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RESEARCH**

APPLICATION NUMBER:

201292Orig1s000

SUMMARY REVIEW

Division Director Summary Review (Amended)

Date	July 11, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	201292
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	November 15, 2012
PDUFA Goal Date	July 15, 2013
Proprietary Name / Established (USAN) Name	GILOTRIF Afatinib
Dosage Forms / Strength	Tablet / 20, 30, and 40 mg tablets
Proposed Indication(s)	“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 [see <i>Clinical Studies (14.1, 14.2)</i>]”
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Shakun Malik
Statistical Review	Jonathan Norton
Pharmacology Toxicology Review	Denali (Dubravka) Kufirin & Shawna Weis
CMC ONDQA Reviews	Haripada Sarker, Li-Shan Hsieh, Ali Al Hakim
Biopharmaceutics Review	Elsbeth Chikhale
Clinical Pharmacology Review	Runyan Jin
OPDP Reviews	Quynh-Van Tran (DPDP) & Karen Dowdy (DMPP)
OSI Review	Lauren Iacono-Connors
CDTL Review	Anthony Murgo
OSE/DMEPA Consult	James Schlick
OSE/DRISK Consult	Suzanne Robottom
Maternal Health Consult	Tammie Brent Howard

OND=Office of New Drugs
 CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology
 OPDP= Office of Prescription Drug Promotion
 DMPP=Division of Medical Policy Programs
 OSI= Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE=Office of Surveillance and Epidemiology
 DRISK=Division of Risk Management
 DMEPA= Division of Medication Error Prevention and Analysis

Division Director Summary Review

1. Introduction

Afatinib (Gilotrif; Boehringer Ingelheim Pharmaceuticals, Inc. (BI)) is a tyrosine kinase inhibitor which covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in down regulation of ErbB signaling. Nonclinical studies demonstrated that at clinically achievable concentrations, afatinib inhibited phosphorylation or proliferation in cell lines bearing wild-type EGFR or bearing common mutations in EGFR (i.e., exon 19 deletions or exon 21 L858R substitution). In addition, at concentrations achieved transiently with afatinib, inhibition was also observed noted in cell lines with a secondary T790M mutation and either exon 19 deletion or exon 21 L858R mutation.

The clinical development program in NSCLC included two trials conducted in patients with NSCLC containing an EGFR mutation as detected by a PCR-based investigation assay who had not received prior treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and two trials conducted in patients who were “clinically enriched” for EGFR mutations but had not been tested and who had received treatment with an EGFR TKI. The latter trials were considered flawed in that the clinical enrichment strategy did not correlate with subsequent EGFR mutation testing. In addition, of the two trials conducted in this population, the randomized trial in this population failed to meet its primary endpoint. Therefore, only studies conducted in patients who were screened for EGFR mutations prior to enrollment were evaluated for efficacy claims,

The primary trial supporting approval was Study 1200.32 (LUX-3), a randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung. In this trial, 345 patients 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 vs. exon 21 L858R vs. other) and race (Asian vs. non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). The key secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). The characteristics for the study population were 65% female, median age of 61 years, baseline ECOG performance status of 0 (39%) or 1 (61%), and 26% Caucasian and 72% Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to afatinib [HR 0.58 (0.43, 0.78), $p < 0.001$], with median PFS of 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. There was no statistically

significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis [HR 0.91 (0.66, 1.25), p=0.55], with a median survival of 28 months in each arm. As the median survival is longer than anticipated with platinum-doublet chemotherapy, cross-over to the afatinib arm may have obscured possible effects of afatinib on survival. In addition, the afatinib also had substantially higher overall response rates (50% vs. 19%). In exploratory analyses, treatment effects varied by the underlying EGFR mutation, with the greatest treatment effect in the subgroup with exon 19 deletions for both PFS and OS and a more modest, but clinically important effect for those with exon 21 L858R substitutions, but with apparent harmful effects for patients with uncommon EGFR mutations receiving afatinib as compared to those receiving chemotherapy.

There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials. In Study 12000.32, the most common adverse reactions ($\geq 20\%$) are diarrhea, rash, stomatitis, paronychia, dry skin, dermatitis acneiform, decreased appetite, and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients in Study 1200.32 consisted of interstitial lung disease (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Areas of special consideration in the review of this application include the enrichment design of Study 1200.32 based on enrollment of patients with specific EGFR mutations, which requires the concurrent approval of a companion diagnostic test. Additional issues that were considered and are discussed in greater detail in this review are

- the safety and efficacy of the proposed dosing regimen
- whether efficacy had been demonstrated in patients with NSCLC bearing uncommon EGFR mutations in Study 1200.32 (LUX-3)
-  (b) (4)
- whether efficacy had been demonstrated for second-line treatment of EGFR mutation-positive NSCLC based on response rates in a relatively small Phase 2 trial (LUX-2 trial)

2. Background

Background on Proposed Indication (non-small cell lung cancer)

There will be an estimated 228,190 new cases of lung cancer and 159,480 deaths from lung cancer in 2013¹. Of these 228,190 cases, approximately 85% are expected to be non-small cell

¹ <http://www.cancer.gov/cancertopics/types/lung>. Accessed March 2, 2013.

lung cancers (NSCLC). Based on SEER data², the estimated 5-year survival rate for patients with metastatic lung cancer is less than 5%. While standard treatment with a platinum-based chemotherapy doublet regimen was considered standard first-line therapy for all patients with NSCLC, emerging evidence has identified subpopulations based on histopathologic diagnosis (e.g., pemetrexed³) or molecular abnormalities (crizotinib⁴) where tumor-based outcomes are superior with targeted therapy. At present, the development paradigm for new drugs for the treatment of NSCLC is moving in the direction of molecularly-targeted agents affecting mutations identified as promoting cancer growth and development.⁵

Available Therapy

Erlotinib: On May 14, 2013, the approved indication for erlotinib was expanded to include the first-line treatment of metastatic NSCLC whose tumors have an epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 substitution (L858R) mutations. The expanded indication is supported by the results of single, investigator-initiated, randomized (1:1), open-label, active-controlled trial (EURTAC trial) conducted in 174 patients receiving first-line treatment for metastatic NSCLC whose tumors had EGFR exon 19 deletion or exon 21 substitution (L858R) mutation as detected by a clinical trial assay at a central academic study site.

The EURTAC trial demonstrated a statistically significant improvement in investigator-determined PFS for patients randomized to erlotinib compared to those randomized chemotherapy [Hazard ratio (HR) 0.34 (95% confidence intervals (CI): 0.23, 0.49), $p < 0.001$] with a doubling of the median progression-free survival from 5.2 months in the chemotherapy arm to 10.4 months in the erlotinib arm. There was no statistically significant difference in survival between the TARCEVA and chemotherapy arms [HR 0.93 (95% CI: 0.64, 1.35)] in an interim analysis, with median survival times of 22.9 months in the erlotinib arm and 19.5 months in the chemotherapy arm. The overall response rate was substantially higher (65% vs. 19%) for the erlotinib arm compared to the chemotherapy arm. The most frequent ($\geq 30\%$) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea and decreased appetite, with a median time to onset of rash of 15 days and median time to onset of diarrhea of 32 days. The most frequent Grade 3-4 adverse reactions in erlotinib-treated patients were rash (14%), dyspnea (8%), and diarrhea (5%). One erlotinib-treated patient experienced fatal hepatic failure and four additional patients experienced Grade 3-4 liver test abnormalities, for a total of five (6%) erlotinib-treated patients with Grade ≥ 3 liver test abnormalities.

Drugs approved for the first-line treatment of metastatic NSCLC, without consideration of EGFR mutation status, and the basis for approval are summarized below.

² <http://seer.cancer.gov/statfacts/html/lungb.html>. Accessed March 2, 2013

³ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021462s015ltr.pdf. Accessed March 2, 2013

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202570s000ltr.pdf. Accessed March 2, 2013

⁵ Genotyping and Genomic Profiling of Non Small-Cell Lung Cancer: Implications for Current and Future Therapies. Li T, Jung H-J, Mack PC, and Gandara DR. J Clin Oncol 45: 3753, 2012.

Paclitaxel protein-bound particles: On October 11, 2012, paclitaxel protein-bound particles was approved, in combination with carboplatin for the first-line treatment of NSCLC, under the provisions of 505(b)(2), relying on the FDA's prior findings of safety and effectiveness for the listed drug, paclitaxel, supported by the results of a single, 1052-patient, open-label, randomized, active-controlled trial. This trial met its primary objective of demonstrating superior overall response rates (33% vs. 25%, $p=0.005$; Odds ratio 1.31) in patients receiving paclitaxel protein-bound particles plus carboplatin as compared to paclitaxel plus carboplatin. Responses appeared to be equally durable in both treatment arms and there were no significant differences in PFS or OS between the two arms.

Crizotinib: On August 26, 2011, crizotinib was approved for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. The approval (accelerated approval) was based on demonstration of unexpected high and durable overall response rates (response rates of 71% and 68% with median response durations of 48.1 and 41.9 weeks) in two single arms trials enrolling a total of 255 patients.

Pemetrexed: On September 26, 2008, pemetrexed was approved, in combination with cisplatin therapy, for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. Approval was based on the results of a multi-center, randomized (1:1), open-label study in 1725 chemo-naïve patients with stage IIIb/IV NSCLC randomized to receive pemetrexed in combination with cisplatin (AC) or gemcitabine in combination with cisplatin (GC). This trial demonstrated clinically relevant differences in survival according to histology favoring the AC arm were observed [HR 0.84 (95% CI: 0.74, 0.96)] for the subgroup of 1252 patients with non-squamous, non-small cell lung cancer in a pre-specified subgroup analysis assessing treatment effect by NSCLC histology. This difference in treatment effect based on histologic subtype was also observed in a trial of single-agent pemetrexed administered as second-line therapy for NSCLC.

Paclitaxel: On June 30, 2008, paclitaxel was approved, in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. Approval was based on the results of a single, randomized, 3-arm, open-label trial conducted in 599 patients with chemotherapy-naïve NSCLC. This trial demonstrated a statistically significant improvement in PFS (median PFS 4.3 vs. 2.7 months, $p<0.05$), overall response rate (25% vs. 12%, $p<0.001$), and a trend towards improved overall survival (median survival 9.3 months vs. 7.4 months) for the combination of paclitaxel 135 mg/m² plus cisplatin as compared to cisplatin alone. The comparison of paclitaxel 250 mg/m² plus cisplatin to cisplatin alone also demonstrated statistically significant improvements in overall survival for progression-free survival and overall response rate with a trend for improvement in overall survival (median survival times of 10 months vs. 7.4 months, $p=0.08$).

Bevacizumab: On October 11, 2006, bevacizumab was approved for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC, in

combination with carboplatin and paclitaxel. Approval was based on the results of a single, randomized, active-controlled, open-label, multicenter study in 875 patients receive first-line therapy for locally advanced, metastatic or recurrent non-squamous, NSCLC. Patients were randomized to receive paclitaxel plus carboplatin alone (PC) or PC plus bevacizumab. The trial demonstrated an improvement in overall survival (median survival 12.3 months vs. 10.3 months: HR 0.80, p-value 0.013].

Gemcitabine: In 1998, gemcitabine was approved, in combination with cisplatin, for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC. Approval was based on the results of two randomized, open-label, trials enrolling 657 patients receiving first line- chemotherapy for locally advanced or metastatic cancer. The results demonstrated improved survival for patients receiving gemcitabine plus cisplatin compared to cisplatin alone (median survival 9.0 vs. 6.7 months, p=0.008) and improvement in time-to-disease progression for patients randomized to receive gemcitabine plus cisplatin compared to etoposide plus cisplatin (median time-to-progression 5.0 vs. 4.1 months, p=0.015) and higher response rates (33% vs. 14%, p=0.01), with no decrement in survival.

Vinorelbine: On December 23, 1994, vinorelbine was approved as a single agent, or in combination with cisplatin, for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC. Approval was based on the results of two randomized, active-controlled trials. The first randomized, open-label, add-on trial compared navelbine plus cisplatin alone in 432 patients receiving first-line chemotherapy for Stage IIIB or IV NSCLC. The second trial was a randomized, 3-arm, open-label, trial in 612 patients with Stage III or IV NSCLC receiving first-line chemotherapy. Patients were randomized to receive vinorelbine alone, vinorelbine plus cisplatin, or vindesine plus cisplatin. These trial demonstrated a significant increase in survival for patients randomized to vinorelbine plus cisplatin compared to cisplatin alone (median survival 7.8 months vs. 6.2 months, p=0.01) and for patients randomized to vinorelbine plus cisplatin compared to vindesine plus cisplatin (median survival 9.2 vs. 7.4 months, p=0.03).

Methotrexate: FDA-approved labeling states that “Methotrexate is used alone or in combination with other anticancer agents in the treatment of lung cancer, particularly squamous cell and small cell types.” The basis for approval is unclear. The use of methotrexate as a treatment for NSCLC has been supplanted by more active agents.

For more than a decade, the standard of care in the United States for treatment of NSCLC was platinum-based doublet chemotherapy. In 2002, the published results of a 4-arm, open-label, randomized (1:1:1:1) trial. The “control” arm was the paclitaxel/carboplatin arm, which was the most commonly used platinum-doublet in the US at the time of this trial and the regimen for which paclitaxel is approved for the treatment of NSCLC. The trial demonstrated similar outcomes for the following regimens:

- Cisplatin plus paclitaxel (control), consisting of paclitaxel, 135 mg/m² over 24-hr period on day 1 and cisplatin, 75 mg/m² on day 2 of each 21-day cycle
- Cisplatin plus gemcitabine, consisting of gemcitabine, 1000 mg/m² on days 1, 8, and 15 and cisplatin, 100 mg/m² on day 1 of each 28-day cycle

- Cisplatin plus docetaxel, consisting of docetaxel, 75 mg/m² on day 1 and cisplatin, 75 mg/m² on day 1 of each 21-day cycle
- Carboplatin plus paclitaxel consisting of paclitaxel, 225 mg/m² over 3-hr period on day 1 and carboplatin, AUC 6.0 mg/mL/min on day 1 of each 21-day cycle

The authors concluded that all the combinations have similar efficacy.⁶ However, because of its more favorable safety profile, the Eastern Collaborative Oncology Group (ECOG) selected carboplatin/paclitaxel as its reference regimen for future studies.

Regulatory History (pre-NDA submission)

December 31, 2003: IND 67,969 for BIBW 2992 (afatinib)

(b) (4)

(b) (4) is allowed to proceed.

July 31, 2007: EOP1 meeting to discuss a planned, randomized, placebo-controlled trial (Protocol 1200.23) of afatinib monotherapy in patients with NSCLC following treatment with erlotinib/ gefitinib and at least one prior line of cytotoxic chemotherapy as a basis for an NDA. The study was designed to enrich for a patient population whose tumors may have acquired the EGFR T790M resistance mutation by requiring at least 12 weeks of treatment with erlotinib or gefitinib prior to study entry. Key agreements or comments on the study design included the following:

- The proposed primary endpoint of PFS. FDA stated that whether an improvement in PFS will support approval will depend on the magnitude of the benefit and the risk benefit ratio. FDA recommended that overall survival as the primary endpoint.
- Claims based on the EORTC QLQ-C30 and LC13 instruments would be considered if results are convincing for all 5 "functioning" domains of the EORTC QLQ-C30 (physical, role, cognitive, emotional, and social), an HRQL claim, the trial is adequately designed and powered for this endpoint, the data are interpretable in light of plans to measure time to deterioration in HRQL, and the standards for demonstrating substantial evidence standard are met after review of the data for missing data points, multiplicity, maintenance of the double-blind and reproducibility.
- FDA stated that a cross-over design was not recommended based on lack of safety and efficacy data with afatinib.
- FDA discouraged the proposal to conduct an interim analysis of PFS to support a request for accelerated approval based on the small number of PFS events
- FDA stated that BI's proposal to verify a request for accelerated approval based on Protocol 1200.23 by submission of the final analysis of overall survival from 1200.23 and an additional trial, Protocol 1200.32, a randomized trial comparing afatinib monotherapy to carboplatin, paclitaxel, and bevacizumab in treatment-naive patients with advanced stage NSCLC whose tumors harbor EGFR activating mutations, with a primary efficacy endpoint for Protocol 1200.32 of PFS, was acceptable however the primary endpoint of 1200.32 should be overall survival.
- FDA agreed that a request for waiver from the requirements of PREA was appropriate

⁶ Schiller JH, Harrington D, Belani CP, et al: Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 346:92-98, 2002.

- FDA stated that a proposal for evaluation effects on QT intervals should be submitted to the IND at this stage of development.

November 9, 2007: Fast Track Designation for afatinib granted [REDACTED] (b) (4) [REDACTED] in response to October 15, 2007 request for designation submitted to IND [REDACTED] (b) (4).

June 6, 2008: teleconference to discuss deficiencies in proposed evaluation of the effects of afatinib on the QT interval. BI agreed to submit a revised plan.

October 16, 2008 EOP1 meeting to discuss the acceptability of the existing clinical data to support the conduct of Protocol 1200.32 and the overall study design specific, endpoints, and statistical analyses for Protocol 1200.32. Key agreements or comments on the study design included the following:

- Enrichment for a patients with tumors having EGFR-mutations based on clinical criteria (adenocarcinoma subtype, never smokers/light smokers) was reasonable strategy, however it may be appropriate to further narrow the indication to patients with adenocarcinoma and the presence of activating EGFR mutations.
- FDA recommended stratification of randomization based on results of EGFR status based on results from analytically-validated test.
- FDA stated that was essential that “review and approval of the drug for indications dependent on the result of an EGFR mutation test shall be accompanied by review and approval of the EGFR mutation test as well.” BIO agreed to contract with a third-party for development of a diagnostic test and to discussion this proposal with CDRH prior to submission of an SPA for Protocol 1200.32.
- The proposed comparator arms were acceptable.
- FDA stated that a substantial, robust improvement in PFS that was clinically meaningful and statistically persuasive, and had an acceptable risk-benefit profile may be considered for regulatory decision-making. FDA cautioned that measurement of PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. BI agreed to remove a proposal for interim analysis for efficacy based on PFS.
- FDA stated that the trial should be powered to assess effects on overall survival; BI agreed to make this a secondary endpoint.
- FDA recommended that sparse PK sampling be obtained in Protocol 1200.32 as well as in Protocol 1200.23 in order to evaluation population PK analyses.
- FDA stated that a dedicated PK study should be conducted in patients with hepatic impairment, that a dedicated DDI study be conducted with ketoconazole and rifampin, and that a formal bioequivalence study would not be required however full PK profiles of all strengths administered in Protocol 1200.32 would be needed based on changes in formulation between Phase 2 and Phase 3 trials.
- With regard to CMC, the NDA should contain 1) comparative test data on drug product batches from both Phase 2 and Phase 3/to-be-marketed drug products using same specification with identification of any new impurities observed at release and at stability; 2) comparative stability test data to bridge between drug products from Phase

2 and Phase 3/to-be-marketed formulation, and 3) comparative in vitro dissolution for drug product from Phase 2 and Phase 3 /to-be-marketed formulations. Also, any other change (e.g. manufacturing, analytical methods) for new formulation and strength should be indicated.

November 6, 2008: Agreement for Special Protocol Assessment to assess the stability of the afatinib drug product.

April 16, 2009: SPA non-agreement letter for Protocol 1200.32 issued. Primary areas of non-agreement were

- The proposed primary endpoint of progression-free survival. FDA stated that a substantial, robust improvement in PFS that was clinically meaningful and statistically persuasive, and has an acceptable risk:benefit profile may be considered for regulatory decision making. However since all previous approvals in the first-line setting of NSCLC were based on overall survival as the primary endpoint, an application based on PFS would likely be referred to the Oncologic Drugs Advisory Committee.
- Lack of proposed plan for assessment of discordance between investigator- and IRC-determined PFS events
- Lack of proposed sensitivity analyses for evaluating the impact of missing data (patients who are removed from study based on investigator-determined PFS events not subsequently confirmed by the IRC)
- Need to demonstrate a highly statistically robust treatment effect, consistent within subgroups, for a single efficacy trial supporting an NME NDA
- Lack of information on the validated test kit to be used to for patient selection

December 15, 2009: preNDA meeting based on results from Protocol 1200.23, supported by results from Protocol 1200.22. Key agreements or comments on the proposed NDA submission the following:

- FDA and BI reached agreement on the schedule and components for a rolling submission of the proposed NDA
- Agreed that QT and hepatic impairment data can be provided post-approval, however FDA requested that BI submit the hepatic impairment protocol (1200.86) for review.
- FDA and BI reached agreement on the proposed exposure- efficacy and exposure-safety analyses, with the proposed clinical PK datasets to be provided.
- FDA agreed that an ISE was not required. FDA and BI reached agreement on the proposed SCS safety groupings. With regard to analyses in the SCS, the statistical reviewers agreed that BI could provide analysis datasets for Tables presented in the SCS however the medical reviewer stated that a follow-up meeting would be required on this issue following submission of item 3 described under the next bullet.
- BI agreed to provide 1) patient narratives for Safety Update Report; 2) case report forms serious adverse events occurring in Protocols 1200.22 and 1200.23; 3) analysis datasets for tables in the SCS.
- Datasets would be compliant with the Data Standard document (UCM189445.pdf) but will use a format and variable names specific to BI and will not be those specified for CDISC and ADAM format.

- BI agreed to submit a detailed document cross-referencing specific tables with datasets and programs for the FDA's review.
- CDRH clarified that results from biomarker analysis performed in Study 1200.23 and any efficacy data from Study 1200.22 would not impact the indication statement.

December 9, 2011: pre-NDA meeting for afatinib to support the following proposed indication “afatinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)”. The proposed NDA package would be based on results of the following trials: 1200.32 (pivotal) and 1200.22, 1200.23, and 1200.42 (3 supportive trials). Key agreements or comments on the proposed NDA submission the following:

- BI acknowledged FDA’s statement that the indication will be a review issue and should reflect the patient population enrolled in the trials.
- FDA could not state whether submission of the PMA was a filing issue for the NDA. BI acknowledged FDA’s statement both the test kit and drug, if approved, should both be approved simultaneously.
- FDA and BI reached agreement on the contents and location of information for the ISE; BI agreed to provide CSRs with efficacy data for Protocols 1200.33 and 1200.72, which also enrolled patients with NSCLC. BI agreed to provide safety data from the proposed trials as well as from Protocols 1200.33, 1200.34, 1200.40, 1200.41, and 1200.72.
- BI and FDA reached agreement on submission of patient narratives as follows: (1) Patient narratives would be submitted from all trials conducted in NSCLC for the following adverse events regardless of relationship to study drug - interstitial lung disease events, decreased LVEF or heart failure, and hepatic failure events regardless of their relationship to study.
- The acceptability of an Expanded Access Program (EAR) would be dependent on the outcome of the 1200.32 trial.

June 5, 2012: Expanded Access Program (EAP) for afatinib in the US (Trial 1200.45), submitted to IND (b)(4) on May 25, 2012, allowed to proceed.

October 10, 2012: Teleconference held and agreement reached on the contents of a complete NDA, in accordance with PDUFA V. There was agreement that no portion of the application would be submitted within the first 30 days of receipt and that a REMS did not appear necessary to ensure safe use. On October 19, 2012, FDA confirmed that the proposed dataset plan was acceptable, via electronic mail message from the RPM.

Regulatory History of NDA 201292

Boehringer Ingelheim requested priority review designation, as the findings demonstrated clinical superiority over the recognized standard of care in first-line EGFR mutation-positive NSCLC (LUX-Lung 3) and evidence of benefit in later lines of treatment, where limited or no alternative treatment options exist (LUX-Lung 1 and LUX-Lung 2). Justification noted that there were no drugs specifically approved for use in patients with EGFR mutation-positive NSCLC and that the LUX-Lung 3 trial demonstrated a clinically

meaningful and statistically robust improvement in progression-free survival for the afatinib-containing arm as compared to those randomized to pemetrexed and cisplatin for the first-line treatment of patients with NSCLC (HR 0.58, p=0.0004) with median PFS times of 11.1 months for the afatinib-containing arm as compared to 6.9 months for chemotherapy alone, based on independent review. In the subset of patients with the two most common EGFR mutations, the treatment effect was larger (HF 0.47, p<0.0001) with median PFS times of 13.6 months for the afatinib-containing arm as compared to 6.9 months for chemotherapy alone. These findings were supported by a clinically meaningful and statistically robust increase in overall response rates (56.1% vs. 22.6%, p<0.0001, independent review).

BI proposed the following indication

(b) (4)

(b) (4)

(b) (4). In this trial, patients randomized to afatinib experienced longer PFS (HR 0.38, p<0.0001 per independent review) with median PFS times of 3.3. months in the afatinib arm compared to 1.1 months for the placebo arm. In addition, the overall response rate was statistically significantly higher (7.4% vs. 0.5%, p= 0.0071), however the difference is not considered clinically important.

3. CMC/Biopharmaceutics

CMC and Biopharmaceutics

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and that there are no outstanding CMC issues that preclude approval.

Afatinib (free base) is a new molecular entity which is chemically synthesized; the salt form is afatinib dimaleate. The drug substance, (b) (4) is (b) (4) generated during synthesis. The synthetic process was optimized during drug development, potential impurities and degradants were identified and are appropriately controlled, the release specification and analytical procedures are described in sufficient detail and validated for their intended uses; since the methods were not novel or complex, additional evaluation by FDA's methods validation staff will be conducted post-approval. Acceptance criteria were justified by batch analysis data and during clinical studies.

The drug product, Gilotrif, will be supplied as film-coated tablets in the following strengths: 40 mg, 30 mg, or 20 mg afatinib (free base), which corresponds to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate. The proposed dissolution methodology, the dissolution acceptance criterion, and the comparative dissolution profiles between the drug product used in the pivotal trials and the proposed commercial drug product were determined to be acceptable. The quality of commercial Afatinib tablets was determined to be acceptable based on assessment of the manufacturing process and process controls and analytical procedures for identification, purity, strength, and stability. Stability testing supports an expiry of 24 months.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

In *in vitro* or nonclinical models, afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR and in cell lines expressing EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations that are achieved, at least transiently, in patients. Afatinib also inhibited *in vitro* proliferation of cell lines over-expressing HER2.

The primary general toxicology studies were conducted in rats and minipigs. The toxicologic findings mirrored the human safety profile, with evidence of gastrointestinal, cutaneous, ocular (corneal atrophy), renal, and pulmonary parenchymal toxicity observed in one or both species tested.

A potential adverse reaction, not observed in clinical trials, was identified by the clinical pharmacologists, based on the observation that the major metabolic products of afatinib are protein adducts, including hemoglobin, and that afatinib was highly associated with red blood cells in all species. This finding has been associated with idiosyncratic adverse reactions.

In safety pharmacology studies, decreased left ventricular ejection fraction was observed in minipigs receiving afatinib at a dose of 30 mg/kg, which correlated with observations in clinical trials. The evaluation for effects on electrophysiology (*in vitro* hERG testing and *in vivo* ECG monitoring in minipigs and rats) were consistent with studies in human subjects, indicating that risk of QT prolongation at the recommended human dose/exposures were low.

Reproductive toxicity studies were conducted in rats and rabbits for evaluation of effect on embryofetal development. Based on these studies, embryofetal toxicity is predicted at the recommended dose and expected exposure with afatinib in humans. Non-clinical studies demonstrated an increased risk of abortion, increased risk of resorption, visceral and skeletal variations (delayed ossification), and lower fetal weights. Studies in female rats also suggested impairment of fertility, based on the observation of decreased number of corpora lutea and increases in pre-implantation loss and early resorptions at exposures expected in humans at the recommended dose and by effects on reproductive organs observed in the general toxicology studies.

Afatinib was present at high concentrations in the milk of lactating rats.

In a dedicated fertility study, evidence of effects on male fertility were identified which included epithelial atrophy and a dose-dependent increase in the incidence of hypospermia

Based on the totality of the *in vitro* testing, including conflicting results between the Ames and other tests, neither afatinib nor its major metabolites are considered to be genotoxic.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The median time to reach peak plasma concentration (T_{max}) was 5 hours after a single oral dose and 3 hours after multiple doses of afatinib. Steady state was attained following 8 days of afatinib administered daily. The elimination half-life was 21-27 hours after a single dose and 45 hours at steady state. The relative bioavailability was 92% (90% CI: 76%, 112%) based on AUC_{0-inf} after a single dose of 20 mg tablet compared to an oral solution.

The major form of afatinib presented in human plasma is covalent adducts to plasma proteins and minor metabolites catalyzed by CYP450 enzymes. A mass balance study suggested that the major route of excretion of afatinib was via feces (85%) while 4% in urine.

Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinical relevant effect on exposure of afatinib. Formal organ impairment studies were not submitted in the NDA and were initially not considered necessary based on the metabolism of afatinib as described in the paragraph above and on the summary results of the population PK analysis. There were no clinically significant differences in exposure between patients with normal, mild or moderate hepatic impairment. In the population PK studies, mild renal impairment has no effect on afatinib systemic exposure and the increases in trough concentrations with moderate renal impairment not considered clinically important based on overall population PK analyses. However, based on a re-analysis of data from Study 1200.32, limited to patients receiving afatinib at 40 mg daily, a clinically important increase in trough concentrations were identified among patients with renal impairment; this has been noted in product labeling and will be further evaluated in a formal organ impairment study to be conducted under a post-marketing requirement.

Based on the regimen used in Study 1200.32, BI proposed a recommended dose of afatinib 40 mg orally once daily, (b) (4). However, in Study 1200.32, only 16 of the 229 patients randomized to afatinib and receiving at least one dose of study drug underwent escalation to the 50 mg dose; of these, 10 were unable to tolerate dosing at 50 mg daily. In addition, the analysis assessing the exposure-response relationship suggests that the 50 mg daily dose does not result in better or similar efficacy. Specifically, in the exposure-efficacy analyses assessing outcomes by exposure quartile in Study 1200.32, patients in the highest quartile for steady state AUC had shorter progression-free survival times as compared to other quartiles – this decrement in PFS was clinically important and similar to that observed in the control arm, suggesting loss of treatment effect. In addition, the results of logistic regression analyses suggested that higher exposure of afatinib increased the risk of experiencing an adverse reaction of NCI CTCAE grade 3 severity or grade 2-3 diarrhea.

In food-effects studies, afatinib exposure was decreased (39% in AUC_{0-inf} and 50% in C_{max}) after a high-fat meal as compared to that under the fasted condition. Product labeling reflects

this information and provides dosing recommendations that afatinib to be taken at least one hour before or two hours after a meal.

Based on evaluation for possible drug interactions, product labeling includes recommendations for reduction in the dose of afatinib in patients who require concomitant P-gp inducers or inhibitors since afatinib is both a substrate and inhibitor of the P-gp transporter. Specifically, clinically important changes in afatinib exposure were observed when afatinib was administered with ritonavir (a P-gp inhibitor) or rifampicin (a P-gp inducer).

6. Clinical Microbiology

Not applicable. Assessment of potential sterility concerns were evaluated by the CMC reviewer who determined that the manufacturing process and controls, which do not involve novel or complex methodology, were adequate to ensure product sterility.

7. Clinical/Statistical-Efficacy

The scope of the clinical program was adequate to evaluate safety and efficacy for the narrowed indication. BI relied primarily on the results of four clinical trials to support labeling claims (b) (4)

Issues relating to study design and outcomes for the three supportive trials (LUX-1, LUX-2, and LUX-5) are briefly described below, while the major efficacy trial supporting the recommendation for approval is summarized in greater detail.

Trials intended to support claims for afatinib in the treatment of patients with NSCLC who (b) (4)

- LUX-Lung 3: The design and results of trial are described in detail below
- LUX-Lung 2: This open-label, single-arm, activity-estimating trial was conducted in 129 patients with locally advanced or metastatic lung adenocarcinoma containing an EGFR mutation who had not received prior EGFR TKI therapy. EGFR mutation status was evaluated by PCR testing with a clinical trials assay. Approximately half these patients had received no prior chemotherapy (n=61) and the remainder had received only on prior line of chemotherapy (n=68) (i.e., after failure of first-line chemotherapy). Approximately three-quarters of the patients received afatinib at a dose of 50 mg daily (n=99) and the remaining 30 patients received afatinib 40 mg daily. The primary endpoint of the trial was determination of overall response. Based on independent review, BI reported that the ORR in the first-line setting was 66% with a median duration of 13.5 months, while the ORR in the second line setting was 57% with a median duration of response of 12.9 months. While these data are supportive, they do not extend the clinical efficacy data described in Study 1200.32 and as a single arm trial, they are not deemed more reliable.

Trials intended to support claims in patients with NSCLC who (b) (4)

- LUX-Lung 1: This was a randomized (2:1), placebo-controlled trial conducted in 585 patients receiving third or fourth line treatment for NSCLC; all patients had previously received 1 or 2 lines of chemotherapy, one of which was required to have been a platinum-containing regimen, and to have progressed after treatment with an EGFR-TKI (either gefitinib or erlotinib). Of the 585 patients, 390 were randomized to receive afatinib 50 mg daily and 195 patients were randomized to matching placebo. Patients were not screened for the presence of EGFR mutations but were considered to be clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. The primary endpoint in this study was OS with a secondary endpoint of PFS.

The study population demographics were female (59%), median age of 61 years, baseline ECOG performance status of 0 or 1 (92%), either White (33%) or Asian (66%). All patients were required to have received prior platinum-containing regimen, 60% had 1 line and 39% had 2 lines of prior chemotherapy for metastatic disease. All patients had received prior EGFR TKI therapy, consisting of erlotinib (55%), gefitinib (40%) or both (5%).

The trial failed to meet its primary endpoint, of demonstration of improved survival, with a median survival of 10.8 months for afatinib-treated patients and 12.0 months for patients in the placebo arm. Therefore, the effects on PFS cannot be considered statistically significant and is of unclear clinical importance with an improvement in median PFS time of 2.2 months for afatinib (median PFS 3.3 months) as compared to placebo (median PFS 1.1 months). Similarly, the higher response rate observed with afatinib is not clinically meaningful as it remains less than 10%.

- LUX-5: This was an open-label, randomized, multicenter trials conducted in 1154 patients with patients with unresectable or metastatic NSCLC. Eligibility criteria were similar to those in the LUX-1 trial. All patients received afatinib 50 mg daily; at the time of disease progression, the subgroup deemed to have clinical benefit (without disease progression for ≥ 12 weeks) received afatinib 40 mg daily plus paclitaxel or to receive investigator's choice chemotherapy.



FDA did not consider the LUX-5 study adequate in design as the patient population enrolled did not correlate with EGFR mutation status. Further, the retrospective analyses conducted are considered exploratory, at best, and do not meet the criteria for substantial evidence of effectiveness as described in FDA's Guidance on Clinical Effectiveness for Drugs and Biologics.

Trial Design – Study 1200.32 (LUX-3)

The efficacy and safety of GILOTRIF for the first-line treatment of EGFR mutation-positive non-squamous, non-small cell lung cancer (NSCLC) was evaluated primarily in Study 1200.32 (LUX-Lung 3), 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.”

The data were deemed reliable based on (b) (4) inspections of six clinical sites and the contract research organization (CRO) responsible for conducting the clinical trial on behalf of BI.

Key eligibility criteria EGFR mutation-positive, metastatic (Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer [AJCC, 6th edition]) NSCLC were established in a randomized, multicenter, open-label trial (Study 1). Patients were randomized (2:1) to the following treatment arms

- afatinib 40 mg orally once daily until disease progression or unacceptable toxicity
- pemetrexed 500 mg/m² intravenously with cisplatin 75 mg/m² intravenously, every 21 days for up to six 21-day cycles

Patients were assessed for tumor status every 6 weeks for the first 48 weeks on study, then every 12 weeks, thereafter. Safety monitoring included assessment of left ventricular ejection fraction at baseline, on day 1 of cycle 4, then every third treatment cycle thereafter.

Randomization was stratified according to EGFR mutation status (exon 19 deletion vs. exon 21 L858R vs. other) and race (Asian vs. non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included objective response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA).

The primary analysis was to occur after 217 PFS events. This sample size assumed 90% power to detect a hazard ratio of 0.64. An interim analysis of survival was pre-specified; it was to occur at the time of the primary analysis, using a stopping boundary of $p < 0.0001$. The final OS analysis is to occur after 209 deaths. At FDA’s request, an updated analysis of survival was requested during review of the submission; this analysis is described in the results presented below, however because it was conducted based on FDA’s request, no adjustment for alpha will be required at the final analysis of OS, which will be submitted as an agreed-upon post-marketing commitment.

Results

A total of 345 patients were enrolled, of whom 230 were randomized to receive afatinib 40 mg daily and 115 were randomized to receive chemotherapy. Demographic characteristics for the study population were 65% female, median age of 61 years, baseline ECOG performance status of 0 (39%) or 1 (61%), and 26% Caucasian and 72% Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

The results of Study 1200.32 provide substantial evidence of effectiveness of afatinib in this patient population. A statistically significant and clinically important improvement in PFS, as determined by the IRC, was demonstrated for patients randomized to afatinib compared to those randomized to chemotherapy; however there was no statistically significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis. The key efficacy results are provided in the following table and the Kaplan-Meier curves for PFS are presented in the figure following the table.

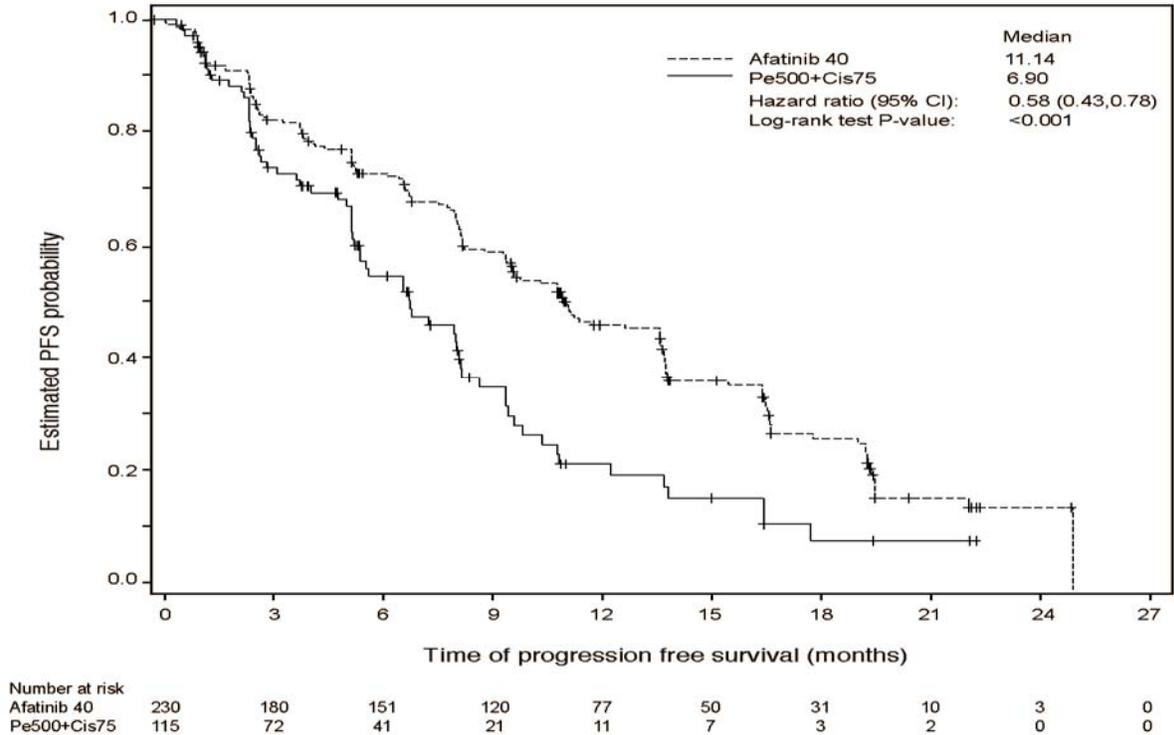
Efficacy Results of Study 1200.32

	BRAND (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-free Survival		
Number of Deaths or Progressions, 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*	<0.001	
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*	0.55	
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

Kaplan-Meier Curve for PFS by Independent Review by Treatment Group for Study 1200.32

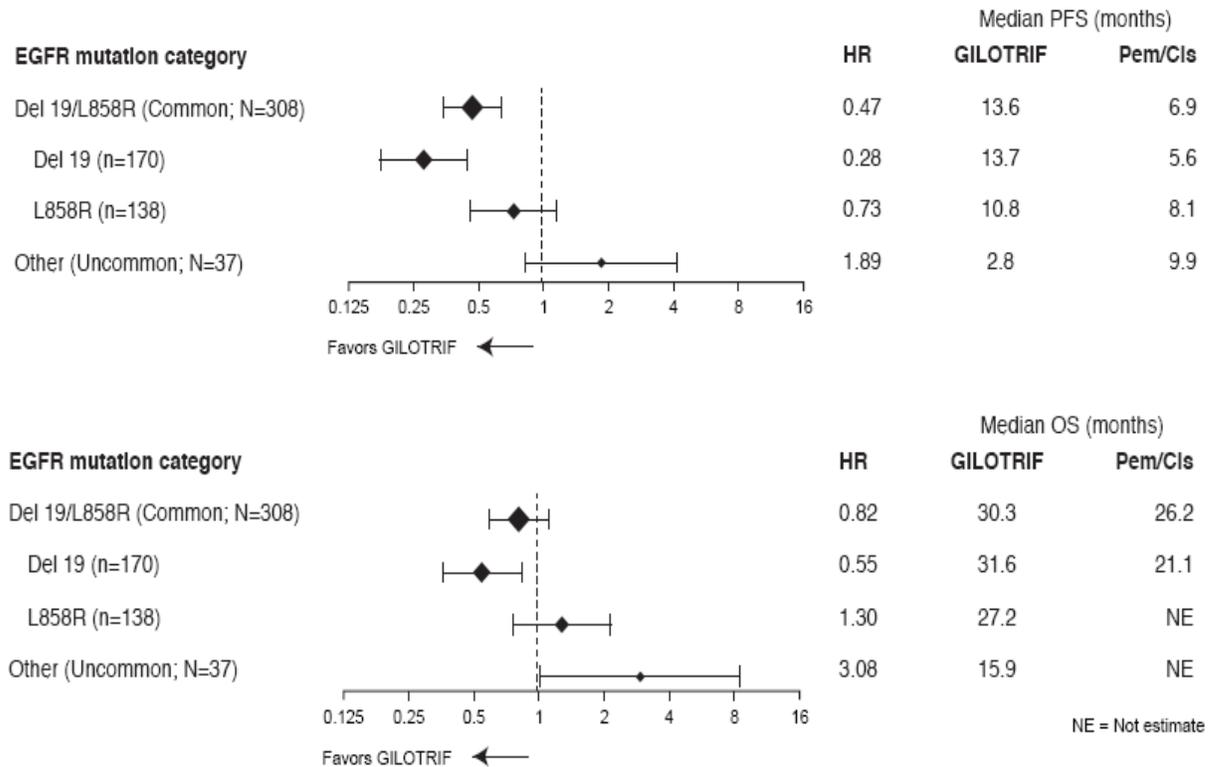


Exploratory analyses by EGFR mutation type

Tumor samples from 264 patients (178 randomized to afatinib and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*[®] EGFR RGQ PCR Kit, which will be approved concurrent with the approval of afatinib. The treatment effects of afatinib were similar in this subpopulation identified by the to-be-marketed companion diagnostic as those observed with the clinical trial assay.

The clinical trial stratified randomization by EGFR mutation type (exon 19 deletions vs. exon 21 L858R substitution vs. other mutations) using the clinical trials assay. Based on concerns that the treatment effect may differ based on the underlying mutation, FDA performed exploratory subgroup analyses for PFS and OS based on the stratification factor of EGFR mutation status and on the subgroup of “common” mutations for which afatinib will be indicated. These data are displayed in the Forest plots, taken from the product labeling and reproduced below.

Forest plot of PFS and OS by Stratification Variables and by Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories in Study 1200.32



Based on these analyses, FDA concluded that the treatment effect is dependent on the underlying EGFR mutation. While PFS and OS show a consistent improvement for afatinib-treated patients, those with “other” mutations show a consistent and worse outcome when receiving afatinib as compared to standard chemotherapy. Similar findings were observed in an additional study of afatinib submitted to the IND (i.e., favorable treatment effects in patients with exon 19 deletions or exon 21 L858R substitutions but not in pooled analyses of patients with other less common mutations). These findings do not rule out the possibility that other less common mutations may benefit however there is insufficient data provided in the NDA to identify such subgroups.

To further investigate the possibility of benefit is specific less common mutations, FDA evaluated the objective response rates in patients with these less common mutations. There were 26 afatinib -treated patients in the “other” (uncommon) EGFR mutations subgroup with nine unique mutation patterns. Of the 26 afatinib-treated patients in the “other” EGFR mutation subgroup, four (15%) achieved a partial response and of the 11 chemotherapy-treated patients in the “other” EGFR mutation subgroup, four (36%) achieved a partial response. Among the afatinib-treated patients, at least one patient with mutations in L858R and T790M, L858R and S768I, S768I alone, or G719X alone achieved a partial response; information on the response rate observed in patients with these mutations are displayed in the table below, reproduced from the product labeling. No responses were seen in afatinib-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).

Objective Tumor Responses in Afatinib-Treated Patients Based on Investigator Assessment in the “Other” (uncommon) EGFR Mutation Subgroup in Study 1200.32

EGFR Mutations	Number of Afatinib-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

The results of Study 1200.32 provide substantial evidence of the effectiveness of afatinib for the first-line treatment of patients with EGFR mutation-positive NSCLC. Exploratory subgroups by EGFR mutation type were conducted by FDA to evaluate for differential treatment effects which may correlate with *in vitro* assessments of inhibitory capacity by mutation site. Although exploratory, the consistency observed for differential treatment effect by mutation type for PFS and OS and the high-level results submitted to the IND for an additional randomized trial of afatinib in a similar population suggest that these findings are real. Such information is important to prescribers and patients to characterize treatment outcomes and will be useful as new agents against this target are developed.

8. Safety

The size of the safety database was adequate; the data based included safety information from more than 3800 patients, including 2135 patients with NSCLC. In addition, safety data were available from randomized, controlled trials of 229 afatinib-treated patients with EGFR mutation-positive, metastatic, non-squamous, NSCLC who were enrolled in Study 1200.32. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure to afatinib was 11.0 months and to pemetrexed/cisplatin chemotherapy was 3.4 months. The overall trial population had a median age of 61 years, 64% of patients who received afatinib and 67% of patients who received pemetrexed/cisplatin were female, and 70% of patients who received afatinib and 72% who receive pemetrexed/cisplatin chemotherapy were Asian.

Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse

reactions in afatinib -treated patients in Study 1200.32 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of afatinib-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with afatinib were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in afatinib-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Adverse Reactions Reported in $\geq 10\%$ of Afatinib-Treated Patients in Study 1200.32

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3* (%)	All Grades (%)	Grade 3* (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis ¹	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/Dermatitis acneiform ²	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections and infestations				
Paronychia ³	58	11	0	0
Cystitis	13	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	29	4	55	4
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*None of the adverse reactions in this table were Grade 4 in severity

¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

²Includes group of rash preferred terms, acne, acne pustular, dermatitis acneiform

³Includes paronychia, nail infection, nail bed infection

**Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported
in ≥5% of Afatinib-Treated Patients in Study 1200.32**

Adverse Reaction	Afatinib n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Alanine aminotransferase increased	11	2	4	0
Hypokalemia ¹	11	4	5	4
Aspartate aminotransferase increased	8	2	2	1

¹Includes hypokalemia, blood potassium decreased

Post-marketing Surveillance

Based on the Non-clinical Pharmacology review, a theoretical risk of idiosyncratic drug reactions, specifically hemolysis, was identified. The potential for this risk is based on the binding of afatinib to hemoglobin. The OSE review staff will be alerted to this potential risk so that monitoring can be targeted for this event.

REMS

Both the clinical review team and the DMEPA consultant agreed that a REMS was not required to ensure safe and effective use of afatinib. The risks of afatinib are adequately conveyed in professional and patient labeling.

PMRs and PMCs

One PMR was requested by the Clinical Pharmacology team to evaluate the pharmacokinetics of afatinib in patients with renal impairment. The rationale for this requirement is discussed in Section 5 of this summary review.

9. Advisory Committee Meeting

This NDA was not referred for review to the Oncologic Drugs Advisory Committee because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. Specifically, the clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

10. Pediatrics

The applicant requested a waiver from the requirements of the Pediatric Research Equity Act (PREA) for pediatric patients less than 18 years of age in the original NDA submission on November 15, 2012. The justification for this requested waiver was that studies are impossible or highly impractical because the number of pediatric patients with non-small cell lung cancer is so small. Since orphan designation was granted for afatinib on December 3, 2012 for “treatment of epidermal growth factor receptor mutation-positive non-small cell lung

cancer (NSCLC) as detected by an FDA-approved test,” afatinib is exempt from the requirements of PREA for this indication and the requested waiver was deemed irrelevant.

11. Other Relevant Regulatory Issues

With the exception of lack of agreement on final labeling for the companion diagnostic, there are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The initial request for proprietary name submitted with the NDA was not accepted by DMEPA based on the potential for medication errors based on writing samples. The second request (GOLTRIF) was submitted March 4, 2013 and determined to be acceptable by DMEPA, OPDP, and DOP2.
- Physician labeling- All major issues were resolved; a summary of clinically important modifications are discussed by labeling section, below
 - Indications and Usage: In agreement with BI and at FDA’s request, the proposed indication was limited to first-line treatment and to the specific EGFR mutations (exon 19 deletions or exon 21 L858R substitution) where efficacy has been established. Added a limitation of use stating that the efficacy of afatinib has not been established for other EGFR mutations.
 - Dosage and Administration: Modified this section to add a new subsection denoting that patient selection using a companion diagnostic test should be used to identify patients for whom afatinib is indicated. (b) (4)
 - (b) (4)
 - (b) (4). Added specific dose modifications for afatinib when given with a P-gp inhibitor or with a P-gp inducer based on the pharmacokinetic data submitted in the NDA as discussed in Section 5 of this review. Edited the recommendations on dose modification for brevity, clarity, and consistency with treatment as administered in Study 1200.32.
 - Dosage Forms and Strength: (b) (4).
 - Warnings and Precautions: Modified to include specific information on the risk of serious adverse reactions in Study 1200.32 or in the overall safety database. Retitled sections on (b) (4) to provide more information on the severity and type of adverse reactions. (b) (4)

- Adverse Reactions: This section was revised to include information specified in FDA Guidance on product labeling for Adverse Reactions, such as description of the study treatment and extent of exposure, description of the patient population demographics, identification of the most serious toxicities and those resulting in treatment discontinuation. The tables of adverse reactions based on Study 1200.32 was modified in accordance with the FDA Guidance on this section to adverse reactions occurring more commonly in the experimental arm than in the control arm ($\geq 5\%$ overall increased risk for any adverse reaction or $\geq 2\%$ increased risk for grade 3-4 adverse reactions). The listing of adverse reactions occurring in less than 10% of patients in Study 1200.32 was modified

(b) (4)

(b) (4)

- Drug Interactions: This section was edited for clarity and to provide data characterizing the effects of rifampin on afatinib based on a specific drug interaction study.
- Use in Specific Populations
 - The subsections on Pregnancy and Nursing Mothers were revised for consistency with the Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. As recommended by the Maternal Health consultant, this section was revised to comply with current regulations but restructured in the spirit of the Proposed Rule. The Geriatric Use subsection was revised to include data on exposure in elderly patients in 3800+ patients and summary statement indicating that there are no apparent differences between older and younger patients. Editorial changes to the subsections on Renal and Hepatic Impairment.
- Overdosage: Edited
- Description:

(b) (4)

(b) (4)

(b) (4)

- Clinical Pharmacology: Edited the subsection on Mechanism of Action for brevity
(b) (4)
[REDACTED]
[REDACTED] Information on lack of clinically significant effects on QT interval placed under the Pharmacodynamic subsection in accordance with evolving policy in the Office of Clinical Pharmacology (b) (4) In the Pharmacokinetics subsection, information on absorption and distribution combined, information on lack of effects in patients based on various demographics factors were combined, information on drug interactions, food effects, and PK in patients with organ impairment edited for brevity.
- Nonclinical Pharmacology/Toxicology: Edited for brevity/essential information. Results of studies assessing effects on fertility briefly described
- Clinical Studies: The results from Studies LUX-2, LUX-1, and LUX-5 were not included in product labeling since FDA concluded that these studies did not provide substantial evidence of effectiveness for reasons discussed in Section 7 of this review. Results of health-related quality of life obtained in Study 1200.32 were not included in product labeling as these are exploratory analyses obtained in an open-label trial. Analyses in subsets based on EGFR mutation type are included in labeling as these are clearly identified as exploratory; in addition, randomization was stratified for this variable, preserving principles of randomization, the results were consistent across endpoints (PFS and OS), other studies of afatinib (IND studies), and other products in this class (erlotinib). Information on uncommon mutations was provided for information only and to aid prescribers in providing information to patients.
- Carton and immediate container labels – no unresolved issues
- Patient labeling: BI submitted patient labeling, which has been revised for alignment with modifications to the physician labeling; there are no unresolved issues with patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment: Unresectable or metastatic NSCLC is a serious and life-threatening disease; there is only one other drug which has been approved (recently) for treatment of NSCLC containing exon 19 deletions or exon 21 L858R EGFR mutations, which poses the potential for lack of availability due to drug shortages. Based on the results of Study 1200.32, afatinib treatment demonstrated a statistically robust and clinically important improvement in progression-free survival for patients randomized to afatinib compared to those randomized chemotherapy [HR 0.58 (95% CI: .43, 0.78), $p < 0.001$] with an approximate doubling of the median progression-free survival from 6.9 months in the chemotherapy arm to 11.1 months in the afatinib arm. There was no statistically significant difference in overall survival between the afatinib and chemotherapy arms, with 84% of the planned events, however effects on survival, if any, may have been obscured by the high rate of post-progression use of an EGFR inhibitor for patients in the chemotherapy arm. In addition, the overall response rate

was substantially higher (50% vs. 19%) for the afatinib arm compared to the chemotherapy arm.

There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials. In Study 12000.32, the most common adverse reactions ($\geq 20\%$) are diarrhea, rash, stomatitis, paronychia, dry skin, dermatitis acneiform, decreased appetite, and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients in Study 1200.32 consisted of interstitial lung disease (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Substantial evidence of effectiveness (an improvement in PFS of a clinically important magnitude) was demonstrated in this trial. While an improvement in overall survival has been used as the basis for most recent drug approvals for the treatment of NSCLC, treatment effects of this magnitude are also considered to be evidence of clinical benefit provided that the risks are acceptable. As stated by FDA during the September 20, 2010 pre-NDA meeting, “consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. Because documentation of PFS assessments is often based on both subjective and objective criteria and these assessments depend on frequency, accuracy, reproducibility and completeness of tumor assessments, it is important that the observed magnitude of effect is robust.” The risks of afatinib treatment are considered acceptable by oncologists and patients for the treatment of NSCLC, a serious and ultimately fatal disease. The serious adverse reactions of afatinib are acceptable given the clinical benefits on PFS and can be mitigated by close monitoring and dose modification.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
The application did not contain a proposed REMS. I concur with the clinical review team and the DRISK consultant that a REMS is not required to ensure safe use or mitigate severe adverse reactions for afatinib for the proposed indication.
- Recommendation for other Postmarketing Requirements and Commitments
 - One PMR will be required to evaluate for the effects of moderate to severe renal impairment on the pharmacokinetics of afatinib. This is based on a re-analysis of the population PK data in Study 1200.32 in patients receiving the recommended dose of afatinib, which demonstrated an increase in trough concentrations by 85% in patients with moderate impairment.
 - One PMC has been agreed-upon, which will be submitting the results of the final analysis of overall survival, so that these data can be included in product labeling, as appropriate.

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/s/

PATRICIA KEEGAN
07/11/2013

Division Director Summary Review

Date	July 5, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	201292
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	November 15, 2012
PDUFA Goal Date	July 15, 2013
Proprietary Name / Established (USAN) Name	GILOTRIF Afatinib
Dosage Forms / Strength	Tablet / 20, 30, and 40 mg tablets
Proposed Indication(s)	“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 [see <i>Clinical Studies (14.1, 14.2)</i>]”
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Shakun Malik
Statistical Review	Jonathan Norton
Pharmacology Toxicology Review	Denali (Dubravka) Kufirin & Shawna Weis
CMC ONDQA Reviews	Haripada Sarker, Li-Shan Hsieh, Ali Al Hakim
Biopharmaceutics Review	Elsbeth Chikhale
Clinical Pharmacology Review	Runyan Jin
OPDP Reviews	Quynh-Van Tran (DPDP) & Karen Dowdy (DMPP)
OSI Review	Lauren Iacono-Connors
CDTL Review	Anthony Murgo
OSE/DMEPA Consult	James Schlick
OSE/DRISK Consult	Suzanne Robottom
Maternal Health Consult	Tammie Brent Howard

OND=Office of New Drugs
 CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology
 OPDP= Office of Prescription Drug Promotion
 DMPP=Division of Medical Policy Programs
 OSI= Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE=Office of Surveillance and Epidemiology
 DRISK=Division of Risk Management
 DMEPA= Division of Medication Error Prevention and Analysis

Division Director Summary Review

1. Introduction

Afatinib (Gilotrif, B) is a tyrosine kinase inhibitor which covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in down regulation of ErbB signaling. Nonclinical studies demonstrated that at clinically achievable concentrations, afatinib inhibited phosphorylation or proliferation in cell lines bearing wild-type EGFR or bearing common mutations in EGFR (i.e., exon 19 deletions or exon 21 L858R substitution). In addition, at concentrations achieved transiently with afatinib, inhibition was also observed noted in cell lines with a secondary T790M mutation and either exon 19 deletion or exon 21 L858R mutation.

The clinical development program in NSCLC included two trials conducted in patients with NSCLC containing an EGFR mutation as detected by a PCR-based investigation assay who had not received prior treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and two trials conducted in patients who were “clinically enriched” for EGFR mutations but had not been tested and who had received treatment with an EGFR TKI. The latter trials were considered flawed in that the clinical enrichment strategy did not correlate with subsequent EGFR mutation testing. In addition, of the two trials conducted in this population, the randomized trial in this population failed to meet its primary endpoint. Therefore, only studies conducted in patients who were screened for EGFR mutations prior to enrollment were evaluated for efficacy claims,

The primary trial supporting approval was Study 1200.32 (LUX-3), a randomized, open-label, multicenter, multinational trial comparing the efficacy of afatinib to cisplatin/pemetrexed chemotherapy doublet for the first-line treatment of metastatic or unresectable, EGFR mutation-positive adenocarcinoma of the lung. In this trial, 345 patients 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 vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). The key secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). The characteristics for the study population were 65% female, median age of 61 years, baseline ECOG performance status of 0 (39%) or 1 (61%), and 26% Caucasian and 72% Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to afatinib [HR 0.58 (0.43, 0.78), $p < 0.001$], with median PFS of 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm. There was no statistically

significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis [HR 0.91 (0.66, 1.25), p=0.55], with a median survival of 28 months in each arm. As the median survival is longer than anticipated with platinum-doublet chemotherapy, cross-over to the afatinib arm may have obscured possible effects of afatinib on survival. In addition, the afatinib also had substantially higher overall response rates (50% vs. 19%). In exploratory analyses, treatment effects varied by the underlying EGFR mutation, with the greatest treatment effect in the subgroup with exon 19 deletions for both PFS and OS and a more modest, but clinically important effect for those with exon 21 L858R substitutions, but with apparent harmful effects for patients with uncommon EGFR mutations receiving afatinib as compared to those receiving chemotherapy.

There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials. In Study 12000.32, the most common adverse reactions ($\geq 20\%$) are diarrhea, rash, stomatitis, paronychia, dry skin, dermatitis acneiform, decreased appetite, and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients in Study 1200.32 consisted of interstitial lung disease (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Areas of special consideration in the review of this application include the enrichment design of Study 1200.32 based on enrollment of patients with specific EGFR mutations, which requires the concurrent approval of a companion diagnostic test. Additional issues that were considered and are discussed in greater detail in this review are

- the safety and efficacy of the proposed dosing regimen
- whether efficacy had been demonstrated in patients with NSCLC bearing uncommon EGFR mutations in Study 1200.32 (LUX-3)
-  (b) (4)
- whether efficacy had been demonstrated for second-line treatment of EGFR mutation-positive NSCLC based on response rates in a relatively small Phase 2 trial (LUX-2 trial)

2. Background

Background on Proposed Indication (non-small cell lung cancer)

There will be an estimated 228,190 new cases of lung cancer and 159,480 deaths from lung cancer in 2013¹. Of these 228,190 cases, approximately 85% are expected to be non-small cell

¹ <http://www.cancer.gov/cancertopics/types/lung>. Accessed March 2, 2013.

lung cancers (NSCLC). Based on SEER data², the estimated 5-year survival rate for patients with metastatic lung cancer is less than 5%. While standard treatment with a platinum-based chemotherapy doublet regimen was considered standard first-line therapy for all patients with NSCLC, emerging evidence has identified subpopulations based on histopathologic diagnosis (e.g., pemetrexed³) or molecular abnormalities (crizotinib⁴) where tumor-based outcomes are superior with targeted therapy. At present, the development paradigm for new drugs for the treatment of NSCLC is moving in the direction of molecularly-targeted agents affecting mutations identified as promoting cancer growth and development.⁵

Available Therapy

Erlotinib: On May 14, 2013, the approved indication for erlotinib was expanded to include the first-line treatment of metastatic NSCLC whose tumors have an epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 substitution (L858R) mutations. The expanded indication is supported by the results of single, investigator-initiated, randomized (1:1), open-label, active-controlled trial (EURTAC trial) conducted in 174 patients receiving first-line treatment for metastatic NSCLC whose tumors had EGFR exon 19 deletion or exon 21 substitution (L858R) mutation as detected by a clinical trial assay at a central academic study site.

The EURTAC trial demonstrated a statistically significant improvement in investigator-determined PFS for patients randomized to erlotinib compared to those randomized chemotherapy [Hazard ratio (HR) 0.34 (95% confidence intervals (CI): 0.23, 0.49), $p < 0.001$] with a doubling of the median progression-free survival from 5.2 months in the chemotherapy arm to 10.4 months in the erlotinib arm. There was no statistically significant difference in survival between the TARCEVA and chemotherapy arms [HR 0.93 (95% CI: 0.64, 1.35)] in an interim analysis, with median survival times of 22.9 months in the erlotinib arm and 19.5 months in the chemotherapy arm. The overall response rate was substantially higher (65% vs. 19%) for the erlotinib arm compared to the chemotherapy arm. The most frequent ($\geq 30\%$) adverse reactions in erlotinib-treated patients were diarrhea, asthenia, rash, cough, dyspnea and decreased appetite, with a median time to onset of rash of 15 days and median time to onset of diarrhea of 32 days. The most frequent Grade 3-4 adverse reactions in erlotinib-treated patients were rash (14%), dyspnea (8%), and diarrhea (5%). One erlotinib-treated patient experienced fatal hepatic failure and four additional patients experienced Grade 3-4 liver test abnormalities, for a total of five (6%) erlotinib-treated patients with Grade ≥ 3 liver test abnormalities.

Drugs approved for the first-line treatment of metastatic NSCLC, without consideration of EGFR mutation status, and the basis for approval are summarized below.

² <http://seer.cancer.gov/statfacts/html/lungb.html>. Accessed March 2, 2013

³ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/021462s015ltr.pdf. Accessed March 2, 2013

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202570s000ltr.pdf. Accessed March 2, 2013

⁵ Genotyping and Genomic Profiling of Non Small-Cell Lung Cancer: Implications for Current and Future Therapies. Li T, Jung H-J, Mack PC, and Gandara DR. J Clin Oncol 45: 3753, 2012.

Paclitaxel protein-bound particles: On October 11, 2012, paclitaxel protein-bound particles was approved, in combination with carboplatin for the first-line treatment of NSCLC, under the provisions of 505(b)(2), relying on the FDA's prior findings of safety and effectiveness for the listed drug, paclitaxel, supported by the results of a single, 1052-patient, open-label, randomized, active-controlled trial. This trial met its primary objective of demonstrating superior overall response rates (33% vs. 25%, $p=0.005$; Odds ratio 1.31) in patients receiving paclitaxel protein-bound particles plus carboplatin as compared to paclitaxel plus carboplatin. Responses appeared to be equally durable in both treatment arms and there were no significant differences in PFS or OS between the two arms.

Crizotinib: On August 26, 2011, crizotinib was approved for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. The approval (accelerated approval) was based on demonstration of unexpected high and durable overall response rates (response rates of 71% and 68% with median response durations of 48.1 and 41.9 weeks) in two single arms trials enrolling a total of 255 patients.

Pemetrexed: On September 26, 2008, pemetrexed was approved, in combination with cisplatin therapy, for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. Approval was based on the results of a multi-center, randomized (1:1), open-label study in 1725 chemo-naïve patients with stage IIIb/IV NSCLC randomized to receive pemetrexed in combination with cisplatin (AC) or gemcitabine in combination with cisplatin (GC). This trial demonstrated clinically relevant differences in survival according to histology favoring the AC arm were observed [HR 0.84 (95% CI: 0.74, 0.96)] for the subgroup of 1252 patients with non-squamous, non-small cell lung cancer in a pre-specified subgroup analysis assessing treatment effect by NSCLC histology. This difference in treatment effect based on histologic subtype was also observed in a trial of single-agent pemetrexed administered as second-line therapy for NSCLC.

Paclitaxel: On June 30, 2008, paclitaxel was approved, in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. Approval was based on the results of a single, randomized, 3-arm, open-label trial conducted in 599 patients with chemotherapy-naïve NSCLC. This trial demonstrated a statistically significant improvement in PFS (median PFS 4.3 vs. 2.7 months, $p<0.05$), overall response rate (25% vs. 12%, $p<0.001$), and a trend towards improved overall survival (median survival 9.3 months vs. 7.4 months) for the combination of paclitaxel 135 mg/m² plus cisplatin as compared to cisplatin alone. The comparison of paclitaxel 250 mg/m² plus cisplatin to cisplatin alone also demonstrated statistically significant improvements in overall survival for progression-free survival and overall response rate with a trend for improvement in overall survival (median survival times of 10 months vs. 7.4 months, $p=0.08$).

Bevacizumab: On October 11, 2006, bevacizumab was approved for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC, in

combination with carboplatin and paclitaxel. Approval was based on the results of a single, randomized, active-controlled, open-label, multicenter study in 875 patients receive first-line therapy for locally advanced, metastatic or recurrent non-squamous, NSCLC. Patients were randomized to receive paclitaxel plus carboplatin alone (PC) or PC plus bevacizumab. The trial demonstrated an improvement in overall survival (median survival 12.3 months vs. 10.3 months: HR 0.80, p-value 0.013].

Gemcitabine: In 1998, gemcitabine was approved, in combination with cisplatin, for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC. Approval was based on the results of two randomized, open-label, trials enrolling 657 patients receiving first line- chemotherapy for locally advanced or metastatic cancer. The results demonstrated improved survival for patients receiving gemcitabine plus cisplatin compared to cisplatin alone (median survival 9.0 vs. 6.7 months, p=0.008) and improvement in time-to-disease progression for patients randomized to receive gemcitabine plus cisplatin compared to etoposide plus cisplatin (median time-to-progression 5.0 vs. 4.1 months, p=0.015) and higher response rates (33% vs. 14%, p=0.01), with no decrement in survival.

Vinorelbine: On December 23, 1994, vinorelbine was approved as a single agent, or in combination with cisplatin, for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC. Approval was based on the results of two randomized, active-controlled trials. The first randomized, open-label, add-on trial compared navelbine plus cisplatin alone in 432 patients receiving first-line chemotherapy for Stage IIIB or IV NSCLC. The second trial was a randomized, 3-arm, open-label, trial in 612 patients with Stage III or IV NSCLC receiving first-line chemotherapy. Patients were randomized to receive vinorelbine alone, vinorelbine plus cisplatin, or vindesine plus cisplatin. These trial demonstrated a significant increase in survival for patients randomized to vinorelbine plus cisplatin compared to cisplatin alone (median survival 7.8 months vs. 6.2 months, p=0.01) and for patients randomized to vinorelbine plus cisplatin compared to vindesine plus cisplatin (median survival 9.2 vs. 7.4 months, p=0.03).

Methotrexate: FDA-approved labeling states that “Methotrexate is used alone or in combination with other anticancer agents in the treatment of lung cancer, particularly squamous cell and small cell types.” The basis for approval is unclear. The use of methotrexate as a treatment for NSCLC has been supplanted by more active agents.

For more than a decade, the standard of care in the United States for treatment of NSCLC was platinum-based doublet chemotherapy. In 2002, the published results of a 4-arm, open-label, randomized (1:1:1:1) trial. The “control” arm was the paclitaxel/carboplatin arm, which was the most commonly used platinum-doublet in the US at the time of this trial and the regimen for which paclitaxel is approved for the treatment of NSCLC. The trial demonstrated similar outcomes for the following regimens:

- Cisplatin plus paclitaxel (control), consisting of paclitaxel, 135 mg/m² over 24-hr period on day 1 and cisplatin, 75 mg/m² on day 2 of each 21-day cycle
- Cisplatin plus gemcitabine, consisting of gemcitabine, 1000 mg/m² on days 1, 8, and 15 and cisplatin, 100 mg/m² on day 1 of each 28-day cycle

- Cisplatin plus docetaxel, consisting of docetaxel, 75 mg/m² on day 1 and cisplatin, 75 mg/m² on day 1 of each 21-day cycle
- Carboplatin plus paclitaxel consisting of paclitaxel, 225 mg/m² over 3-hr period on day 1 and carboplatin, AUC 6.0 mg/mL/min on day 1 of each 21-day cycle

The authors concluded that all the combinations have similar efficacy.⁶ However, because of its more favorable safety profile, the Eastern Collaborative Oncology Group (ECOG) selected carboplatin/paclitaxel as its reference regimen for future studies.

Regulatory History (pre-NDA submission)

December 31, 2003: IND 67,969 for BIBW 2992 (afatinib) [REDACTED]

(b) (4)

[REDACTED] is allowed to proceed.

July 31, 2007: EOP1 meeting to discuss a planned, randomized, placebo-controlled trial (Protocol 1200.23) of afatinib monotherapy in patients with NSCLC following treatment with erlotinib/gefitinib and at least one prior line of cytotoxic chemotherapy as a basis for an NDA. The study was designed to enrich for a patient population whose tumors may have acquired the EGFR T790M resistance mutation by requiring at least 12 weeks of treatment with erlotinib or gefitinib prior to study entry. Key agreements or comments on the study design included the following:

- The proposed primary endpoint of PFS. FDA stated that whether an improvement in PFS will support approval will depend on the magnitude of the benefit and the risk benefit ratio. FDA recommended that overall survival as the primary endpoint.
- Claims based on the EORTC QLQ-C30 and LC13 instruments would be considered if results are convincing for all 5 "functioning" domains of the EORTC QLQ-C30 (physical, role, cognitive, emotional, and social), an HRQL claim, the trial is adequately designed and powered for this endpoint, the data are interpretable in light of plans to measure time to deterioration in HRQL, and the standards for demonstrating substantial evidence standard are met after review of the data for missingness, multiplicity, maintenance of the double-blind and reproducibility.
- FDA stated that a cross-over design was not recommended based on lack of safety and efficacy data with afatinib.
- FDA discouraged the proposal to conduct an interim analysis of PFS to support a request for accelerated approval based on the small number of PFS events
- FDA stated that BI's proposal to verify a request for accelerated approval based on Protocol 1200.23 by submission of the final analysis of overall survival from 1200.23 and an additional trial, Protocol 1200.32, a randomized trial comparing afatinib monotherapy to carboplatin, paclitaxel, and bevacizumab in treatment-naive patients with advanced stage NSCLC whose tumors harbor EGFR activating mutations, with a primary efficacy endpoint for Protocol 1200.32 of PFS, was acceptable however the primary endpoint of 1200.32 should be overall survival.
- FDA agreed that a request for waiver from the requirements of PREA was appropriate

⁶ Schiller JH, Harrington D, Belani CP, et al: Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 346:92-98, 2002.

- FDA stated that a proposal for evaluation effects on QT intervals should be submitted to the IND at this stage of development.

November 9, 2007: Fast Track Designation for afatinib granted (b) (4)
 (b) (4) in response to October 15, 2007 request for designation submitted to IND (b) (4).

June 6, 2008: teleconference to discuss deficiencies in proposed evaluation of the effects of afatinib on the QT interval. BI agreed to submit a revised plan.

October 16, 2008 EOP1 meeting to discuss the acceptability of the existing clinical data to support the conduct of Protocol 1200.32 and the overall study design specific, endpoints, and statistical analyses for Protocol 1200.32. Key agreements or comments on the study design included the following:

- Enrichment for a patients with tumors having EGFR-mutations based on clinical criteria (adenocarcinoma subtype, never smokers/light smokers) was reasonable strategy, however it may be appropriate to further narrow the indication to patients with adenocarcinoma and the presence of activating EGFR mutations.
- FDA recommended stratification of randomization based on results of EGFR status based on results from analytically-validated test.
- FDA stated that was essential that “review and approval of the drug for indications dependent on the result of an EGFR mutation test shall be accompanied by review and approval of the EGFR mutation test as well.” BIO agreed to contract with a third-party for development of a diagnostic test and to discussion this proposal with CDRH prior to submission of an SPA for Protocol 1200.32.
- The proposed comparator arms were acceptable.
- FDA stated that a substantial, robust improvement in PFS that was clinically meaningful and statistically persuasive, and had an acceptable risk-benefit profile may be considered for regulatory decision-making. FDA cautioned that measurement of PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. BI agreed to remove a proposal for interim analysis for efficacy based on PFS.
- FDA stated that the trial should be powered to assess effects on overall survival; BI agreed to make this a secondary endpoint.
- FDA recommended that sparse PK sampling be obtained in Protocol 1200.32 as well as in Protocol 1200.23 in order to evaluation population PK analyses.
- FDA stated that a dedicated PK study should be conducted in patients with hepatic impairment, that a dedicated DDI study be conducted with ketoconazole and rifampin, and that a formal bioequivalence study would not be required however full PK profiles of all strengths administered in Protocol 1200.32 would be needed based on changes in formulation between Phase 2 and Phase 3 trials.
- With regard to CMC, the NDA should contain 1) comparative test data on drug product batches from both Phase 2 and Phase 3/to-be-marketed drug products using same specification with identification of any new impurities observed at release and at stability; 2) comparative stability test data to bridge between drug products from Phase

2 and Phase 3/to-be-marketed formulation, and 3) comparative in vitro dissolution for drug product from Phase 2 and Phase 3 /to-be-marketed formulations. Also, any other change (e.g. manufacturing, analytical methods) for new formulation and strength should be indicated.

November 6, 2008: Agreement for Special Protocol Assessment to assess the stability of the afatinib drug product.

April 16, 2009: SPA non-agreement letter for Protocol 1200.32 issued. Primary areas of non-agreement were

- The proposed primary endpoint of progression-free survival. FDA stated that a substantial, robust improvement in PFS that was clinically meaningful and statistically persuasive, and has an acceptable risk:benefit profile may be considered for regulatory decision making. However since all previous approvals in the first-line setting of NSCLC were based on overall survival as the primary endpoint, an application based on PFS would likely be referred to the Oncologic Drugs Advisory Committee.
- Lack of proposed plan for assessment of discordance between investigator- and IRC-determined PFS events
- Lack of proposed sensitivity analyses for evaluating the impact of missing data (patients who are removed from study based on investigator-determined PFS events not subsequently confirmed by the IRC)
- Need to demonstrate a highly statistically robust treatment effect, consistent within subgroups, for a single efficacy trial supporting an NME NDA
- Lack of information on the validated test kit to be used to for patient selection

December 15, 2009: preNDA meeting based on results from Protocol 1200.23, supported by results from Protocol 1200.22. Key agreements or comments on the proposed NDA submission the following:

- FDA and BI reached agreement on the schedule and components for a rolling submission of the proposed NDA
- Agreed that QT and hepatic impairment data can be provided post-approval, however FDA requested that BI submit the hepatic impairment protocol (1200.86) for review.
- FDA and BI reached agreement on the proposed exposure- efficacy and exposure-safety analyses, with the proposed clinical PK datasets to be provided.
- FDA agreed that an ISE was not required. FDA and BI reached agreement on the proposed SCS safety groupings. With regard to analyses in the SCS, the statistical reviewers agreed that BI could provide analysis datasets for Tables presented in the SCS however the medical reviewer stated that a follow-up meeting would be required on this issue following submission of item 3 described under the next bullet.
- BI agreed to provide 1) patient narratives for Safety Update Report; 2) case report forms serious adverse events occurring in Protocols 1200.22 and 1200.23; 3) analysis datasets for tables in the SCS.
- Datasets would be compliant with the Data Standard document (UCM189445.pdf) but will use a format and variable names specific to BI and will not be those specified for CDISC and ADAM format.

- BI agreed to submit a detailed document cross-referencing specific tables with datasets and programs for the FDA's review.
- CDRH clarified that results from biomarker analysis performed in Study 1200.23 and any efficacy data from Study 1200.22 would not impact the indication statement.

December 9, 2011: pre-NDA meeting for afatinib to support the following proposed indication “afatinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s)”. The proposed NDA package would be based on results of the following trials: 1200.32 (pivotal) and 1200.22, 1200.23, and 1200.42 (3 supportive trials). Key agreements or comments on the proposed NDA submission the following:

- BI acknowledged FDA’s statement that the indication will be a review issue and should reflect the patient population enrolled in the trials.
- FDA could not state whether submission of the PMA was a filing issue for the NDA. BI acknowledged FDA’s statement both the test kit and drug, if approved, should both be approved simultaneously.
- FDA and BI reached agreement on the contents and location of information for the ISE; BI agreed to provide CSRs with efficacy data for Protocols 1200.33 and 1200.72, which also enrolled patients with NSCLC. BI agreed to provide safety data from the proposed trials as well as from Protocols 1200.33, 1200.34, 1200.40, 1200.41, and 1200.72.
- BI and FDA reached agreement on submission of patient narratives as follows: (1) Patient narratives would be submitted from all trials conducted in NSCLC for the following adverse events regardless of relationship to study drug - interstitial lung disease events, decreased LVEF or heart failure, and hepatic failure events regardless of their relationship to study.
- The acceptability of an Expanded Access Program (EAR) would be dependent on the outcome of the 1200.32 trial.

June 5, 2012: Expanded Access Program (EAP) for afatinib in the US (Trial 1200.45), submitted to IND (b) (4) on May 25, 2012, allowed to proceed.

October 10, 2012: Teleconference held and agreement reached on the contents of a complete NDA, in accordance with PDUFA V. There was agreement that no portion of the application would be submitted within the first 30 days of receipt and that a REMS did not appear necessary to ensure safe use. On October 19, 2012, FDA confirmed that the proposed dataset plan was acceptable, via electronic mail message from the RPM.

Regulatory History of NDA 201292

Boehringer Ingelheim requested priority review designation, as the findings demonstrated clinical superiority over the recognized standard of care in first-line EGFR mutation-positive NSCLC (LUX-Lung 3) and evidence of benefit in later lines of treatment, where limited or no alternative treatment options exist (LUX-Lung 1 and LUX-Lung 2). Justification noted that there were no drugs specifically approved for use in patients with EGFR mutation-positive NSCLC and that the LUX-Lung 3 trial demonstrated a clinically

meaningful and statistically robust improvement in progression-free survival for the afatinib-containing arm as compared to those randomized to pemetrexed and cisplatin for the first-line treatment of patients with NSCLC (HR 0.58, p=0.0004) with median PFS times of 11.1 months for the afatinib-containing arm as compared to 6.9 months for chemotherapy alone, based on independent review. In the subset of patients with the two most common EGFR mutations, the treatment effect was larger (HF 0.47, p<0.0001) with median PFS times of 13.6 months for the afatinib-containing arm as compared to 6.9 months for chemotherapy alone. These findings were supported by a clinically meaningful and statistically robust increase in overall response rates (56.1% vs. 22.6%, p<0.0001, independent review).

BI proposed the following indication

(b) (4)

(b) (4)

(b) (4) In this trial, patients randomized to afatinib experienced longer PFS (HR 0.38, p<0.0001 per independent review) with median PFS times of 3.3. months in the afatinib arm compared to 1.1 months for the placebo arm. In addition, the overall response rate was statistically significantly higher (7.4% vs. 0.5%, p= 0.0071), however the difference is not considered clinically important.

3. CMC/Biopharmaceutics

CMC and Biopharmaceutics

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and that there are no outstanding CMC issues that preclude approval.

Afatinib (free base) is a new molecular entity which is chemically synthesized; the salt form is afatinib dimaleate. The drug substance, (b) (4) is (b) (4) generated during synthesis. The synthetic process was optimized during drug development, potential impurities and degradants were identified and are appropriately controlled, the release specification and analytical procedures are described in sufficient detail and validated for their intended uses; since the methods were not novel or complex, additional evaluation by FDA's methods validation staff will be conducted post-approval. Acceptance criteria were justified by batch analysis data and during clinical studies.

The drug product, Gilotrif, will be supplied as film-coated tablets in the following strengths: 40 mg, 30 mg, or 20 mg afatinib (free base), which corresponds to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate. The proposed dissolution methodology, the dissolution acceptance criterion, and the comparative dissolution profiles between the drug product used in the pivotal trials and the proposed commercial drug product were determined to be acceptable. The quality of commercial Afatinib tablets was determined to be acceptable based on assessment of the manufacturing process and process controls and analytical procedures for identification, purity, strength, and stability. Stability testing supports an expiry of 24 months.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

In *in vitro* or nonclinical models, afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR and in cell lines expressing EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations that are achieved, at least transiently, in patients. Afatinib also inhibited *in vitro* proliferation of cell lines over-expressing HER2.

The primary general toxicology studies were conducted in rats and minipigs. The toxicologic findings mirrored the human safety profile, with evidence of gastrointestinal, cutaneous, ocular (corneal atrophy), renal, and pulmonary parenchymal toxicity observed in one or both species tested.

A potential adverse reaction, not observed in clinical trials, was identified by the clinical pharmacologists, based on the observation that the major metabolic products of afatinib are protein adducts, including hemoglobin, and that afatinib was highly associated with red blood cells in all species. This finding has been associated with idiosyncratic adverse reactions.

In safety pharmacology studies, decreased left ventricular ejection fraction was observed in minipigs receiving afatinib at a dose of 30 mg/kg, which correlated with observations in clinical trials. The evaluation for effects on electrophysiology (*in vitro* hERG testing and *in vivo* ECG monitoring in minipigs and rats) were consistent with studies in human subjects, indicating that risk of QT prolongation at the recommended human dose/exposures were low.

Reproductive toxicity studies were conducted in rats and rabbits for evaluation of effect on embryofetal development. Based on these studies, embryofetal toxicity is predicted at the recommended dose and expected exposure with afatinib in humans. Non-clinical studies demonstrated an increased risk of abortion, increased risk of resorption, visceral and skeletal variations (delayed ossification), and lower fetal weights. Studies in female rats also suggested impairment of fertility, based on the observation of decreased number of corpora lutea and increases in pre-implantation loss and early resorptions at exposures expected in humans at the recommended dose and by effects on reproductive organs observed in the general toxicology studies.

Afatinib was present at high concentrations in the milk of lactating rats.

In a dedicated fertility study, evidence of effects on male fertility were identified which included epithelial atrophy and a dose-dependent increase in the incidence of hypospermia

Based on the totality of the *in vitro* testing, including conflicting results between the Ames and other tests, neither afatinib nor its major metabolites are considered to be genotoxic.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The median time to reach peak plasma concentration (T_{max}) was 5 hours after a single oral dose and 3 hours after multiple doses of afatinib. Steady state was attained following 8 days of afatinib administered daily. The elimination half-life was 21-27 hours after a single dose and 45 hours at steady state. The relative bioavailability was 92% (90% CI: 76%, 112%) based on AUC_{0-inf} after a single dose of 20 mg tablet compared to an oral solution.

The major form of afatinib presented in human plasma is covalent adducts to plasma proteins and minor metabolites catalyzed by CYP450 enzymes. A mass balance study suggested that the major route of excretion of afatinib was via feces (85%) while 4% in urine.

Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinical relevant effect on exposure of afatinib. Formal organ impairment studies were not submitted in the NDA and were initially not considered necessary based on the metabolism of afatinib as described in the paragraph above and on the summary results of the population PK analysis. There were no clinically significant differences in exposure between patients with normal, mild or moderate hepatic impairment. In the population PK studies, mild renal impairment has no effect on afatinib systemic exposure and the increases in trough concentrations with moderate renal impairment not considered clinically important based on overall population PK analyses. However, based on a re-analysis of data from Study 1200.32, limited to patients receiving afatinib at 40 mg daily, a clinically important increase in trough concentrations were identified among patients with renal impairment; this has been noted in product labeling and will be further evaluated in a formal organ impairment study to be conducted under a post-marketing requirement.

Based on the regimen used in Study 1200.32, BI proposed a recommended dose of afatinib 40 mg orally once daily, (b) (4). However, in Study 1200.32, only 16 of the 229 patients randomized to afatinib and receiving at least one dose of study drug underwent escalation to the 50 mg dose; of these, 10 were unable to tolerate dosing at 50 mg daily. In addition, the analysis assessing the exposure-response relationship suggests that the 50 mg daily dose does not result in better or similar efficacy. Specifically, in the exposure-efficacy analyses assessing outcomes by exposure quartile in Study 1200.32, patients in the highest quartile for steady state AUC had shorter progression-free survival times as compared to other quartiles – this decrement in PFS was clinically important and similar to that observed in the control arm, suggesting loss of treatment effect. In addition, the results of logistic regression analyses suggested that higher exposure of afatinib increased the risk of experiencing an adverse reaction of NCI CTCAE grade 3 severity or grade 2-3 diarrhea.

In food-effects studies, afatinib exposure was decreased (39% in AUC_{0-inf} and 50% in C_{max}) after a high-fat meal as compared to that under the fasted condition. Product labeling reflects

this information and provides dosing recommendations that afatinib to be taken at least one hour before or two hours after a meal.

Based on evaluation for possible drug interactions, product labeling includes recommendations for reduction in the dose of afatinib in patients who require concomitant P-gp inducers or inhibitors since afatinib is both a substrate and inhibitor of the P-gp transporter. Specifically, clinically important changes in afatinib exposure were observed when afatinib was administered with ritonavir (a P-gp inhibitor) or rifampicin (a P-gp inducer).

6. Clinical Microbiology

Not applicable. Assessment of potential sterility concerns were evaluated by the CMC reviewer who determined that the manufacturing process and controls, which do not involve novel or complex methodology, were adequate to ensure product sterility.

7. Clinical/Statistical-Efficacy

The scope of the clinical program was adequate to evaluate safety and efficacy for the narrowed indication. BI relied primarily on the results of four clinical trials to support labeling claims [REDACTED] (b) (4).

[REDACTED]. Issues relating to study design and outcomes for the three supportive trials (LUX-1, LUX-2, and LUX-4) are briefly described below, while the major efficacy trial supporting the recommendation for approval is summarized in greater detail.

Trials intended to support claims for afatinib in the treatment of patients with NSCLC who have not received prior EGFR TKI therapy

- LUX-Lung 3: The design and results of trial are described in detail below
- LUX-Lung 2: This open-label, single-arm, activity-estimating trial was conducted in 129 patients with locally advanced or metastatic lung adenocarcinoma containing an EGFR mutation who had not received prior EGFR TKI therapy. EGFR mutation status was evaluated by PCR testing with a clinical trials assay. Approximately half these patients had received no prior chemotherapy (n=61) and the remainder had received only on prior line of chemotherapy (n=68) (i.e., after failure of first-line chemotherapy). Approximately three-quarters of the patients received afatinib at a dose of 50 mg daily (n=99) and the remaining 30 patients received afatinib 40 mg daily. The primary endpoint of the trial was determination of overall response. Based on independent review, BI reported that the ORR in the first-line setting was 66% with a median duration of 13.5 months, while the ORR in the second line setting was 57% with a median duration of response of 12.9 months. While these data are supportive, they do not extend the clinical efficacy data described in Study 1200.32 and as a single arm trial, they are not deemed more reliable.

Trials intended to support claims in patients with NSCLC who have received prior EGFR TKI therapy

- LUX-Lung 1: This was a randomized (2:1), placebo-controlled trial conducted in 585 patients receiving third or fourth line treatment for NSCLC; all patients had previously received 1 or 2 lines of chemotherapy, one of which was required to have been a platinum-containing regimen, and to have progressed after treatment with an EGFR-TKI (either gefitinib or erlotinib). Of the 585 patients, 390 were randomized to receive afatinib 50 mg daily and 195 patients were randomized to matching placebo. Patients were not screened for the presence of EGFR mutations but were considered to be clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. The primary endpoint in this study was OS with a secondary endpoint of PFS.

The study population demographics were female (59%), median age of 61 years, baseline ECOG performance status of 0 or 1 (92%), either White (33%) or Asian (66%). All patients were required to have received prior platinum-containing regimen, 60% had 1 line and 39% had 2 lines of prior chemotherapy for metastatic disease. All patients had received prior EGFR TKI therapy, consisting of erlotinib (55%), gefitinib (40%) or both (5%).

The trial failed to meet its primary endpoint, of demonstration of improved survival, with a median survival of 10.8 months for afatinib-treated patients and 12.0 months for patients in the placebo arm. Therefore, the effects on PFS cannot be considered statistically significant and is of unclear clinical importance with an improvement in median PFS time of 2.2 months for afatinib (median PFS 3.3 months) as compared to placebo (median PFS 1.1 months). Similarly, the higher response rate observed with afatinib is not clinically meaningful as it remains less than 10%.

- LUX-5: This was an open-label, randomized, multicenter trials conducted in 1154 patients with patients with unresectable or metastatic NSCLC. Eligibility criteria were similar to those in the LUX-1 trial. All patients received afatinib 50 mg daily; at the time of disease progression, the subgroup deemed to have clinical benefit (without disease progression for ≥ 12 weeks) received afatinib 40 mg daily plus paclitaxel or to receive investigator's choice chemotherapy.

(b) (4)

FDA did not consider the LUX-5 study adequate in design as the patient population enrolled did not correlate with EGFR mutation status. Further, the retrospective analyses conducted are considered exploratory, at best, and do not meet the criteria for substantial evidence of effectiveness as described in FDA's Guidance on Clinical Effectiveness for Drugs and Biologics.

Trial Design – Study 1200.32 (LUX-3)

The efficacy and safety of GILOTRIF for the first-line treatment of EGFR mutation-positive non-squamous, non-small cell lung cancer (NSCLC) was evaluated primarily in Study 1200.32 (LUX-Lung 3), 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.”

The data were deemed reliable based on (b) (4) inspections of six clinical sites and the contract research organization (CRO) responsible for conducting the clinical trial on behalf of BI.

Key eligibility criteria EGFR mutation-positive, metastatic (Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer [AJCC, 6th edition]) NSCLC were established in a randomized, multicenter, open-label trial (Study 1). Patients were randomized (2:1) to the following treatment arms

- afatinib 40 mg orally once daily until disease progression or unacceptable toxicity
- pemetrexed 500 mg/m² intravenously with cisplatin 75 mg/m² intravenously, every 21 days for up to six 21-day cycles

Patients were assessed for tumor status every 6 weeks for the first 48 weeks on study, then every 12 weeks, thereafter. Safety monitoring included assessment of left ventricular ejection fraction at baseline, on day 1 of cycle 4, then every third treatment cycle thereafter.

Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included objective response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA).

The primary analysis was to occur after 217 PFS events. This sample size assumed 90% power to detect a hazard ratio of 0.64. An interim analysis of survival was pre-specified; it was to occur at the time of the primary analysis, using a stopping boundary of $p < 0.0001$. The final OS analysis is to occur after 209 deaths. At FDA’s request, an updated analysis of survival was requested during review of the submission; this analysis is described in the results presented below, however because it was conducted based on FDA’s request, no adjustment for alpha will be required at the final analysis of OS, which will be submitted as an agreed-upon post-marketing commitment.

Results

A total of 345 patients were enrolled, of whom 230 were randomized to receive afatinib 40 mg daily and 115 were randomized to receive chemotherapy. Demographic characteristics for the study population were 65% female, median age of 61 years, baseline ECOG performance status of 0 (39%) or 1 (61%), and 26% Caucasian and 72% Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

The results of Study 1200.32 provide substantial evidence of effectiveness of afatinib in this patient population. A statistically significant and clinically important improvement in PFS, as determined by the IRC, was demonstrated for patients randomized to afatinib compared to those randomized to chemotherapy, however there was no statistically significant difference for overall survival between the treatment arms at the interim analysis conducted at 84% of the planned events for the final analysis. The key efficacy results are provided in the following table and the Kaplan-Meier curves for PFS are presented in the figure following the table.

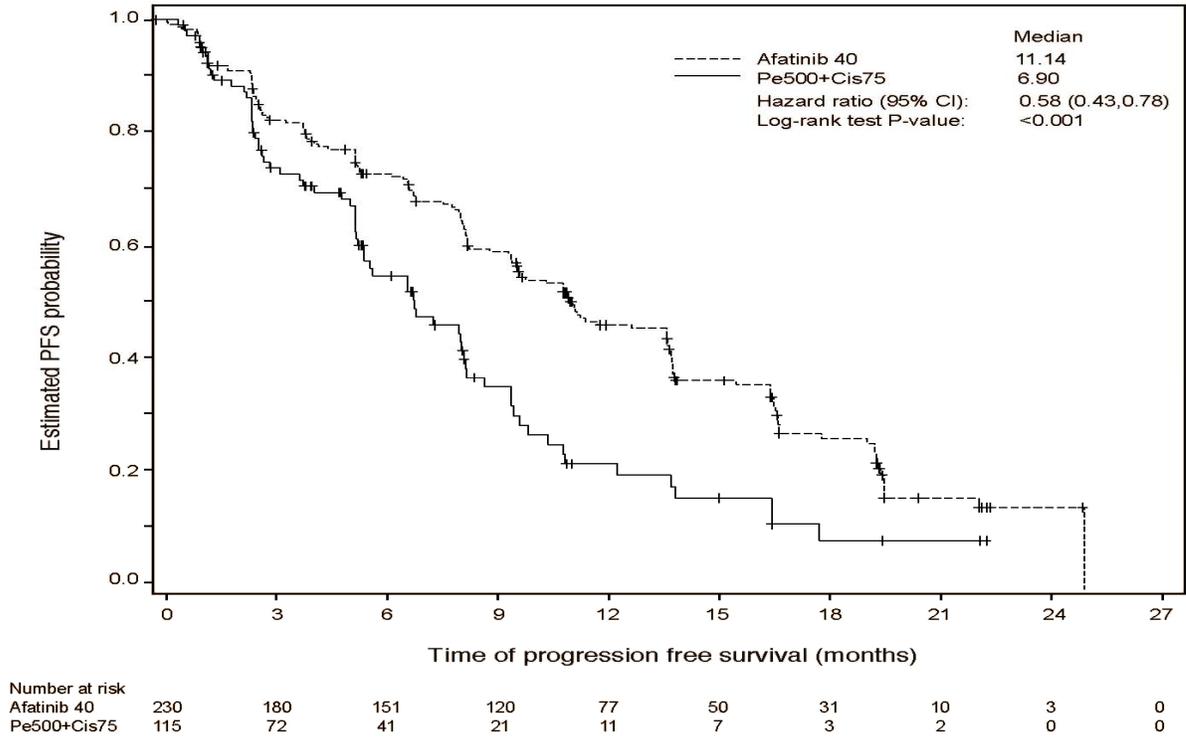
Table 3: Efficacy Results of Study 1

	BRAND (N=230)	Pemetrexed/Cisplatin (N=115)
Progression-free Survival		
Number of Deaths or Progressions, 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*	<0.001	
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*	0.55	
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 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group

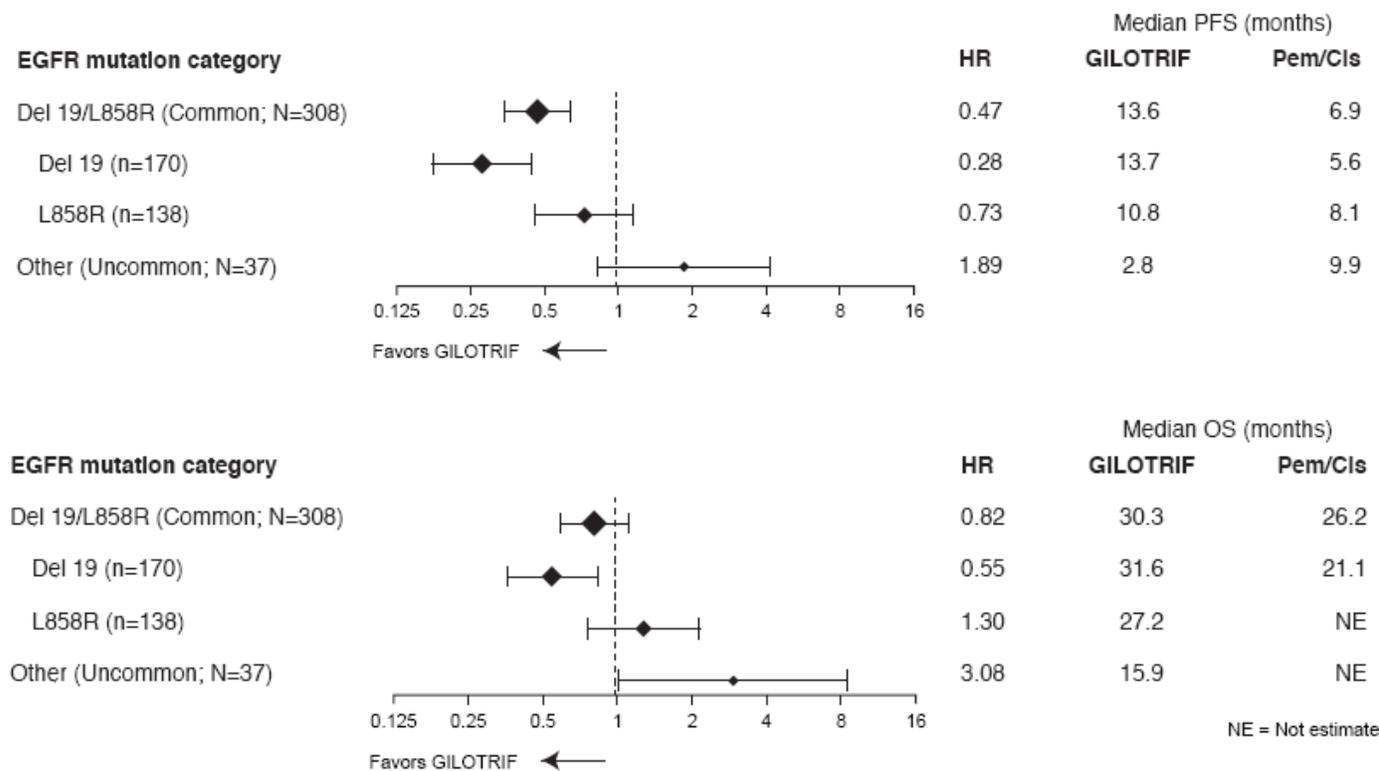


Exploratory analyses by EGFR mutation type

Tumor samples from 264 patients (178 randomized to afatinib and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*[®] EGFR RGQ PCR Kit, which will be approved concurrent with the approval of afatinib. The treatment effects of afatinib were similar in this subpopulation identified by the to-be-marketed companion diagnostic as those observed with the clinical trial assay.

The clinical trial stratified randomization by EGFR mutation type (exon 19 deletions vs. exon 21 L858R substitution vs. other mutations) using the clinical trials assay. Based on concerns that the treatment effect may differ based on the underlying mutation, FDA performed exploratory subgroup analyses for PFS and OS based on the stratification factor of EGFR mutation status and on the subgroup of “common” mutations for which afatinib will be indicated. These data are displayed in the Forest plots, taken from the product labeling and reproduced below.

Figure 2 Forest plot of PFS and OS for Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories



Based on these analyses, FDA concluded that the treatment effect is dependent on the the underlying EGFR mutation. While PFS and OS show a consistent improvement for afatinib-treated patients, those with “other” mutations show a consistent and worse outcome when receiving afatinib as compared to standard chemotherapy. Similar findings were observed in an additional study of afatinib submitted to the IND (i.e., favorable treatment effects in patients with exon 19 deletions or exon 21 L858R substitutions but not in pooled analyses of patients with other less common mutations). These findings do not rule out the possibility that other less common mutations may benefit however there is insufficient data provided in the NDA to identify such subgroups.

To further investigate the possibility of benefit is specific less common mutations, FDA evaluated the objective response rates in patients with these less common mutations. There were 26 afatinib -treated patients in the “other” (uncommon) EGFR mutations subgroup with nine unique mutation patterns. Of the 26 afatinib-treated patients in the “other” EGFR mutation subgroup, four (15%) achieved a partial response and of the 11 chemotherapy-treated patients in the “other” EGFR mutation subgroup, four (36%) achieved a partial response. Among the afatinib-treated patients, at least one patient with mutations in L858R and T790M, L858R and S768I, S768I alone, or G719X alone achieved a partial response; information on the response rate observed in patients with these mutations are displayed in the table below, reproduced from the product labeling. No responses were seen in afatinib-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 4 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the “Other” (uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

The results of Study 1200.32 provide substantial evidence of the effectiveness of afatinib for the first-line treatment of patients with EGFR mutation-positive NSCLC. Exploratory subgroups by EGFR mutation type were conducted by FDA to evaluate for differential treatment effects which may correlate with *in vitro* assessments of inhibitory capacity by mutation site. Although exploratory, the consistency observed for differential treatment effect by mutation type for PFS and OS and the high-level results submitted to the IND for an additional randomized trial of afatinib in a similar population suggest that these findings are real. Such information is important to prescribers and patients to characterize treatment outcomes and will be useful as new agents against this target are developed.

8. Safety

The size of the safety database was adequate; the data based included safety information from more than 3800 patients, including 2135 patients which NSCLC. In addition, safety data were available from randomized, controlled trials of 229 afatinib-treated patients with EGFR mutation-positive, metastatic, non-squamous, NSCLC who were enrolled in Study 1200.32. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure to afatinib was 11.0 months and to pemetrexed/cisplatin chemotherapy was 3.4 months. The overall trial population had a median age of 61 years, 64% of patients who received afatinib and 67% of patients who received pemetrexed/cisplatin were female, and 70% of patients who received afatinib and 72% who receive pemetrexed/cisplatin chemotherapy were Asian.

Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse

reactions in afatinib -treated patients in Study 1200.32 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of afatinb-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with afatinib were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in afatinib-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Table X Adverse Reactions Reported in ≥10% of Afatinib-Treated Patients in Study 1

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3* (%)	All Grades (%)	Grade 3* (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis ¹	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/Dermatitis acneiform ²	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections and infestations				
Paronychia ³	58	11	0	0
Cystitis	13	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	29	4	55	4
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*None of the adverse reactions in this table were Grade 4 in severity

¹Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

²Includes group of rash preferred terms, acne, acne pustular, dermatitis acneiform

³Includes paronychia, nail infection, nail bed infection

Table X Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported in ≥5% of Afatinib-Treated Patients in Study 1

	Afatinib n=229	Pemetrexed/Cisplatin n=111
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Adverse Reaction	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Alanine aminotransferase increased	11	2	4	0
Hypokalemia ¹	11	4	5	4
Aspartate aminotransferase increased	8	2	2	1

¹Includes hypokalemia, blood potassium decreased

Post-marketing Surveillance

Based on the Non-clinical Pharmacology review, a theoretical risk of idiosyncratic drug reactions, specifically hemolysis, was identified. The potential for this risk is based on the binding of afatinib to hemoglobin. The OSE review staff will be alerted to this potential risk so that monitoring can be targeted for this event.

REMS

Both the clinical review team and the DMEPA consultant agreed that a REMS was not required to ensure safe and effective use of afatinib. The risks of afatinib are adequately conveyed in professional and patient labeling.

PMRs and PMCs

One PMR was requested by the Clinical Pharmacology team to evaluate the pharmacokinetics of afatinib in patients with renal impairment. The rationale for this requirement is discussed in Section 5 of this summary review.

9. Advisory Committee Meeting

This efficacy supplement was not referred for review to the Oncologic Drugs Advisory Committee because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. Specifically, the clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

10. Pediatrics

The applicant requested a waiver from the requirements of the Pediatric Research Equity Act (PREA) for pediatric patients less than 18 years of age in the original NDA submission on November 15, 2012. The justification for this requested waiver was that studies are impossible or highly impractical because the number of pediatric patients with non-small cell lung cancer is so small. Since orphan designation was granted for afatinib on December 3, 2012 for “treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer (NSCLC) as detected by an FDA-approved test,” afatinib is exempt from the requirements of PREA for this indication and the requested waiver was deemed irrelevant.

11. Other Relevant Regulatory Issues

With the exception of lack of agreement on final labeling for the companion diagnostic, there are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The initial request for proprietary name submitted with the NDA was not accepted by DMEPA based on the potential for medication errors based on writing samples. The second request (GOLTRIF) was submitted March 4, 2013 and determined to be acceptable by DMEPA, OPDP, and DOP2.
- Physician labeling- All major issues were resolved; a summary of clinically important modifications are discussed by labeling section, below
 - Indications and Usage: In agreement with BI and at FDA's request, the proposed indication was limited to first-line treatment and to the specific EGFR mutations (exon 19 deletions or exon 21 L858R substitution) where efficacy has been established. Added a limitation of use stating that the efficacy of afatinib has not been established for other EGFR mutations.
 - Dosage and Administration: Modified this section to add a new subsection denoting that patient selection using a companion diagnostic test should be used to identify patients for whom afatinib is indicated. (b) (4)
 - Dosage and Administration: (b) (4)
 - Dosage and Administration: (b) (4) Added specific dose modifications for afatinib when given with a P-gp inhibitor or with a P-gp inducer based on the pharmacokinetic data submitted in the NDA as discussed in Section 5 of this review. Edited the recommendations on dose modification for brevity, clarity, and consistency with treatment as administered in Study 1200.32.
 - Dosage Forms and Strength: (b) (4)
 - Warnings and Precautions: Modified to include specific information on the risk of serious adverse reactions in Study 1200.32 or in the overall safety database. Retitled sections on "Skin Adverse Reactions" and "Pregnancy" to provide more information on the severity and type of adverse reactions. (b) (4)

- Adverse Reactions: This section was revised to include information specified in FDA Guidance on product labeling for Adverse Reactions, such as description of the study treatment and extent of exposure, description of the patient population demographics, identification of the most serious toxicities and those resulting in treatment discontinuation. The tables of adverse reactions based on Study 1200.32 was modified in accordance with the FDA Guidance on this section to adverse reactions occurring more commonly in the experimental arm than in the control arm ($\geq 5\%$ overall increased risk for any adverse reaction or $\geq 2\%$ increased risk for grade 3-4 adverse reactions). The listing of adverse reactions occurring in less than 10% of patients in Study 1200.32 was modified

(b) (4)

(b) (4)

- characterizing the effects of rifampin on afatinib based on a specific drug interaction study.
- Use in Specific Populations
 - The subsections on Pregnancy and Nursing Mothers was revised for consistency with the Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. As recommended by the Maternal Health consultant, this section was revised to comply with current regulations but restructured in the spirit of the Proposed Rule. The Geriatric Use subsection was revised to include data on exposure in elderly patients in 3800+ patients and summary statement indicating that there are no apparent differences between older and younger patients. Editorial changes to the subsections on Renal and Hepatic Impairment.
- Overdosage: Edited
- Description:
- Clinical Pharmacology: Edited the subsection on Mechanism of Action for brevity

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Information on lack of clinically significant effects on QT interval placed under the Pharmacodynamic subsection in accordance with evolving policy

in the Office of Clinical Pharmacology (b) (4) In the Pharmacokinetics subsection, information on absorption and distribution combined, information on effects in patients based on demographics combined, information on drug interactions, food effects, and PK in patients with organ impairment edited for brevity.

- Nonclinical Pharmacology/Toxicology: Edited for brevity/essential information. Results of studies assessing effects on fertility briefly described
- Clinical Studies: The results from Studies LUX-2, LUX-1, and LUX-5 were not included in product labeling since FDA concluded that these studies did not provide substantial evidence of effectiveness for reasons discussed in Section 7 of this review. Results of health-related quality of life obtained in Study 1200.32 were not included in product labeling as these are exploratory analyses obtained in an open-label trial. Analyses in subsets based on EGFR mutation type are included in labeling as these are clearly identified as exploratory; in addition, randomization was stratified for this variable, preserving principles of randomization, the results were consistent across endpoints (PFS and OS), other studies of afatinib (IND studies), and other products in this class (erlotinib). Information on uncommon mutations were provided for information only and to aid prescribers in providing information to patients.
- Carton and immediate container labels – no unresolved issues
- Patient labeling: BI submitted patient labeling, which has been revised for alignment with modifications to the physician labeling; there are no unresolved issues with patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment: Unresectable or metastatic NSCLC is a serious and life-threatening disease; there is only one other drug which has been approved (recently) for treatment of NSCLC containing exon 19 deletions or exon 21 L858R EGFR mutations, which poses the potential for lack of availability due to drug shortages. Based on the results of Study 1200.32, afatinib treatment demonstrated a statistically robust and clinically important improvement in progression-free survival for patients randomized to erlotinib compared to those randomized chemotherapy [HR 0.58 (95% CI: .43, 0.78), $p < 0.001$] with an approximate doubling of the median progression-free survival from 6.9 months in the chemotherapy arm to 11.1 months in the erlotinib arm. There was no statistically significant difference in overall survival between the afatinib and chemotherapy arms, with 84% of the planned events, however effects on survival, if any, may have been obscured by the high rate of post-progression use of an EGFR inhibitor for patients in the chemotherapy arm. In addition, the overall response rate was substantially higher (50% vs. 19%) for the afatinib arm compared to the chemotherapy arm.

There was adequate evaluation of safety, with data from more than 3800 patients across multiple clinical trials. In Study 12000.32, the most common adverse reactions ($\geq 20\%$) are diarrhea, rash, stomatitis, paronychia, dry skin, dermatitis acneiform, decreased appetite, and pruritus. Serious adverse reactions were reported in 29% of patients treated with afatinib. The most frequent serious adverse reactions reported in patients treated with afatinib were diarrhea (6.6%), vomiting (4.8%), and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in afatinib-treated patients in Study 1200.32 consisted of interstitial lung disease (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Substantial evidence of effectiveness (an improvement in PFS of a clinically important magnitude) was demonstrated in this trial. While an improvement in overall survival has been used as the basis for most recent drug approvals for the treatment of NSCLC, treatment effects of this magnitude are also considered to be evidence of clinical benefit provided that the risks are acceptable. As stated by FDA during the September 20, 2010 pre-NDA meeting, “consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. Because documentation of PFS assessments is often based on both subjective and objective criteria and these assessments depend on frequency, accuracy, reproducibility and completeness of tumor assessments, it is important that the observed magnitude of effect is robust.” The risks of erlotinib treatment are considered acceptable by oncologists and patients for the treatment of NSCLC, a serious and ultimately fatal disease. The serious adverse reactions of afatinib are acceptable given the clinical benefits on PFS and can be mitigated by close monitoring and dose modification.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
The application did not contain a proposed REMS. I concur with the clinical review team and the DRISK consultant that a REMS is not required to ensure safe use or mitigate severe adverse reactions for afatinib for the proposed indication.
- Recommendation for other Postmarketing Requirements and Commitments
 - One PMR will be required to evaluate for the effects of moderate to severe renal impairment on the pharmacokinetics of afatinib. This is based on a re-analysis of the population PK data in Study 1200.32 in patients receiving the recommended dose of afatinib, which demonstrated an increase in trough concentrations by 85% in patients with moderate impairment.
 - One PMC has been agreed-upon, which will be submit the results of the final analysis of overall survival, so that these data can be included in product labeling, as appropriate.

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/s/

PATRICIA KEEGAN
07/05/2013