 3 - 6***	End of Treatment	Follow-up	Observation period
Visit abbreviation	**SV1**	**SV2****	**CxV1[a]**	**CxV2[a]**	**CxV1[a]**	**EOT**	**FUx[b]**	**OP**
Days	**Up to 6 weeks before treatment**	**Up to 28 days before treatment**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**21 days after Course 6 Day 1 (± 7 days) or If patient does not complete 6 courses, 0-14 days after decision to end treatment**	**Every 21 days after EOT visit (± 7 days) ******	**Every 60 days after last follow-up visit (± 15 days)**
Informed Consent 1	X (1)							
Informed Consent 2		X (2)						
Demographics	X							
Medical History		X						
Review of In-/Exclusion criteria		X						
Randomisation		X (3)						
Complete physical examination (4)		X				X		
Limited physical examination (4)			X		X		X	
Vital Signs		X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	
HRQOL and caregiver support assessment			X		X	X	X	
12 Lead Digital ECG (5)		X	X (5)					
ECHO or MUGA (6)		X	X (6)					
Safety lab (7)		X	X		X	X	X	
Pregnancy test		X						
Tumour biopsy for EGFR mutation analysis (8)	X						X (8)	
Blood sample for EGFR mutation analysis (9)			X (9)				X (9)	
Blood sample for DNA banking (10)			X (10)					
Tumour assessment (11)		X	See schedule below (11)					
Concomitant medications		X	X	X	X	X	X	
Adverse events and healthcare usage		X	X	X	X	X	X	
Dispense Trial drugs			X		X			
Chemotherapy			X		X			
Termination of trial medication						X		
Trial Completion							X	
Collection of vital status information (12)								X

* The screening visits are identical for all patients but have been included on both flow charts for clarity.

** EGFR mutation analysis will be performed at Screening visit 1. Only patients who test positive for an EGFR activating mutation should proceed to Screening visit 2. Procedures which are performed as part of routine clinical care prior to receiving the EGFR mutation test result do not need to be repeated at Screening visit 2 if they are within the allowed time window (within 28 days prior to treatment).

*** Courses 1-6 are each 3 weeks (21 days).

**** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment.

a x is the number of the treatment course

b x is the number of the follow-up visit

1 Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

2 Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.

3 Treatment must commence as soon as possible after randomisation, but within 2 days at the latest.

4 Includes height (at screening only) and weight.

5 A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening and then at any other timepoint if clinically indicated.

6 ECHO or MUGA will be performed at Screening and then at any other timepoint if clinically indicated.

7 Includes haematology, serum biochemistry, and urinalysis.

8 Tumour biopsy to be collected at screening visit 1 for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Tumour biopsy at follow-up (at the time of PD) is optional.

9 A single blood sample for EGFR mutation testing is mandatory at start of treatment and should be taken on Day 1 of Course 1. A single blood sample at follow-up (at the time of PD) for EGFR mutation testing is optional.

10 The blood sample for DNA banking is optional. Separate consent must be obtained. The sample may be taken any time after randomisation, but preferably on Course1 Day1.

11 Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment Assessment will be performed at the following timepoints until progression or start of further treatment for disease;
Screening visit 2
During week 6 (35-42 days after randomisation)
During week 12 (77-84 days after randomisation)
During week 18 (119-126 days after randomisation)
During week 24 (161-168 days after randomisation)
During week 30 (203-210 days after randomisation)
Every 6 weeks thereafter until progression/ start of further treatment. After week 48, assessments will be performed every 12 weeks.

12 Collection of information on progression, further treatment and death. Information should be collected from the patient notes or by telephone contact with the patient. A formal study visit is not required.

SAFETY ASSESSMENT

During the screening phase of the trial, the patient's condition was assessed (e.g., documentation of history / concomitant diagnoses and diseases), and subsequently all relevant changes from baseline were noted.

Patients were required to report spontaneously any adverse events (AEs) as well as the dates of onset and end of these events. Specific questions were to be asked wherever required or useful to more precisely describe an AE and to allow a grading according to CTCAE, Version 3.

A carefully written record of all AEs was to be kept by the investigator in charge of the trial. Records of AEs were to include data on the date of onset, end date and CTCAE grading of the event as well as any treatment or action required for the event and its outcome.

Regular and continuing assessment of safety was to be performed at least once per course during the first six courses and every three weeks thereafter.

Dose reduction schemes were provided for patients who experience specified adverse events and who, at the discretion of the investigator, could derive benefit from continuing treatment on the protocol.

Adverse events with an onset during therapy with trial medication or within 21 days after discontinuation of drug intake were considered as "on-treatment". Adverse events which are not yet recovered at the End of Treatment visit were to be followed up until recovery or in case of persistence sufficient characterization of the toxic effects had been achieved and the investigator and Boehringer Ingelheim agreed not to pursue them further. Adverse events that occur between Follow-up 1 (21 days after End of Treatment) and the final follow-up visit were only to be reported if they are considered related to trial medication or procedures by the investigator. Adverse events occurring after the final follow-up visit (during the observation period) were to be reported only if considered serious (SAEs) and related to trial medication or procedures. Data regarding deaths which are not related to trial medication will be collected for the purposes of assessing the overall survival endpoint but these deaths will not be reported as SAEs.

Dose reduction scheme for afatinib:

In the event of treatment-related toxicities, the treatment with afatinib was to be handled according to the schedule

Dose reduction was always to follow a treatment pause. In the event of a treatment pause, subsequent visits/courses could not be delayed.

Patients were to discontinue treatment if they experience deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3.

In the event of a prolonged (≥7 consecutive days) Grade 2 drug-related event which was poorly tolerated by the patient, the investigator may have choose to pause the medication for up to 14 days to allow the patient to recover followed by a dose reduction.

In the event of any unrelated adverse events or unrelated serious adverse events, the investigator may have chosen to pause the medication for up to 7 days to allow the patient to recover without dose reduction. If the investigator chooses to pause the medication for more than 7 days and believed that the patient would derive clinical benefit from continuing medication, the decision to continue medication was to be made by the BI clinical monitor in agreement with the investigator.

DOSE REDUCTION SCHEME FOR AFATINIB

AE type and grade	Action	Dose reduction scheme
Events related to study drug; • Any drug related AE CTCAE Grade ≥3. • CTCAE Grade ≥2 diarrhoea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration. • CTCAE Grade ≥2 nausea and/or vomiting persisting for 7 or more consecutive days despite anti-emetic treatment/ hydration. • CTCAE Grade ≥2 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline.	Pause treatment with BIBW 2992 until patient has recovered to CTCAE Grade ≤ 1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤ 1 or baseline[1] within 14 days study treatment should be permanently discontinued[2].	If patient was receiving 50mg, resume treatment at a dose of 40mg. If patient was receiving 40mg, resume treatment at a dose of 30mg. If patient was receiving 30mg, resume treatment at a dose of 20mg. If patient was receiving 20mg, discontinue BIBW 2992.

1 Baseline is defined as the CTCAE grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator, but has not recovered within 14 days, the further treatment of the patient will be decided by the BI clinical monitor in agreement with the investigator.

Management of Rash following treatment with Afatinib

An early approach to management of rash was recommended to be followed by the Investigators. The patients were to be informed to strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.

In addition to dose interruption and or reduction topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel, pimecrolimus 1% cream, a combination of local and systemic therapies including systemic antibiotics (doxycycline or minocycline etc.), antihistamines (diphenhydramine, etc.) could be used. Oral prednisone (short term i.e., <14 days treatment) could have been added at Investigator's discretion.

Management of Diarrhea following treatment with Afatinib

Close monitoring and proactive management of diarrhea was recommended. Loperamide was to be available at the start of therapy and kept with the patient at all times and the patients were instructed to start loperamide therapy if any diarrhea was experienced.

For CTCAE Grade 3 diarrhea or CTCAE Grade 2 diarrhea lasting ≥ 2 days (48 hours) despite adequate antidiarrheal treatment, afatinib treatment was paused until recovery to CTCAE ≤ Grade 1 and resumed at a reduced dose.

If despite optimal supportive care and a treatment pause, diarrhea does not resolve to CTC Grade ≤1 within 14 days, the patient was taken off the study with appropriate follow up.

Dose reduction scheme for Chemotherapy
Pemetrexed/ Cisplatin chemotherapy was to be administered at the investigator site and prepared and administered in accordance with the current summary of product characteristics.
Hematology was to be checked prior to commencing each course and treatment could be delayed if platelet count is <100,000 cells/ mm^3 or ANC is < 1500 cells/ mm^3.
The patient was to be given supportive care (such as anti-emetics, hydration and vitamin supplements) during chemotherapy in accordance with the current summary of product characteristics and institutional guidelines.
In the event of treatment related adverse events, the treatment with chemotherapy was to be delayed and/or the dose was to be reduced in accordance with the guidance in the current summary of product characteristics (SPC).
In the event of a delay due to adverse events, subsequent courses and assessments was also to be delayed, with the exception of the tumor assessment which had to be performed according to the original schedule.

Discontinuation of patients from study medication
A patient was to be discontinued from further study medication in the following circumstances:

- The patient withdrew consent.
- The patient had documented disease progression
- The patient was no longer able to participate in the treatment phase (e.g. due to surgery, concomitant diagnoses, concomitant therapies, or for administrative reasons). The investigator was to record the reason for a patient's removal in the electronic case report form (eCRF).
- Significant deviation from the protocol or eligibility criteria. The decision to continue or discontinue treatment was to be made by BI's clinical monitor in agreement with the investigator.
- Diagnosis of interstitial lung disease.
- Requirement to stop treatment due to AEs

A patient was to be withdrawn from the trial in the following circumstances:

- Requirement for further treatment of NSCLC after the first FU visit (21 days after EOT).
- The patient withdrew consent to all further study procedures and elected to discontinue participation in the trial.
- The trial was terminated by the sponsor.

Patients who prematurely discontinued the study medication or the trial were not replaced.

Data monitoring committee
A data monitoring committee (DMC) was responsible for assessing the safety and efficacy data to ensure the overall safety of the patients treated in this trial. This DMC was an independent multidisciplinary group and comprised 3 voting members, including 1 independent statistician and 2 independent oncologists. The DMC was to provide the sponsor with advice about the conduct of the trial and the integrity of the data. In particular, the DMC was to periodically

review trial data; evaluate the safety of the patients on the basis of adverse event and laboratory data by blinded treatment groups; review the quality of the data; and monitor the overall integrity, scientific merit, and conduct of the trial. Based on the monitoring and evaluation of data throughout the trial, the DMC was to provide the sponsor with advice whether the trial should continue as planned, be modified, be suspended, or be discontinued.

Radiological imaging and central independent review
A central independent review of tumor response on the basis of radiological images and relevant clinical information was performed by experts affiliated with the contract research organization (CRO) (b) (4). This central imaging unit ensured an independent blinded assessment of tumor response based on a uniform interpretation of radiographic image data for all patients enrolled in the trial. The procedures of the central independent review were defined in the 'Independent Review Charter'.

Protocol amendments
The clinical trial protocol was amended twice;
Amendment 1: dated 06 May 2010: Exclusion criterion was modified. Treatment with any of the prohibited concomitant medications was intended to apply to afatinib arm patients however the consent process took place before randomization, it was this necessary for the applicant to cover both treatment arms with this exclusion criterion.
It was specified that the list of restricted medications refers to all patients randomized. An additional explanatory paragraph was added that the concomitant use of potent P-gp inhibitors and inducers was to be avoided during treatment with afatinib.
Amendment 2: dated 09 May 2011
Several changes and corrections were introduced.

- The original protocol allowed for collection of AEs and concomitant medications as well as collection of demographic information at the first screening visit; this was not covered by the first informed consent. This error was corrected with protocol amendment 2.
- The strict time window for afatinib intake was removed to accommodate the individual patient's daily schedule.
- The storage conditions for afatinib were corrected to match the labeling in the USA and Canada.
- The concomitant medication for patients randomized to treatment with pemetrexed / cisplatin was modified to allow for local variation in the pre-treatment with folic acid.
- The time window of the on-treatment period was modified to match the planned safety analysis with other afatinib trials.

Changes introduced by the trial statistical analysis plan

The Clinical Trial Plan described that the effect of afatinib on PFS compared with pemetrexed / cisplatin chemotherapy was to be tested at the 1-sided 0.025 significance level. This is identical to the effect of afatinib being tested at the more commonly used 2-sided 0.05 significance level if the treatment effect is in favor of afatinib. To aid in the interpretation of this trial, 2-sided p-values were therefore used.

An additional censoring rule for the determination of PFS was added to cover a scenario that had not been considered at the time of protocol writing. Patients with an assessment of 'Non-PD' by central independent review, more than one consecutive missed assessment, and an assessment of 'Non-PD' according to the imaging after the missed assessments were to be censored at the date of the last assessment of 'Non-PD'.

The comparison of AEs over a period of time equivalent to 6 courses of chemotherapy was replaced by exposure-adjusted AE incidence rate summaries which do not exclude any treatment-emergent AEs.

A list of pre-specified AEs of special interest (i.e., diarrhea, and the grouped terms for 'rash/acne', 'renal insufficiency', 'leukopenia', and 'neuropathy') was added.

For laboratory parameters, the focus of the analyses was changed as follows: low values for hemoglobin, WBC count, neutrophils, lymphocytes, platelets, potassium, sodium, and GFR and high values for creatinine, AST, ALT, total bilirubin, ALKP, and CPK.

Protocol Violations

More patients randomized to the afatinib arm (28.3%) than patients in the chemotherapy arm (15.7%) were reported to have important protocol violations.

The most frequent protocol violations were intake of incorrect trial medication (mainly not following the protocol pre-specified dose modification scheme; afatinib 15.2% of patients; chemotherapy 1.7%), violations of the entrance criteria (afatinib 7.0%; chemotherapy 10.4%), and non-adherence to safety-related withdrawal criteria (patient continued in the study after PD according to RECIST 1.1; afatinib 6.1%; chemotherapy 0.9%).

No patients with a protocol violation have been excluded from the primary analysis

TABLE 6: PATIENTS WITH IMPORTANT PROTOCOL VIOLATIONS

	Afatinib N (%)	Chemotherapy N (%)	Total N (%)
Patients	230 (100.0)	115 (100.0)	345 (100.0)
Patients with at least 1 important protocol violation[1]	65 (28.3)	18 (15.7)	83 (24.1)
Entrance criteria not met[2]	16 (7.0)	12 (10.4)	28 (8.1)
Written informed consent signed too late or procedure performed prior to written informed consent	3 (1.3)	2 (1.7)	5 (1.4)
Incorrect trial medication taken[3]	35 (15.2)	2 (1.7)	37 (10.7)
Randomisation not followed	8 (3.5)	1 (0.9)	9 (2.6)
Non-compliance	1 (0.4)	0 (0.0)	1 (0.3)
Non-adherence to safety-related withdrawal criteria	14 (6.1)	1 (0.9)	15 (4.3)

[1] A patient could be counted under more than 1 category.
[2] Laboratory values did not meet the entrance criteria; baseline imaging more than 28 days before treatment start; diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung incorrect; or other deviation from the entrance criteria.
[3] The most frequent protocol violations in this category were violation of the dose escalation or dose reduction scheme for afatinib; and administration of an afatinib 50 mg starting dose.

6 Review of Efficacy

Efficacy Summary

6.1 Indication:

Afatinib is indicated for the first line the treatment of patients with locally metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test

6.1.2 Demographics

Demographic characteristics were generally well balanced between the 2 treatment arms. The trial population was as intended for this trial and representative for patients with NSCLC with EGFR mutations. The overall trial population had a mean age of 60.3 years, two thirds of patients were female, more than two thirds of patients were from Asia and most patients never smoked (afatinib 67.4%; chemotherapy 70.4%).

TABLE 7: DEMOGRAPHICS BY TREATMENT

	Afatinib		Chemotherapy		Total	
Patients [N (%)]	230	(100.0)	115	(100.0)	345	(100.0)
Gender [N (%)]						
Male	83	(36.1)	38	(33.0)	121	(35.1)
Female	147	(63.9)	77	(67.0)	224	(64.9)
Age, mean (StD) [years]	60.5 (10.1)		59.9 (10.0)		60.3 (10.1)	
Age categories [N (%)]						
<65 years	140	(60.9)	71	(61.7)	211	(61.2)
≥65 years	90	(39.1)	44	(38.3)	134	(38.8)
Race group [N (%)]						
Caucasian	61	(26.5)	30	(26.1)	91	(26.4)
Eastern Asian	165	(71.7)	83	(72.2)	248	(71.9)
Other Asian	1	(0.4)	0	(0.0)	1	(0.3)
Other	3	(1.3)	2	(1.7)	5	(1.4)
Geographical region [N (%)]						
Europe	47	(20.4)	27	(23.5)	74	(21.4)
North America	2	(0.9)	0	(0.0)	2	(0.6)
Asia	160	(69.6)	83	(72.2)	243	(70.4)
Other	21	(9.1)	5	(4.3)	26	(7.5)
Smoking status [N (%)]						
Never smoked	155	(67.4)	81	(70.4)	236	(68.4)
Ex-smoker	70	(30.4)	32	(27.8)	102	(29.6)
Current smoker	5	(2.2)	2	(1.7)	7	(2.0)
Weight, mean (StD) [kg]	61.06 (12.87)		58.53 (12.08)		60.22 (12.65)	
Body mass index, mean (StD) [kg/m²]	23.855 (4.053)		22.963 (3.995)		23.557 (4.050)	
ECOG performance score at baseline [N (%)]						
0	92	(40.0)	41	(35.7)	133	(38.6)
1	138	(60.0)	73	(63.5)	211	(61.2)
2	0	(0.0)	1	(0.9)	1	(0.3)

Stratification factors

Randomization was stratified by EGFR mutation category (L858R vs. Del 19 vs. "Other") and Race (Asian vs. Non-Asian).

These stratification factors were well balanced across the treatment arms. The majority of patients were Asian (72.2% of patients in each treatment arm) and most patients had a tumor sample with an EGFR mutation categorized as either Del 19 alone (afatinib 49.1% of patients; chemotherapy 49.6%) or L858R alone (39.6% vs. 40.9%).

TABLE 8: STRATIFICATION FACTORS AT BASELINE BY TREATMENT

	Afatinib N (%)		Chemotherapy N (%)		Total N (%)	
Patients	230	(100.0)	115	(100.0)	345	(100.0)
EGFR mutation category						
L858R[1]	91	(39.6)	47	(40.9)	138	(40.0)
Del 19 alone	113	(49.1)	57	(49.6)	170	(49.3)
Other	26	(11.3)	11	(9.6)	37	(10.7)
Race category						
Asian	166	(72.2)	83	(72.2)	249	(72.2)
Non-Asian	64	(27.8)	32	(27.8)	96	(27.8)

The remaining 11.3% of patients in the afatinib arm and the remaining 9.6% of patients in the chemotherapy arm had a tumor sample with an EGFR mutation categorized as 'Other' (i.e., EGFR mutations other than L858R or Del 19). This subgroup of patients with 'Other' EGFR mutations was very small (afatinib 26 patients; chemotherapy 11 patients). This small subgroup of patients with 'Other' EGFR mutations was genetically heterogeneous; altogether 10 different genetic subtypes of 'Other' EGFR mutations were identified. The frequencies of patients with tumors with these EGFR mutations were not balanced between the treatment arms.

TABLE 9: PATIENTS WITH 'OTHER' EGFR MUTATIONS BY TREATMENT

	EGFR mutation	Afatinib N (%)		Chemotherapy N (%)		Total N (%)	
Patients		230	(100.0)	115	(100.0)	345	(100.0)
'Other' EGFR mutation							
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)

6.1.3 Subject Disposition

TABLE 10: DISPOSITIONS OF PATIENTS

	Afatinib N (%)	Chemotherapy N (%)	Total N (%)
Patients enrolled			1269
Patients not randomised			924
Patients randomised	230	115	345
Patients not treated	1	4	5
Patients treated	229 (100.0)	111 (100.0)	340 (100.0)
Treatment discontinued	164 (71.6)	111 (100.0)	275 (80.9)
Completed 6 courses of chemotherapy	n.a.	60 (54.1)	60 (17.6)
Progressive disease	133 (58.1)	19 (17.1)	152 (44.7)
Other AE	23 (10.0)	17 (15.3)	40 (11.8)
Non-compliance with protocol	1 (0.4)	4 (3.6)	5 (1.5)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Refusal to continue intake of study medication	6 (2.6)	11 (9.9)	17 (5.0)
Other	1 (0.4)	0 (0.0)	1 (0.3)
On treatment at the cut-off date	65 (28.4)	0 (0.0)	65 (19.1)

6.1.4 Analysis of Primary Endpoint(s)

Primary analysis of progression-free survival by central independent review
Overall, 152 patients (66.1%) in the afatinib arm and 69 patients (60.0%) in the chemotherapy arm experienced an event contributing to the primary PFS analysis, i.e., disease progression as determined by central independent review or death, after incorporating the primary censoring rules.
The primary endpoint was PFS, based upon the evaluation of tumor imaging according to the modified RECIST version 1.1 criteria and the clinical information provided for each patient as reviewed by independent radiologists and an independent oncologist. The primary analysis of PFS considered all data collected until the cut-off date (09 February 2012), i.e., the estimated date of the 217th PFS event as determined by central independent review. The trial was planned to achieve a statistical power of 90% for PFS.

Censoring rules for the primary PFS analysis
Patients without a PFS event prior to the cut-off date were censored at the date of the last evaluable tumor imaging. Patients who were randomized but never received any study medication were censored at the date of randomization unless they died before the second scheduled assessment. Further censoring rules had been specified in the clinical trial protocol.

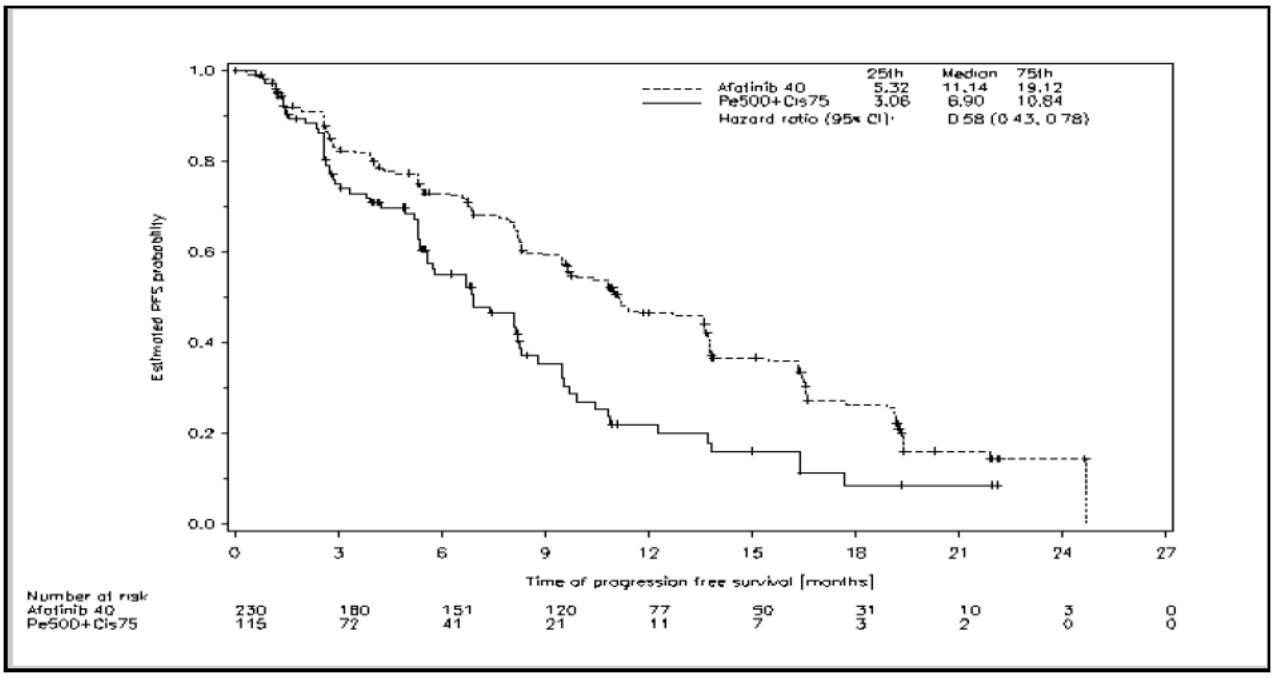
TABLE 11: EFFICACY RESULTS

AFATINIB VS. PEMETREXED/CISPLATIN BASED ON PRIMARY ANALYSIS (INDEPENDENT REVIEW)

	BRAND (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-free Survival		
Number of Death or Progression, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-free Survival (months)	11.1	6.9
95% CI	(9.6,13.6)	(5.4,8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test P-value*	0.0003	
Overall Survival		
Number of deaths, N (%)	116 (50.4%)	59 (51.2%)
Median Overall Survival (months)	28.1	28.2
95% CI	(24.6,33.0)	(20.7,33.2)
HR (95% CI)	0.91 (0.66, 1.25)	
Stratified Log-Rank Test P-value*	0.52	
Objective Response Rate (CR + PR)		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

*STRATIFIED BY EGFR MUTATION STATUS AND RACE. CR=COMPLETE RESPONSE; PR=PARTIAL RESPONSE

FIGURE 3: KAPLAN-MEIER CURVE FOR PFS BY INDEPENDENT REVIEW BY TREATMENT GROUP (ITT)



A total of 78 patients (33.9% of randomized patients) in the afatinib arm and 46 patients (40.0%) in the chemotherapy arm were censored in the primary PFS analysis. The main reasons for

censoring differed between the 2 treatment arms: In the afatinib arm, 23.0% of patients were censored because they were alive and progression-free at the cut-off date. In contrast, 28.7% of chemotherapy patients were classified as having been censored due to the start of a new anti-cancer therapy

Investigators stopped tumor imaging after they judged that a patient had progressed. Most patients then began additional anti-cancer treatment.

TABLE 12: SUMMARY OF CENSORING FOR PFS

Based on central independent review

A similar percentage of randomized patients in both treatment arms had PD due to target lesion progression (afatinib 39.3%; chemotherapy 34.8%), the subset of patients with target lesion progression and new lesions was also similar in both treatment arms (6.0% vs. 5.8%).
In addition, the percentage of patients with PD due to new lesions without target lesion progression was similar in both treatment arms (afatinib 22.7%; chemotherapy 23.2%).

Sensitivity analyses:
Progression-free survival was also analyzed based on investigator assessment, using the same censoring rules as for the primary PFS analysis. The point estimates and 95% CIs for the median of PFS of this analysis were consistent with the results of the primary PFS analysis.
The median PFS based on investigator assessment was 11.07 months in the afatinib arm and 6.70 months in the chemotherapy arm (HR 0.488; $p < 0.0001$), i.e., the difference in median PFS time was 4.37 months.

Differences between the central independent review and the investigator assessment were analyzed in more detail. Overall, central independent review and investigator assessment agreed in more than two-thirds of the cases in identifying a PFS event (concordant results in the afatinib

arm 80.5%; chemotherapy 72.2%). All measures of the treatment effect on PFS, i.e., HR, median PFS time, the difference in median PFS time between the 2 treatment arms, the estimated probability of being alive and progression-free over time, and the difference in Kaplan-Meier estimates between the two treatment arms were consistent, based on central independent review and based on investigator assessment. The consistency of the PFS results based on central independent review and based on investigator assessment indicates that, despite the differential censoring, the results of the primary analysis of PFS were in favor of the afatinib arm.

TABLE 13: COMPARISONS OF PFS

Based on central independent review and on investigator assessment

	Afatinib		Chemotherapy		Treatment effect between the 2 treatment arms	
	Central independent review	Investigator assessment	Central independent review	Investigator assessment	Central independent review	Investigator assessment
Hazard ratio vs. chemotherapy[1]					0.577	0.488
Median PFS time [months]	11.14	11.07	6.90	6.70	4.24	4.37
3 months %[2]	82.8	85.1	75.1	79.5	7.7	5.6
6 months %[2]	73.0	72.4	55.1	51.3	17.9	21.1
12 months %[2]	46.5	46.1	22.0	17.0	24.5	29.1
18 months %[2]	26.4	30.1	8.6	7.2	17.8	22.9

[1] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race.
[2] Estimated probability of being alive and progression-free at the respective landmark time point.

Both assessment methods were also compared with regard to the concordance in the date of progression. Most of the discordant PD dates were earlier by central independent review than by investigator assessment (afatinib 47.2%; chemotherapy 34.5%).

The impact of differences in censoring between the central independent review and the investigator assessment on the primary endpoint PFS was also analyzed. Investigators stopped tumor imaging after they detected PD in a patient. The potential for differential censoring arose when the central independent review classified such patients as not having progressed at the last available imaging time.

A sensitivity analysis was conducted to further assess the effect of censoring patients in the primary analysis who according to the investigator had progressed at the last imaging assessment. This analysis assigned PD at their next scheduled tumor assessment. The results of this analysis were intermediate between those of the central independent review and investigator assessment (HR 0.52; 95% CI 0.398, 0.682; p <0.0001).

Two additional analyses examined the impact of differences between the central independent review and the investigator assessments, i.e., assuming the extreme worst case or the symmetric worst case.

For the extreme worst case, if one assessment determined PD and the other assessment determined non-PD, patients randomized to treatment with chemotherapy were assigned as non-PD and patients randomized to treatment with afatinib were assigned as PD. If the assessments differed in the date of progression, the latest date was used for patients randomized to treatment with chemotherapy and the earliest date was used for patients randomized to treatment with afatinib. For the symmetric worst case, if one assessment determined PD and the other determined non-PD, patients were assigned as PD. If the assessments differed in the date of progression, the earliest date of progression was used.

Under both scenarios, median PFS was longer in the afatinib arm than in the chemotherapy arm. The treatment benefit of afatinib over chemotherapy was statistically significant for the symmetric worst case; the hazard ratio was similar to the result of the primary PFS analysis. For the extreme worst case scenario, the treatment benefit of afatinib over chemotherapy did not reach statistical significance. This was considered plausible given the bias towards chemotherapy introduced by this analysis.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints in this trial were
Objective response (defined as complete response [CR], or partial response [PR]) (time to objective response, duration of objective response) , Disease control (defined as a patient with objective response or stable disease [SD]) (duration of disease control)

TABLE 14: BEST OVERALL TUMOR RESPONSE

Based on central independent review

	Afatinib N (%)	Chemotherapy N (%)
Patients	230 (100.0)	115 (100.0)
Disease control	207 (90.0)	93 (80.9)
Objective response	129 (56.1)	26 (22.6)
Complete response	1 (0.4)	0 (0.0)
Partial response	128 (55.7)	26 (22.6)
Stable disease	62 (27.0)	61 (53.0)
Non-CR / Non-PD	16 (7.0)	6 (5.2)
Progressive disease	15 (6.5)	11 (9.6)
SD or Non-CR / Non-PD for less than 35 days	0 (0.0)	1 (0.9)
Non-evaluable	8 (3.5)	11 (9.6)

Overall survival (OS)

OS (months) was defined as the time from randomization to death, that was to be formally analyzed twice. The first analysis submitted with the NDA (at the time of the primary PFS analysis) and the second was to be performed at a time when more complete information was available on OS. To preserve the overall 1-sided α-level of 0.025, a Haybittle-Peto stopping boundary was used (p-value <0.0001) for the first analysis.

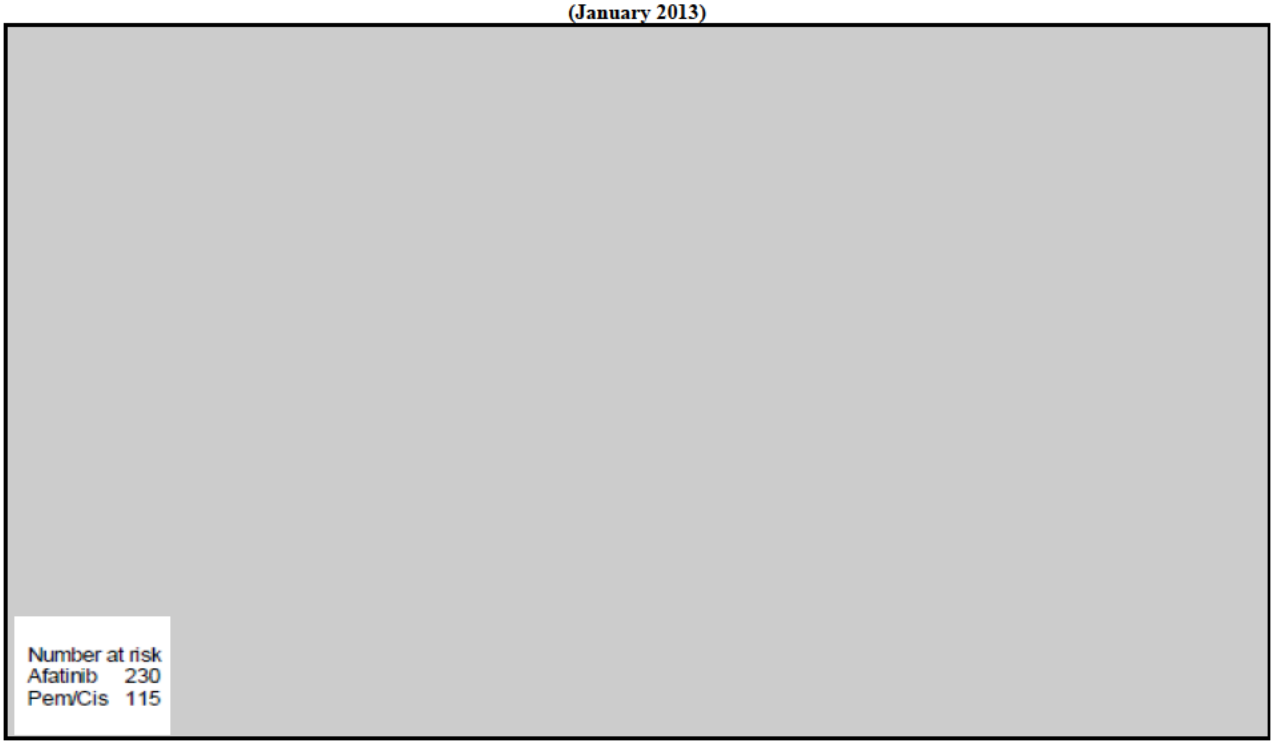
Patients alive at the cut-off date were censored at the date they were last known to be alive.

The clinical trial report for trial 1200.32 provided in the original NDA 201292 submission thus included a first interim analysis. An update of the interim analysis for trial 1200.32 was provided by the applicant in response to FDA request (based on ~50% of OS events).
The database was locked on January 21, 2013 for this analysis.
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, with the observed hazard ratio of 0.907 favoring afatinib.

The applicant stated that the final analysis from trial 1200.32 as specified by the protocol is expected around December 2013. This will be a Post Marketing Commitment (PMC).

FIGURE 4: KAPLAN-MEIER CURVES OF OVERALL SURVIVAL

(January 2013)



The OS data (as with other targeted therapy trials) may be confounded due to subsequent therapies. Two-thirds of afatinib patients received chemotherapy after discontinuation of afatinib. Conversely, more than two-thirds of patients randomized to chemotherapy were treated subsequently with an EGFR-TKI.

TABLE 15: SUMMARY OF SUBSEQUENT ANTI-CANCER THERAPY

	Afatinib N (%)	Chemotherapy N (%)
Patients	230	115
Discontinued study treatment	164 (100.0)	111 (100.0)
Any new anti-cancer therapy	118 (72.0)	89 (80.2)
Systemic anti-cancer therapy	114 (69.5)	89 (80.2)
Chemotherapy (or chemotherapy-based combination)	102 (62.2)	36 (32.4)
Platinum-based	80 (48.8)	7 (6.3)
Single agent chemotherapy	39 (23.8)	29 (26.1)
Platinum-based + bevacizumab	15 (9.1)	0 (0.0)
Single agent + bevacizumab	4 (2.4)	1 (0.9)
Other chemotherapy combinations	3 (1.8)	3 (2.7)
EGFR TKI	39 (23.8)	72 (64.9)
Erlotinib	24 (14.6)	39 (35.1)
Gefitinib	15 (9.1)	40 (36.0)
Afatinib	0 (0.0)	3 (2.7)[1]
Other	5 (3.0)	4 (3.6)
EGFR TKI-containing combination	2 (1.2)	8 (7.2)
Erlotinib in combination	2 (1.2)	6 (5.4)
Gefitinib in combination	0 (0.0)	2 (1.8)
Radiotherapy	18 (11.0)	9 (8.1)

6.1.7 Subpopulations

The treatment effect of afatinib was similar in relevant subgroups defined by gender, age, race, geographical region, and ECOG performance score at baseline.

Randomization was stratified by race (Asian, non-Asian) and mutation type (Del19, L858R, other).

The results were similar for Asians vs. non-Asians, however differences among EGFR mutation strata were observed. The pattern among strata for PFS paralleled that of OS, with the benefit of afatinib seen most clearly among patients with Del19. Patients classified into the catch-all "Other" categories showed a worse estimate of overall survival for afatinib compared with chemotherapy.

FIGURE 5: OVERVIEW OF SUBGROUPS WITH THE PRIMARY ANALYSIS OF PFS

FIGURE 6: OVERALL SURVIVAL WITHIN SUB-GROUPS

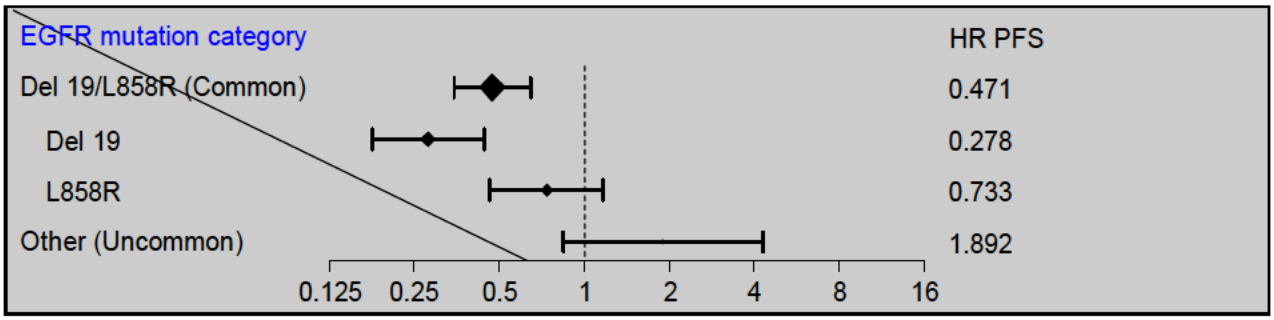
The majority of patients enrolled in pivotal 1200.32 had a tumor sample with an EGFR mutation categorized as either Exon 19 deletion(49%) or Exon 21 (L858R) [40%] while a small number (11%)] were of the "Other" mutation category.
This small cohort of 10 different genetic subtypes were distributed in an unbalanced way in the afatinib (N=26) and chemotherapy (N=11) treatment groups.

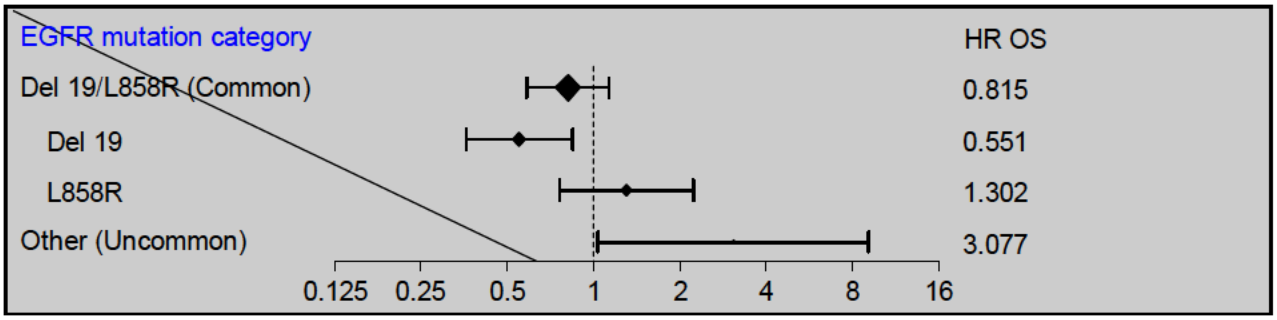
TABLE 16: EXPLORATORY EFFICACY RESULTS ANALYSES

Study 1200.32 by EGFR Mutation Subgroup

	BRAND	**Pemetrexed/Cisplatin**
Progression-free Survival, Patients with Del19 Mutation	**N=113**	**N=57**
Number of Death or Progression, N (%)	67 (59%)	35 (61%)
Median Progression-free Survival (months)	13.7	5.6
HR (95% CI)	0.28 (0.18, 0.44)	
Progression-free Survival, Patients with L858R Mutation	**N=91**	**N=47**
Number of Death or Progression, N (%)	63 (69%)	26 (55%)
Median Progression-free Survival (months)	10.8	8.1
HR (95% CI)	0.73 (0.46, 1.16)	
Progression-free Survival, Patients with Other Mutation	**N=26**	**N=11**
Number of Death or Progression, N (%)	22 (85%)	8 (73%)
Median Progression-free Survival (months)	2.8	9.9
HR (95% CI)	1.89 (0.84, 4.28)	

FIGURE 7: FOREST PLOT OF PFS AND OS FOR EGFR MUTATION CATEGORIES





On exploratory efficacy results analyses in the study by EGFR mutation within the pre-specified subgroup of patients with 'common' EGFR mutations [i.e., Exon 19 deletion or Exon 21 (L858R) mutation], the benefit seems to be driven by Exon 19 deletion subgroup while in patients with "Other" mutation category there seems to be a possible detrimental effect on PFS and OS.

There were 26 afatinib-treated patients in the "other" mutations subgroup with nine unique mutation patterns, none of these 26 patients achieved a complete response, and four achieved a partial response. No responses were seen in BRAND-treated patients with the following mutations T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (N=1), exon 20 insertion (N=6), and L861Q alone (N=3).

TABLE 17: ORR IN AFATINIB TREATED PATIENTS

(BASED ON INVESTIGATOR ASSESSMENT) IN THE "OTHER" EGFR MUTATION SUBGROUP

EGFR Mutations	Number of BRAND-Treated Patients	Number of patients with Partial Responses
L858R and T790M	5	1
L858R and S768I	2	1
S768I	1	1
G719X	3	1

Reviewer's Comment: There is limited data to support to use of afatinib in the less common mutations with a possible detrimental effect. Therefore, the indication for afatinib will be limited to patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

6.1.8 Analysis of Supportive Studies

1) **Study 1200.23 [LUX-Lung 1]** 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.

(b) (4)

Methods: Study 1200.23 was a Phase IIb/III randomized double-blind, multinational, multicenter study with 86 centers in 15 countries trial of Afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients who had failed erlotinib or gefitinib and had previously received 1 or 2 lines of chemotherapy.

The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg BRAND orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195). Patients were randomized to afatinib or placebo in a 2:1 ratio. Afatinib was to be administered at 50 mg/day starting dose, with the option to reduce to 40 mg/day or 30 mg/day, according to a pre-specified, protocol defined dose-reduction scheme based on toxicity grade.

The trial population was clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks and the tissue confirmation for EGFR mutations was not required.

FIGURE 8: STUDY SCHEMA STUDY 1200.23

Primary endpoint: Overall survival (OS),
Secondary Endpoints:

- Progression-Free Survival (PFS);
- Objective tumor response duration of disease control;
- Time to and duration of objective response;
- HRQoL, and
- PK

7.1.2 Demographics

A total of 585 patients were randomized and treated in the study. Demographic data were balanced between the two treatment groups.
The mean age was 58 years (range 30 to 85 years) and 68.7% were <65 years. The majority of patients were non-smokers (62.6%), and (92.3%) had a baseline ECOG PS of 0 or 1.

Prior to enrollment, all patients were to develop progressive disease following EGFR TKI.
The majority (91.8%) of patients had received a clinical benefit from prior EGFR TKI (45.0% had a best response of CR or PR, and 46.8% had SD).
All patients failed prior chemotherapy, with 99.5% having received at least one platinum-based chemotherapy regimen.

TABLE 18: SUMMARY OF DEMOGRAPHICS STUDY 1200.23

	Placebo	Afatinib	Total
Total randomized [N (%)]	195 (100.0)	390 (100.0)	585 (100.0)
Gender [N (%)]			
Male	78 (40.0)	159 (40.8)	237 (40.5)
Female	117 (60.0)	231 (59.2)	348 (59.5)
Baseline ECOG performance score [N (%)]			
0	53 (27.2)	92 (23.6)	145 (24.8)
1	127 (65.1)	268 (68.7)	395 (67.5)
2	15 (7.7)	30 (7.7)	45 (7.7)
Race/ethnicity [N (%)]			
Caucasian	72 (36.9)	121 (31.0)	193 (33.0)
Eastern Asian[1]	110 (56.4)	227 (58.2)	337 (57.6)
Other Asian	12 (6.2)	38 (9.7)	50 (8.5)
Other	1 (0.5)	4 (1.0)	5 (0.9)
Age at entry [years]			
Mean (Std[2])	59 (10.4)	58 (10.8)	58 (10.6)
Median (min, max[3])	59 (32, 82)	58 (30, 85)	58 (30, 85)
Age category 1 [N (%)]			
< 65 years	127 (65.1)	275 (70.5)	402 (68.7)
≥ 65 years	68 (34.9)	115 (29.5)	183 (31.3)
Smoking history [N (%)]			
Never smoked	121 (62.1)	245 (62.8)	366 (62.6)
<15 pack years + stopped >1 year before diagnosis	13 (6.7)	27 (6.9)	40 (6.8)
Current or other ex-smokers	61 (31.3)	118 (30.3)	179 (30.6)

EGFR mutation status: The mutation status of a patient was not required for study entry; however, if available, the mutation status was recorded. The trial was designed to clinically enrich for EGFR mutations, by requiring that all patients have at least 12 weeks of prior therapy with erlotinib or gefitinib. In the study, 186/585(32%) of the patients had tissue available for testing at either the local lab or central lab. Of the patients tested, 96 were positive for EGFR mutation, with the most common deletions being Del 19 and L858R. There was a high degree of imbalance between the two arms on this retrospective analysis of EGFR mutation status and a high degree of discrepancy was noted between the types of EGFR mutations reported by the central lab verses the local lab. Of the 141 patients with tissue test results, 68% were found to be positive for EGFR mutations.

Key Inclusion criteria:

1. Patients with pathologic confirmation of NSCLC Stage III-B (with pleural effusion) adenocarcinoma or Stage IV adenocarcinoma who have failed at least one but not more than two lines of cytotoxic chemotherapy (including adjuvant chemotherapy). One of the chemotherapy regimens must have been platinum-based.

2. Progressive disease following at least 12 weeks of treatment with erlotinib (Tarceva®) or gefitinib (Iressa®);

Analysis of Primary Endpoint(s)

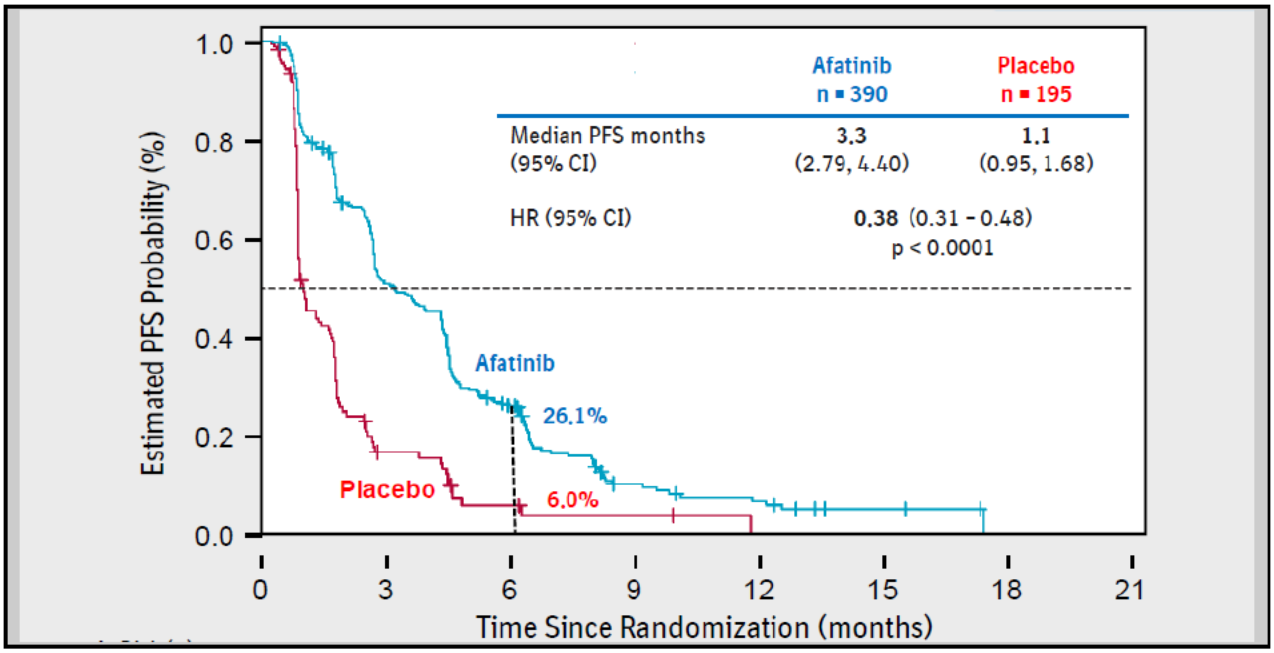
The primary analysis of OS was conducted when 358 deaths were reported; an Intent-to-Treat (ITT) approach was utilized for this analysis. The log-rank test, stratified by baseline ECOG performance score (0, 1 vs. 2) and gender (male vs.female), were used to test for the effect of afatinib at the one-sided 0.025 significance level.

The median OS for placebo was 12.0 months and for afatinib was 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35).

FIGURE 9: OVERALL SURVIVAL STUDY 1200.23

Secondary endpoints:
Progression free survival:
The median PFS time (by independent review) was 3.3 months for the afatinib group and 1.1 months for the placebo group (HR=0.38, p <0.0001).

FIGURE 10: PROGRESSION FREE SURVIVAL BY IRC



A higher proportion of afatinib-treated patients compared to placebo-treated patients showed a significant worsening for the symptoms of appetite loss, diarrhea, sore mouth, and dysphagia.
All 585 patients randomized were treated and included in the safety analyses.
More patients in the afatinib group received a reduced dose of study medication and at least one AE was reported in 86.2% of placebo patients and 98.5% of afatinib patients.

TABLE 19: ADVERSE EVENTS IN STUDY 1200.23

All grades		Afatinib	Placebo
	Diarrhea	86.9%	9.2%
	Rash/acne	78.5%	15.9%
	stomatitis	62.3%	4.6%
	nail effect	39.2%	1.0%
CTCAE Grade 3 or higher		**56.7%**	**24.6%**
	diarrhea	16.9%	
	Rash	9.0%	
Drug related Adverse Events		**95.4%**	**37.9%**
Study drug permanently discontinued due to AEs		17.9%	6.2%
Drug related Serious Adverse Events		10.0%	(0.5%)
AEs during the treatment period that led to death.		**11.0%**	**7.2%**

The study failed its primary endpoint of OS with the median OS for placebo of 12.0 months and afatinib of 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35). Secondary endpoint of PFS, based on independent review showed a median PFS time of 3.3 months for the afatinib group and 1.1 months for the placebo group (HR=0.38, p <0.0001).

Reviewer's comment: (b) (4) The study failed its primary end-point of OS and had a marginal PFS benefit as secondary end-point with significantly higher toxicity noted in the afatinib arm. In addition the population was not well defined. The tissue for EGFR mutations was tested in a small number of patients retrospectively and was not balanced between the treatment arms with a very high discrepancy noted in the results of tests from central laboratory vs. local laboratories.

2 **Study 1200.22 [LUX-Lung 2]:** A Phase II, single arm multicenter study of afatinib conducted at 7 centers in Taiwan and 23 in the United States in patients with non-small cell lung cancer with EGFR activating mutations.

All patients must have had biopsy samples available and the EGFR mutation status was determined in all patients prior to start of treatment with afatinib.

Primary Objectives: Efficacy of afatinib defined by

- the objective response rate (ORR) ,(complete response [CR], partial response [PR]) in patients with advanced non-small cell lung cancer (NSCLC) Stage IIIB or IV whose tumors harbor activating mutations within exon 18 to exon 21 of EGFR

Secondary Objectives:

- Safety,
- Pharmacokinetics

The study enrolled a total of 129 patients including 61 first-line patients (23 who received a starting dose of 40 mg and 38 who received a starting dose of 50 mg) and 68 second-line patients (7 who received a starting dose of 40 mg and 61 who received a starting dose of 50 mg).

The patients' mean age at study entry was 62 years, and most patients were Asian (86.8%), had never smoked (63.6%) and had an ECOG performance score of zero (64.3%).

The most common EGFR mutations identified were in-frame exon 19 deletions 40.3% [52/129]) and the exon 21 point mutation L858R 41.9% [54/129].

Study **1200.22** explored two afatinib starting doses (40 mg and 50 mg) in EGFR TKI-naïve patients with NSCLC with EGFR mutations. Data from this phase II trial of 129 EGFR TKI-naïve patients with NSCLC with EGFR mutations who had either received prior chemotherapy or received afatinib as first-line treatment in the first-line similar rates of response were seen regardless of the line of treatment, the starting dose (40 mg or 50 mg), by gender (men and women), by country (Taiwan and USA), by race (Asians and Caucasians), and by the type of the two most common EGFR mutations (Del19 and L858R).

AEs that reached Grade 3 were reported more frequently in the 50 mg starting dose group compared with the 40 mg starting dose group (58.6% vs. 43.3%).

TABLE 20: EFFICACY DATA (INDEPENDENT REVIEW)

Reviewer's Comment: (b) (4) *Response rates were similar with more Grade 3 toxicities noted in higher dose.*

3 **1200.42 [LUX-Lung 5]:** A 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.

The study comprised 2 stages: Part A and Part B. Patients were to be treated with 50 mg afatinib daily in Part A of the study and were to continue with this regimen as long as they tolerated therapy and did not undergo disease progression. Afatinib was to be dosed continuously over the entire treatment period, with a dose-reduction scheme (in a first step to 40 mg daily and in a second step to 30 mg daily) to be implemented if predefined drug-related AEs occurred.

Patients with a best response of stable disease or better for at least 12 weeks during afatinib monotherapy in Part A were eligible to be randomized into Part B of the trial. Upon disease progression, eligible patients were to be randomized to further treatment with either 40 mg afatinib daily plus 80 mg/m2 paclitaxel weekly (Part B, A+P) or the investigator's choice of chemotherapy (Part B, ICC). The investigator choice chemotherapy could only comprise of a single cytotoxic agent.

The primary endpoint

Part A
Progression-free survival (PFS) based on investigator assessment.
Secondary endpoint

- Objective tumor response
- time to and duration of objective response,
- overall survival (OS),
- tumor shrinkage, disease control and duration of disease control

The original protocol specified OS after treatment in Part B of the trial as primary endpoint. The primary endpoint was changed to PFS through Protocol Amendment 4 (dated 12 Jan 2011).

A total of 1299 patients were enrolled; of these, 1154 patients were entered into Part A of the trial and received at least 1 dose of afatinib.

The 1154 patients formed the treated set which was used for all efficacy and safety analyses. At the time of database lock for the interim analysis, 77.6% of patients had discontinued study treatment without being randomized into Part B,13.9% had discontinued treatment in Part A and had been randomized into Part B, and 8.6% of patients were still on treatment in Part A.

Of the treated patients, 56.7% were female. The mean age was 60.1 years. Similar proportions of patients were of Eastern Asian origin (42.5%) and Caucasian race (39.4%). At baseline, 29.5% of patients had an ECOG PS of 0, 59.9% had an ECOG PS of 1, and 10.6% had an ECOG PS of 2. The percentage of never-smokers was 53.6%, the remainder being ex-smokers or current smokers. The majority of patients (98.6%) had NSCLC stage IV; 1.3% of patients had stage IIIB disease (with pleural or pericardial effusions). The predominant tumor histology was

adenocarcinoma (85.4%); 7.9% of patients had squamous cell carcinoma. 64.6% of patients had received 3 or more previous chemotherapies. 68.0% of patients had received erlotinib only, 25.5% had received gefitinib only, 6.4% had received both erlotinib as well as gefitinib, and 1 patient (0.1%) had received neither erlotinib nor gefitinib.

The analysis of tumor samples for EGFR mutation status was not mandatory. Archived tumor biopsy specimens were to be obtained and were to be analyzed by a central laboratory, using the Therascreen® EGFRv2 kit (DxS Ltd./Qiagen).

For the interim analysis, results from central testing were available for 110 patients, including 84 patients with evaluable samples. Of the 84 patients, 49 patients (58.3%) were mutation positive and 35 patients (41.7%) were mutation negative. The most frequent mutation types were del19 in 27 of 49 mutation positive patients and L858R in 20 of 49 patients. One patient had both del19 and L858R; 1 patient had an 'other' mutation (G719X)

The interim analysis included 872 patients (75.6%) with PFS event, i.e. disease progression or death. Median PFS was 3.25 months (95% CI 2.85, 3.81). The percentage of patients with confirmed objective tumor response was 7.6% (95% CI 6.16, 9.31)

Reviewer's comment: At the time of Interim analysis of Part A of the study showed a PFS that was marginal with a marginal response rate. The Sponsor submitted an update on the study after the NDA submission informing the FDA of premature closure of the study based on DSMB recommendation due to safety concerns.

7 Review of Safety

Safety Summary

7.1 Methods

The evaluation of clinical safety is based on the treated set (TS) of patients, i.e. all patients who received at least 1 dose of study medication (over 3800 patients).

Data from the clinical program of afatinib were analyzed in different safety analysis sets (SAF), each representing a particular stratum of safety data and data from SAF-1 to SAF-5 were analyzed.

- SAF-1 and SAF-2 include EGFR tyrosine kinase inhibitor (TKI) treatment-naïve patients with NSCLC who received an afatinib starting dose of 40 mg;
- SAF-3 and SAF-4 include EGFR TKI pre-treated patients with NSCLC who received an afatinib starting dose of 50 mg;

- SAF-5 includes all patients with cancer who received any starting dose of afatinib (to identify infrequent but yet possibly clinically important adverse events associated with afatinib treatment).

SAF-1 and SAF-3 presented clinical data from randomized, controlled studies; SAF-2, SAF-4, and SAF-5 present pooled clinical study data.

For analyses of some of the important identified and potential risks, grouped MedDRA PTs of adverse events and standardized MedDRA queries (SMQs) were used.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

TABLE 21: CLINICAL TRIALS USED FOR SAFETY ASSESSMENT

Targeted patient population	Starting dose	SAF	Studies	Number of patients
EGFR TKI treatment- naïve patients (first line)	Afatinib 40 mg	SAF-1	1200.32	340
		SAF-2	1200.22[1], 1200.32, 1200.34, 1200.123	497
EGFR TKI pre-treated patients (last line)	Afatinib 50 mg	SAF-3	1200.23	585
		SAF-4	1200.23, 1200.33, 1200.41[2], 1200.42	1638
All patients with cancer	Any dose	SAF-5	47 cancer trials[3]	3865

7.1.2 Categorization of Adverse Events

- Gastrointestinal,
- Cutaneous,
- Interstitial lung disease (ILD),
- Hepatic,
- Opthomological and
- Cardiac.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

SAF-5 was the largest safety analysis set and was intended to facilitate the identification of infrequent adverse events. This SAF included the pooled data for all patients exposed to afatinib in cancer trials, irrespective of their cancer type, trial phase/design, afatinib starting dose, and whether afatinib was administered as monotherapy or as part of a combination regimen. The only afatinib-treated groups excluded from SAF-5 were: patients with head and neck cancer treated in

the double-blind, placebo-controlled trial 1200.131 (presented separately as SAF-6), healthy and non-cancer patient volunteers (SAF-7), patients treated under the named-patient use program (SAF-8.1), and patients from investigator-initiated studies (SAF-8.2). It was appreciated that SAF-5 would be heterogeneous with regard to patient tumor type, the treatment administered (monotherapy and combination therapy, using different afatinib starting doses, and varying treatment durations), and study design.

SAF-5 was primarily used to identify infrequent or unexpected yet possibly clinically important adverse events associated with afatinib treatment.

7.2 Adequacy of Safety Assessments in Trial 200.32

The evaluation of safety was based on the analysis of AEs, clinical laboratory evaluations, physical examinations, and vital signs. The treated set (TS) was used for safety analyses. The treated set included all randomized patients who were documented to have taken at least 1 dose of study medication (i.e., afatinib or pemetrexed /cisplatin). The afatinib TS included all randomized patients who were documented to have taken at least 1 dose of afatinib. All data collected until the cut-off date (09 February 2012) were included in the analyses.
During screening (i.e., from screening visit 1 to screening visit 2), the investigator had to report only AEs and SAEs related to the patient's participation in the trial. From the informed consent at screening visit 2 to the first FU visit, the investigator had to report all AEs and SAEs regardless of the causality; this included all deaths. From the first to the final FU visit, the investigator was to report all AEs and SAEs considered related to the study medication or procedures. Afterwards, only SAEs considered related to the study medication or procedures were to be reported. Death was an endpoint in this trial and was followed separately.

The analysis of AEs was based on the concept of treatment-emergent adverse events. AEs with onset after the first administration of study medication and within 28 days after the last administration of study medication were considered to be on-treatment.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics

Trial 1200.32: Exposure to study medication was assessed by treatment duration. Off-drug periods due to non-compliance or AEs between the first and last doses of study treatment administration were included as treatment time. For both treatment arms, 21 days were considered a treatment course.
Patients in the afatinib arm could receive treatment until progression of disease or until occurrence of treatment-related pre-specified AEs. In the pivotal study 1200.32, a total of 229 patients received afatinib treatment. At the time of data cut-off, the mean duration of treatment in the afatinib arm was 335.4 days; the median duration of treatment was 336.0 days. The maximum duration of treatment observed until the cut-off date was 827 days.
Overall, 111 patients received chemotherapy in this study. Patients in the chemotherapy arm could receive up to 6 courses of pemetrexed / cisplatin treatment, provided no progression of the disease or AEs requiring discontinuation of treatment occurred.

7.2.2 Explorations for Dose Response in Trial 1200.22 and 1200.32

In the study 1200.32, Afatinib was given as 40 mg once daily (q.d.) dose with possible dose escalation to 50 mg q.d. according to the protocol-defined dose escalation schema.

Patients with limited side effects during course 1 were to increase the afatinib dose to 50 mg once daily from course 2 onwards.

In the study, the patients treated with afatinib with a starting dose of 40 mg po per day:

- 16/230 patients were dose escalated to 50 mg.
- Of the 16 patients, 13 received afatinib 50 mg for 21 days or more, 10/16 patients needed at least one dose reduction and 5/10 needed 2 dose reductions.

No improved efficacy was noted in this small subset of patients who received the higher dose of afatinib on exploratory analysis.

Study 1200.22: was an open-label, single-arm trial, in which the efficacy and safety of Afatinib in EGFR-TKI naïve patients with locally advanced or metastatic lung adenocarcinoma with EGFR mutations was assessed. Patients were enrolled in the first-line (n=61) or second-line setting (n=68) after failure of first-line chemotherapy. The trial enrolled 129 patients who received either 40 mg (n=30) or 50 mg (n=99) of Afatinib orally once daily.

In the study the 2 starting doses of 40 mg and 50 mg showed similar efficacy, with a better tolerability observed with the 40 mg starting dose.

7.3 Major Safety Results

Pivotal NSCLC trial (1200.32), SAF-1

The SAF-1 set comprised all patients in the pivotal NSCLC trial (1200.32), who received at least 1 dose of study medication. These data informed on the safety profile for first-line treatment with the afatinib 40 mg starting dose administered once daily as continuous monotherapy, in EGFR TKI-naïve patients with locally-advanced or metastatic NSCLC with EGFR mutations.

Patients who showed good tolerability to afatinib in the first 21-day treatment course could undergo dose escalation to 50 mg once daily; patients experiencing intolerable side effects at any time during treatment were to undergo up to 3 protocol-defined dose-reduction steps (to the lowest dose of 20 mg once daily).

All patients in the afatinib arm (100.0%) and (98.2%) in the chemotherapy arm reported at least 1 AE during the study. Furthermore, almost all patients in both treatment arms reported drug-related AEs (afatinib 99.6%; chemotherapy 95.5%).

7.3.1 Deaths

On-treatment, (13) 5.7% of patients in the afatinib arm had AEs with fatal outcome. In addition, 1 patient who had received afatinib died of sepsis more than 28 days after the discontinuation of study medication; this was reported by the investigator as an SAE. The reported causes of death were progressive disease (6 patients), pulmonary toxicity (3 patients including 2 with Interstitial Lung Disease), sepsis (1 patient), pneumonia (1 patient) and 2 patients where cause of death was unknown.

In the chemotherapy arm, 2.7% of patients had fatal AEs on treatment and no death was reported as an SAE during the post-study period.

FATAL AE'S ON-TREATMENT OR THE POST-STUDY PERIOD

	Afatinib N (%)	Chemotherapy N (%)
Patients	229 (100.0)	111 (100.0)
Patients with fatal AEs	14 (6.1)	3 (2.7)
During the on-treatment period[1]	13 (5.7)	3 (2.7)
During the post-study period[2]	1 (0.4)	0 (0.0)

[1] AEs with onset after the first administration of study medication and within 28 days after the last administration of study medication were considered to be on-treatment.
[2] AEs with onset more than 28 days after the last administration of study medication were considered to be post-study.

Based on the reported preferred terms, all deaths during the on-treatment period were attributed to the underlying cancer disease by the PI and the applicant, except for 2 patients in the afatinib arm who died of infections and 3 patients (2 in the afatinib arm and 1 in the chemotherapy arm) who died of unknown causes.

FATAL AE'S WITH ONSET DURING THE ON-TREATMENT PERIOD

	Afatinib N (%)	Chemotherapy N (%)
Patients	229 (100.0)	111 (100.0)
Patients with fatal AEs	13 (5.7)	3 (2.7)
Infections and infestations	2 (0.9)	0 (0.0)
Pneumonia	1 (0.4)	0 (0.0)
Sepsis	1 (0.4)	0 (0.0)
Neoplasm benign, malignant and unspecified (including cysts and polyps)	4 (1.7)	1 (0.9)
Neoplasm malignant	1 (0.4)	1 (0.9)
Metastases to central nervous system	1 (0.4)	0 (0.0)
Metastases to meninges	1 (0.4)	0 (0.0)
Neoplasm progression	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (1.3)	1 (0.9)
Acute respiratory distress syndrome	2 (0.9)	0 (0.0)
Dyspnoea	1 (0.4)	1 (0.9)
General disorders and administration site conditions	4 (1.7)	1 (0.9)
Death	2 (0.9)	1 (0.9)
Disease progression	2 (0.9)	0 (0.0)

Case narratives were provided by the applicant for all patients in the afatinib arm who experienced drug related fatal events; for all patients in the afatinib arm who experienced a liver-related event at the time of death; and for all patients in the chemotherapy arm who died not due to disease progression. Most of the patients died had confounding medical factors noted.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were reported for 29% of patients in the afatinib arm, 27.1% of patients required hospitalization and 5.7% of patients had SAEs with fatal outcome. In the chemotherapy arm, a total of 22.5% of the patients had SAEs, 18.0% of patients required hospitalization and SAEs with fatal outcome were reported for 2.7% of patients.

The most frequently reported SAE was diarrhea (6.6% of patients), vomiting (4.8%) dyspnea, fatigue and hypokalemia (1.7% each).

Six patients in the afatinib arm (2.6%) were reported with SAEs of CTCAE Grade 4; 3 of these patients had hypokalemia. In 2 of the 3 patients, hypokalemia was associated with diarrhea. Other SAEs comprised dehydration (3 patients), acute pre-renal failure (1 patient), and hypernatremia (1 patient). One patient in the afatinib arm had an SAE ‘liver function test abnormal.
In the chemotherapy arm, 22.5% of patients experienced SAEs; in 3.6% of patients and the most frequent SAEs were vomiting, fatigue, and pleural effusion (2.7% of patients each).

7.3.3 Dropouts and/or Discontinuations

In the afatinib arm, 57% of patients experienced AEs that led to dose reduction most frequent adverse reaction being diarrhea (20%), rash/acne (19%), nail effects (13%), and stomatitis (10%).

In the 1200.32 trial 14.0% of patients in afatinib arm experienced AEs that led to permanent discontinuation of trial treatment and the most frequent adverse reactions were diarrhea (1.3%), ILD, (0.9%), and nail effects (0.9%).

In the chemotherapy arm, 16.2% of patients experienced AEs leading to dose reduction and 15.3% of patients experienced AEs leading to permanent treatment discontinuation.

7.3.4 Significant Adverse Events

ADVERSE REACTIONS REPORTED IN ≥10% OF AFATINIB TREATED PATIENTS IN STUDY 1200.32

	BRAND n=229			**Pemetrexed/Cisplatin n=111**		
Adverse Reaction	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Gastrointestinal disorders						
Diarrhea	96	15	0	23	2	0
Stomatitis	71	8	0	15	1	0
Cheilitis	12	0	0	1	0	0
Skin and subcutaneous tissue disorders						
Rash	90	16	0	11	0	0
Pruritus	21	0	0	1	0	0
Dry skin	31	0	0	2	0	0
Infections and infestations						
Paronychia	58	11	0	0	0	0
Cystitis	13	1	0	5	0	0
Metabolism and nutrition disorders						
Decreased appetite	29	4/4.8	0	55	4	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	17	0	0	2	0	0
Rhinorrhea	11	0	0	6	0	0
Investigations						
Weight decreased	17/17.9	1	0	14	1	0
General disorders and administration site conditions						
Pyrexia	12	0	0	6	0	0
Eye disorders						
Conjunctivitis	11	0	0	3	0	0

7.3.5 Laboratory Findings

Safety laboratory examinations during this trial included hematology, biochemistry, and urinalysis. Blood and urine samples were collected at the time points specified in the flow chart in the protocol and analyzed in a laboratory facility at or close to the investigational site. The clinical laboratory evaluation focused on low values for hemoglobin, WBC count, neutrophils, lymphocytes, platelets, potassium, sodium, and GFR and on high values for creatinine, AST, ALT, total bilirubin, ALKP, and CPK.

Laboratory parameters were graded according to CTCAE version 3.0 and were analyzed descriptively for values at baseline, last value on treatment, and changes from baseline.

Liver function test abnormalities (including elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed in patients receiving afatinib. These elevations were mainly transient and did not lead to discontinuation of treatment.

ADVERSE REACTIONS OF LABORATORY ABNORMALITIES FROM THE INVESTIGATIONS SOC REPORTED IN ≥5% OF AFATINIB -TREATED PATIENTS IN STUDY 1200 32

	BRAND n=229		**Pemetrexed/Cisplatin n=111**	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Preferred term	%	%	%	%
Alanine aminotransferase increased	10.9	1.7	3.6	0.0
Hypokalaemia[1]	10.5	4.4	4.5	3.6
Aspartate aminotransferase increased	8 3	1.7	1.8	0.9

7.4 Supportive Safety Results

7.4.1 Afatinib integrated safety database

This evaluation of clinical safety is based on the treated set (TS) of patients, i.e. all patients who received at least 1 dose of study medication (over 3800 patients), including more than 1638 NSCLC patients treated with afatinib 50 mg monotherapy and more than 497 NSCLC patients treated with afatinib 40 mg monotherapy. Data from the clinical programe of afatinib were analyzed in different safety analysis sets (SAF's), each representing a particular stratum of safety data.

The safety evaluation of afatinib is based on the data from more than 3800 patients

SAF-1 and SAF-2 include EGFR tyrosine kinase inhibitor (TKI) treatment-naïve patients with NSCLC who received an afatinib starting dose of 40 mg; SAF-3 and SAF-4 include EGFR TKI pre-treated patients with NSCLC who received an afatinib starting dose of 50 mg; SAF-5 includes all patients with cancer who received any starting dose of afatinib (to identify infrequent but yet possibly clinically important adverse events associated with afatinib treatment).

For analyses of some of the important identified and potential risks, grouped MedDRA PTs of adverse events and standardized MedDRA queries (SMQs) were used.

Diarrhea (including dehydration and renal impairment secondary to diarrhea)
Diarrhea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. A high proportion of afatinib-treated patients (>85%) experienced diarrhea, and for about 20% of patient's diarrhea necessitated afatinib dose interruption and reduction
As a consequence of diarrhea and associated dehydration, pre-renal azotemia and renal insufficiency may be observed.
No grade 5 adverse events of diarrhea were reported in patients treated with afatinib in clinical trials; however, 3 patients were reported to have a fatal outcome in the named-patient use program as a consequence of diarrhea.
In Pivotal study 1200.32 Diarrhea a significantly higher proportion of patients in the afatinib 40 mg group was reported with diarrhea as compared with the chemotherapy group (96.1% vs. 22.5%, respectively; hazard ratio 11.49, nominal p≤0.0001). 14.8% of patients experienced CTCAE grade 3 diarrhea and 6.6% of these events were classified as SAEs. In addition, 20%

needed dose reduction or interruption and 90% needed therapy with anti-diarrheal treatments and/or intravenous hydration.

Rash/acne

Rash is a known mechanistic side effect associated with EGFR inhibition and EGFR TKIs.
A high proportion of afatinib-treated patients (>75%) experienced rash/acne, and 10% to 20% of patientneed afatinib dose interruption and reduction for rash/acne. The majority of patients needed therapy for rash/acne.
6 patients experiencing events that were grade 3; of these, 2 patients each experienced exfoliative rash, Stevens-Johnson syndrome, and toxic skin eruption.
In one patient, the Stevens-Johnson syndrome began 10 days after stopping afatinib, was reported as non-serious and considered not related to afatinib treatment; the patient was also receiving multiple concomitant mediations, including vancomycin.
In the other patient with Stevens-Johnson syndrome, the patient recovered from all events. Both events of toxic skin eruption were non-serious and coded from the reported term of toxiderma. One of these patients discontinued afatinib treatment due to the event but at the same time underwent disease progression while the other required dose reduction but was able to continue afatinib therapy.
In Pivotal study 1200.32, a significantly higher proportion of patients in the afatinib 40 mg group was reported with rash/acne as compared with the chemotherapy group (90.0% vs. 10.8%, respectively; hazard ratio 17.97, $p \leq 0.0001$).
For 74% of patients receiving afatinib 40 mg the severity of rash/acne was CTCAE grade 1 or 2, for 16% CTCAE grade 3, and few cases were classified as SAEs (0.4% of patients).
In the afatinib group, 19.2% of patients underwent afatinib dose reduction to manage their rash/acne. Therapy was required in 82.1%. No patients in SAF-1 discontinued afatinib treatment due the rash/acne.

Interstitial lung disease

ILD is a rare and serious (potentially fatal) adverse event reported with other EGFR TKIs.
59 patients who experienced 60 events were identified from the broad SMQ search. Thirty-eight patients (1.0%) experienced grade ≥3 ILD-like events, 15 cases (0.4%) of which were fatal. Of the 59 cases identified using the broad ILD SMQ, based on causality assessment by the investigator and/or the company, 28 cases were considered related to the study drug and 31 cases were considered not related to the study drug.
The overall ILD frequency calculated by including all cases identified using the broad ILD SMQ was 1.5%; the frequency of related cases was 0.7%.
Asians made up 40% of the total number of patients exposed to afatinib at any dose; and slightly more than half (54%) of patients identified using the broad ILD SMQ in SAF-5 were Asian. Of all events identified using the broad SMQ search, 6 of 59 cases were reported from Japan, 4 of which were assessed as drug related.

In pivotal study 1200.32, 7 patients (3.1%) in the afatinib 40 mg group were identified from the broad SMQ search, none in the chemotherapy group. Four of 7 cases were considered not related to afatinib (lung infiltration, pneumonitis, radiation pneumonitis, and 1 case of fatal acute

respiratory distress syndrome deemed secondary to pneumonia). Three of the 7 cases were considered related to afatinib comprising 1 fatal case of acute respiratory distress syndrome and 2 ILD cases. Grade ≥3 ILD-like events were experienced by 3 patients (1.3%) and comprised acute respiratory distress syndrome (2 fatal cases) and ILD (1 case)

Keratitis
29 patients (0.8%) were reported with corneal disorders with the most common preferred term being keratitis (17 patients [0.4%]). Of these 2 patients were reported with grade 3 events and no patients were reported with events of grade >3; 1 patient was reported with keratitis considered not related to afatinib treatment, and 1 patient discontinued due to drug-related keratitis which resolved. No events of corneal perforation were reported

Decreased LVEF/heart failure
The potential for HER2 inhibition with the monoclonal antibody trastuzumab to induce cardiac adverse events necessitates that the cardiac safety profile is carefully assessed for agents that act via a similar mechanism, such as the EGFR/HER2 TKIs. Monitoring LVEF at baseline and at routine intervals was required in all afatinib clinical trials.

Potentially clinically-significant changes in LVEF were defined as a ≥20% reduction from baseline and a decrease to below the institutional lower limit of normal (or to below 50% if the institutional lower limit of normal was not known).

Twenty-four (32 patients overall in SAF-5) experienced potentially clinically significant LVEF reductions.
Six patients were identified from the heart failure SMQ with a fatal heart failure event.

- Two patients experienced acute left ventricular failure considered drug-related, comprising 1 patient during treatment with afatinib 40 mg in trial 1200.23 and 1 patient during treatment in trial 1200.42.
- One patient experienced drug-related acute pulmonary edema during treatment with afatinib 40 mg with paclitaxel and cisplatin in trial 1200.37.
- The remaining 3 cases were considered not related to the study medication and comprised 1 patient with cardiac failure in trial 1200.23, 1 patient with cardiopulmonary failure being treated with afatinib 50 mg in trial 1200.42 and 1 patient with cardiopulmonary failure in trial 1200.28.

In pivotal study 1200.32, 3 patients treated with the afatinib 40 mg starting dose and 1 patient treated with chemotherapy were identified by these criteria as having a potentially clinically-significant reduction in LVEF. For the 3 afatinib-treated patients LVEF reductions were transient and resolved despite ongoing afatinib therapy.

Hepatic failure Hepatic impairment has been observed with EGFR TKIs; a background risk of hepatic toxicity including liver metastases needs to be considered. Hepatic failure has been included in the labeling of all EGFR TKIs.

In the larger SAF-5 set, 10.1% of patients (95% CI 9.1%, 11.1%) were reported with adverse events indicative of hepatic impairment. Overall 7 patients in SAF-5 experienced fatal hepatic adverse events: of these 3 patients experienced hepatic adverse events that were considered drug-related.
One patient in trial 1200.23 experienced fatal events of acute renal failure and acute hepatic failure that began approximately 10 days after starting afatinib treatment, and occurred concomitantly with infectious hepatitis; 1 patient with cytolytic hepatitis and disease progression in trial 1200.42; and 1 patient with congestive heart failure and hepatic failure in trial 1200.42. The four remaining fatal hepatic adverse events were considered not related to the study medication but were associated with progressive disease and/or sepsis

Evaluation of laboratory parameters
To further analyze hepatic events, laboratory parameters were considered in greater detail.
In pivotal study 1200.32, comparable proportions of patients in both treatment groups were reported with an adverse event indicative of hepatic impairment (17.5% of patients in the afatinib 40 mg group and 11.7% in chemotherapy group; hazard ratio 0.83, p = 0.5858).
Two patients in the chemotherapy group and 8 patients in the afatinib group had ALT elevations to >5x ULN; all elevations were transient and no patients discontinued treatment due to the event.
Pooled clinical trial data indicate that only patients with impaired hepatic function at baseline had an increased likelihood of experiencing elevated ALT or AST levels or an adverse event of hepatic impairment.

Pancreatitis
Pancreatitis is listed as an uncommon adverse event identified during the use of the EGFR TKI gefitinib, and is listed as common adverse event for trastuzumab.
Cases of pancreatitis were identified by the narrow SMQ for acute pancreatitis.
A total of 14 adverse events of (acute) pancreatitis were identified in 13 patients in SAF-5 (n = 3865). No specific risk factors for pancreatitis were identified. Nine of the 14 occurrences of pancreatitis resulted in hospitalization; treatment resulted in full recovery for all patients with a documented outcome, except for 1 patient where pancreatitis was attributed to cancer progression. One additional case of pancreatitis was reported from a patient in the named patient use program.

7.4.2 Electrocardiograms (ECGs)

The effect of multiple doses of afatinib (50 mg once daily) on the QTc interval was evaluated in an open label, single arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study **1200.22** explored 2 afatinib starting doses (40 mg and 50 mg) in EGFR TKI-naïve patients with NSCLC with EGFR mutations. Data from this phase II trial of 129 EGFR TKI-naïve patients with NSCLC with EGFR mutations.
In this study AEs that reached Grade 3 were reported more frequently in the 50 mg starting dose group compared with the 40 mg starting dose group (58.6% vs. 43.3%).

7.5.2 Time Dependency for Adverse Events

None noted

7.5.3 Drug-Demographic Interactions

Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

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 Study 1200.32, 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.

7.5.5 Drug-Drug Interactions

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers
Administration of a strong P-gp inhibitor (ritonavir at 200 mg BID) 1 hour before administration of BRAND increased systemic exposure to afatinib by 48%. There was no change in afatinib exposure when the inhibitor was administered simultaneously with or 6 hours after BRAND. BRAND should be administered at the same time as a P-gp inhibitor (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone).

Concomitant treatment with a strong P-gp inducer (rifampicin at 600 mg once daily for 7 days) decreased exposure to afatinib by 34%. Other strong P-gp inducers (such as carbamazepine, phenytoin, phenobarbital, and St. John's Wort) may also decrease exposure to afatinib.

In vitro data indicated that drug-drug interactions with afatinib due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely.

Refer to Clinical Pharmacology review for details

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted with afatinib. No clear mutagenic or genotoxic potential was identified in *in vitro* assays or in the *in vivo* bone marrow micronucleus assay, Comet assay, or a 4-week oral mutation study in the Muta™ Mouse.

In a dedicated fertility study, male and female rats received afatinib daily by oral administration at doses of 4, 6, or 8 mg/kg. In males at doses of 6 mg/kg (approximately equal to exposure by AUC in patients at the recommended dose) or greater there was an increase in the incidence of low or no sperm count, though overall fertility was not affected; decreases in sperm count were supported by findings of atrophy in the testes, seminal vesicles, and prostate in general toxicology studies. In females, at the high dose of 8 mg/kg (approximately 0.6 times the exposure by AUC in patients at the recommended dose) there was a mild decrease in the number of corpora lutea along with mild increases in pre-implantation loss and early resorptions. In a 4-week general toxicology study, female rats had decreases in ovarian weights at all dose levels; organ weight had not fully recovered by the end of a 2-week recovery period

7.6.2 Human Reproduction and Pregnancy Data

Afatinib approval will receive Pregnancy Category D

Based on its mechanism of action, afatinib can cause fetal harm when administered to a pregnant woman. Afatinib was embryotoxic and abortifacient at late gestational stages in rabbits at doses greater than 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose). In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC of the recommended human dose) there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryofetal development study in rats there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure at the recommended human dose).

Nursing Mothers
It is not known whether this drug is present in human milk. Afatinib was present in the milk of lactating rats at concentrations 80-150 folds higher than those found in plasma from 1 to 6 hours after administration.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of afatinib in pediatric patients have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose was reported in two healthy adolescents each of whom ingested 360 mg of BRAND (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase (<1.5 times ULN). Both subjects recovered.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/References

1. American Cancer Society: Cancer Facts and Figures 2011. Atlanta, Ga: American cancer Society, 2011.
2. Jemal A, Siegel R, Ward E, et al. (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
3. Ries L, Eisner M, Kosary C, et al., eds.: Cancer Statistics Review, 1975-2002. Bethesda, MD: National Cancer Institute, 2005
4. Beasley MB, Brambilla E, Travis WD The 2004 World Health Organization classification of lung tumors. Semin Roentgenol 40:90–97(2005)
5. Mok TS, Wu YL, Thongprasert S, et al.: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361 (10): 947-57, 2009.
6. Zhou C, Wu Y-L, Chen G, et al: Efficacy results from the randomized phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin plus gemcitabine in Chinese advanced non-small cell lung cancer patients with EGFR activating mutations. 35th ESMO Congress. Abstract LBA13. Presented October 9, 2010.
7. Pao W, Miller VA, Politi KA, Rieley GJ, Somwar R, Zakowski MF et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005;2:1-11.
8. Kobayashi S, Boggon TJ, Dayaram T, Jaenne PA, Kocher O. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2005;352(8):786-792.
9. Pao W, Balak MN, Riely GJ, Li AR, Zakowski MF, Ladanyi M et al. Molecular analysis of NSCLC patients with acquired resistance to gefitinib or erlotinib. 42nd Ann Mtg of the Am Soc Clin Oncol (ASCO), Atlanta, 2-6 June 2006. J Clin Oncol 2006; 24 (18S) Suppl Abstr 7078.
10. Mitsudomi T, Kosaka T, Endoh H, Yoshida K, Hida T, Tsubi M et al. Mutational analysis of the EGFR gene in lung cancer with acquired resistance to gefitinib. 42nd Ann. Mtg of the Am Soc Clin Oncol (ASCO), Atlanta, 2-6 June 2006. J Clin Oncol 2006;24(18S)(Suppl)Abstr 7074
11. Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW et al. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci USA 2005;102(21):7665-7670.

9.2 Labeling Recommendations

The label will be finalized after input from the applicant

9.3 Advisory Committee Meeting

Oncology Drug Advisory Committee meeting was not held however; we plan to discuss the NDA "indication sought" with two outside consultants who are Lung Cancer experts (Drs. Steven Krasnow from the Washington D.C Veteran Affairs Hospital and Dr Arun Rajan from the thoracic team at NCI) and a patient representative.

In addition we discussed the limitation of the afatinib in patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) and limitation of afatinib use in patients whose tumors have other EGFR mutations at a CDERCenter Director's Briefing .

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/s/

SHAKUNTALA M MALIK
04/22/2013

CLINICAL FILING CHECKLIST FOR NDA 201292

NDA Number: 201292 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc. **Stamp Date:** November 15th, 2012

Drug Name: Afatinib **NDA Type:** 505(b)(1) NME

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1) NME
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

CLINICAL FILING CHECKLIST FOR NDA 201292

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Study Number: 1200.32 Study Title: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harboring an EGFR-activating mutation **Arms:** 2 **Sample Size**: Arm A= 230, Arm B=115 **Indication:** 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 (1) Supportive Studies : 1)1200.22: A Phase II single-arm trial of BIBW 2992 in non-small cell lung cancer patients with EGFR activating mutations 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 3) 1200.42: Phase III randomised trial of BIBW 2992 plus weekly paclitaxel versus investigator's choice of chemotherapy following BIBW 2992 monotherapy in non-small cell lung cancer patients failing previous erlotinib or gefitinib treatment				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				SPA Non-Agreement Letter for IND 67,969, BIBW 2992 was issued by the FDA on April 17, 2009. On May 27, 2009 in a follow up response the FDA stated "whether PFS is acceptable as the primary endpoint will be a review issue. The FDA added that in general, a substantial, robust improvement in PFS that is clinically meaningful

CLINICAL FILING CHECKLIST FOR NDA 201292

	Content Parameter	Yes	No	NA	Comment
					and statistically persuasive, and has an acceptable risk benefit profile may be considered for regulatory decision making"
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				QT team to address
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Reviewer's guide included
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?				This is a review issue
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 201292

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		The applicant has committed to provide them if FDA requests them anytime during the review process
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

CLINICAL FILING CHECKLIST FOR NDA 201292

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

NONE

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

SHAKUNTALA M MALIK
01/09/2013