CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 20, 2013
From	Anthony J. Murgo, M.D., M.S.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 201292
Applicant	Boehringer Ingelheim
Date of Submission	November 14, 2012 (Received November 15, 2012)
PDUFA Goal Date	July 15, 2013
Proprietary Name / Established (USAN) names	Gilotrif®/Afatinib
Dosage forms / Strength	Film-coated tablets/20, 30, 40 mg, [redacted] (b) (4)
Proposed Indication(s)	As proposed: [BRAND]# 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) as detected by an FDA-approved test. Approved indication: GILOTRIF is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations.
Recommended:	Approval##

#Proprietary name (Gilotrif) was approved after the submission of the NDA.
This recommendation is contingent on satisfactory resolution of outstanding matters (see Sections 11 and 12, below).

Cross Discipline Team Leader Review

1. Introduction

This section provides an overview of the basic regulatory and scientific facts of the application and some of the complexities encountered during the review. Also, please refer to Section 2.5 of the Clinical Review dated April 22, 2013 for a detailed summary of the pre-submission regulatory history for this application.

On November 14, 2012, Boehringer Ingelheim (BI) submitted this 505(b)(1) NDA (201292) in support of the NME afatinib (previously known as BIBW 2992) for the following proposed indication: locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. The starting dose proposed is 40 mg administered orally once daily.

A Pre-NDA Meeting under PDUFA V was held October 10, 2012. The application was filed January 11, 2013 with priority review status. The primary support (pivotal trial results) for efficacy comes from a single randomized controlled trial: Study 1200.32 (LUX-Lung 3), a phase 3 study of afatinib versus chemotherapy (pemetrexed plus cisplatin) as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung with an EGFR mutation. The study met its primary endpoint of progression-free survival (PFS) showing a statistically significant and clinically meaningful 4.2 month improvement in the median PFS in the afatinib arm as compared to the chemotherapy arm [11.1 months vs. 6.9 months; HR 0.58; (95% CI 0.43, 0.78); p-value 0.0003 (log-rank test)]. The vast majority of patients in this trial had tumors with common EGFR mutations categorized as either Exon 19 deletion or Exon 21 (L858R). The results from three other studies (1200.22, 120023, 1200.42) submitted to support the indication were included in the application but based on FDA review were considered inadequate to support efficacy claims (see below).

The Midcycle Meeting was held February 7, 2013 during which the review team identified several potential problems with the application. The status of the review and the areas of potential concern were conveyed to the Applicant in a Midcycle telecommunication on February 20, 2013, during which FDA conveyed that there were no plans for an Advisory Committee meeting. Please refer to the Project Manager's memo signed March 5, 2013 for the agenda and deliberations from that teleconference.

A Late Cycle Meeting (face-face) with the applicant was held on May 7, 2013 during which the below list of "substantive review issues" were discussed (most previously conveyed in the Midcycle telecommunication noted above). Also refer to the Late Cycle Meeting Minutes signed by the DOP2 Division Director Patricia Keegan, M.D. on May 16, 2013.

- FDA reiterated that the results of "supportive" Study 1200.23 do not support the proposed indication (b) (4)

(b) (4) BI indicated its understanding of FDA's assessment and there was no further discussion at the meeting on this issue.

- FDA reiterated that there are limited data in study 1200.32 and "supportive" Study 1200.22 (b) (4). BI expressed their understanding on this issue.
- FDA reiterated that there are limited data to support to use of afatinib in the less common EGFR mutations. The vast majority of patients had tumors bearing exon 19 deletions or exon 21 (L858R) substitution mutations. In addition, the limited data submitted from patients with the less common mutations suggest that there is a possible detrimental effect on PFS and OS. FDA asked BI what, if any, studies are ongoing or planned to evaluate the efficacy of afatinib in patients whose tumors harbor uncommon EGFR mutations. BI indicated that it does not have any planned or ongoing studies to evaluate the efficacy of afatinib in NSCLC patients with uncommon EGFR mutations. However, BI noted a study that enrolled additional patients with uncommon EGFR mutations (Study 1200.34) and that they submitted top-line data from that study to FDA in March 2013. They further indicated that the clinical study report was submitted to IND (b) (4) on May 7, 2013, the same day of the Late Cycle Meeting. BI stated that it would not be possible to do a randomized, controlled trial in uncommon mutations and that overall response rate is the best way to look at the data. BI inquired if FDA would be willing to review this data as part of this NDA review. FDA responded that it would be acceptable to submit this information to the NDA (b) (4), after the action is taken on the original NDA submission.
- FDA prompted a discussion about the manufacturing site inspection (conducted November 5-12, 2013) and the deficiencies which that led to the issuance of a Form 483 memo (issued November 12, 2012). BI acknowledged receipt of the related Warning Letter on May 6, 2013, and noted that they were working to respond to the issues outlined in the letter.
- FDA reiterated concerns about outstanding issues and information requests pertaining to the companion diagnostic test, which will need to be adequately addressed prior to approval. BI noted that they are in continual contact with the test developer Qiagen, and voiced that the response to the CDRH information request is on track.
- FDA noted the need for a Post-Marketing Commitment to provide the final overall survival analysis from Study 1200.32 to better characterize the effects of afatinib treatment on overall survival. BI noted that the formal full clinical trial report will be available in April 2014. It was decided to extend the final submission date to 4/30/2014 in order to allow for submission of the complete clinical trial report.
- FDA conveyed that a limitation of use in the label is appropriate given the small number of patients tested and potential decrease in progression free survival (PFS) and overall survival (OS) in afatinib-treated patients with "other" less common EGFR mutations. BI raised their concerns with the language in the indication section "limitation of use" which they interpret meaning lack of effect. FDA stated that as currently worded in the PI, it is clear that the safety and efficacy have not been established, and that it is not intended as a contraindication. FDA noted that if BI can provide a compelling reason that this limitation of use would prevent use in necessary patient populations, FDA might revisit the issue. FDA noted that the issue will be discussed further internally.

- BI conveyed several other suggested modifications in FDA edits of the draft labeling. FDA would consider them in ongoing review.

The substantive issues above were addressed during the course of the review and numerous communications, including labeling negotiations.

2. Background

This section provides scientific, clinical and regulatory background information not already covered in the Introduction Section, above.

Lung cancer remains the leading cause of cancer deaths in United States. The 5 year survival rate for patients with lung cancer remains dismal, around 15%. NSCLC comprises about 85% of the lung cancer cases. Although surgery remains the only curative modality for this disease, most of these patients (70%) present at advanced stage and thus are not surgical candidates. Until relatively recently first-line treatment for advanced NSCLC was platinum-based doublet chemotherapy. With the discovery of molecular targets and targeted therapies, new treatment options have evolved and continue to be discovered and developed, including EGFR tyrosine kinase inhibitors, with a particular interest in agents that are active in inhibiting tumors that harbor EGFR driver mutations.

The EGFR small molecule inhibitor erlotinib (Tarceva^{TM}) obtained approval on May 14, 2013 for a supplemental indication for first line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. This is essentially the same indication considered for use in the current afatinib application (see Section12). The erlotinib indication contains the following limitation of use statement: safety and efficacy of TARCEVA have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution. This same limitation of use will be applied to the labeling of afatinib. Unlike the afatinib study (see below), the EGFR mutation test used in the erlotinib study detected only exon 19 deletion and exon 21 mutation.

Afatinib is a kinase inhibitor that covalently binds to the EGFR, HER2 and HER4 kinase domains and irreversibly inhibits the tyrosine kinase autophosphorylation of the EGFR receptor family with down-regulation of signaling.

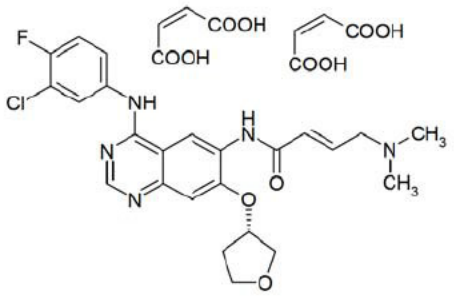
As noted above in the Introduction Section, the pivotal efficacy study 1200.32 met its pre-specified primary endpoint of PFS. This study was limited to patients with EGFR mutation-positive, metastatic nonsquamous, NSCLC. The laboratory test for EGFR mutations used in this study detects a variety of mutations other than exon 19 deletion or exon 21 (L858R) substitution. However, the vast majority of the patients enrolled had a tumor sample with an EGFR mutation categorized as either exon 19 deletion [170/345(49%)] or exon 21 (L858R) substitution [138/345(40%)]. A very small number of patients [37/345(11%)] had tumor samples that were in the "Other" mutation category. See Section 7 for details on this study.

Please refer to the minutes of the Late-Cycle Meeting, outlined above in Section 1, for problematic elements of the application, (b) (4) (b) (4) (b) (4) (b) (4) and that the Indication Section of label will likely include a Limitation of Use statement; manufacturing site inspection deficiencies; and pending review issues regarding the companion diagnostic test. The resolution of pending issues is discussed in relevant sections below.

3. CMC/Device

Chemical name, structural formula, molecular formula, and molecular weight are shown below:

2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-(2E)-, (2Z)-2-butenedioate (1:2)



Molecular Formula:	$C_{24}H_{25}ClFN_5O_3 \cdot 2\ C_4H_4O_4$ or $C_{32}H_{33}ClFN_5O_{11}$
Molecular Weight:	718.1 g/mol (salt form), 485.9 g/mol (free base)

General product quality:

Gilotrif, Afatinib film-coated tablets, contain 40 mg, 30 mg, or 20 mg of afatinib (free base) corresponding to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate. (b) (4), (b) (4)

I concur with the CMC conclusion that the application, from a Chemistry Manufacturing and Control perspective approvable, as noted the review signed by the primary and secondary reviewer on April 22, 2013. However, the CMC reviewers did note that the recommendation

does not take into consideration the status of the cGMP status of the manufacturing site(s) inspection results which were still pending.

Biopharmaceutics (product quality)

According to the biopharmaceutics review, the Applicant provided comparative dissolution profiles to show that the final formulation (FF) drug product used in the Phase 3 clinical trials has a similar dissolution profile as the commercial FF drug product. The biopharmaceutics reviewers found the dissolution methodology and dissolution acceptance criteria acceptable. I concur with the conclusion of the reviewers that from the biopharmaceutics perspective, the application is approvable, as noted in the pharmaceutical review signed by primary and secondary reviewer on April 22, 2013.

Facilities review/inspection

The BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG manufacturing facility of the drug substance and drug product, located in Rhein Germany, was inspected by the FDA from November 5, 2012 through November 12, 2012. Significant violations of current good manufacturing practice (CGMP) for the manufacture of APIs and the CGMP regulations for finished pharmaceuticals were identified. These violations cause APIs and drug product(s) manufactured at the same facility, including afatinib, to be considered adulterated.
At the conclusion of this inspection, the field investigator conveyed deficiencies to the representative of the facility. The applicant submitted responses to the deficiencies, conveyed in the FDA 483 Form, between November 2012 and February 28, 2013. A Warning Letter conveying significant violations to CGMP was issued on May 6, 2013. At the time of the Late Cycle Meeting on May 7, 2013, BI acknowledged receipt of the Warning Letter and noted that they were working to respond to the issues outlined in the letter. CDER/OC/OMPQ/Division of International Drug Quality indicated that they would communicate the final status of its review of BI's response as soon as possible.

Because of concerns that failure to adequately address the deficiencies in the Warning Letter could delay the approval of afatinib, the clinical review division considered the potential consequences of a complete response action for a drug that fills an unmet medical need. This concern was expressed by Division of Oncology Products 2 (DOP2) in a memo directed to Carmelo Rosa, Psy.D, Division Director CDER-Office of Compliance OMPQ/DIDQ (signed by the DOP2 Div. Dir. on June 7, 2013). DOP2 requested consideration for regulatory discretion to allow the release of the afatinib based medical necessity. Currently there is only one drug, erlotinib (Tarceva®, OSI) approved for treatment of NSCLC patients whose tumors contain EGFR mutations. Although erlotinib is approved for this same indication, the drug supply would be considered vulnerable, as there is no assurance that the single alternative will provide an adequate drug supply for this unmet medical need. In addition, certain patients may not tolerate erlotinib and may require treatment with afatinib. The DOP2 clinical review team's opinion was that some discretion in enforcement regarding this matter was appropriate given the medical necessity.

Device

This is not a combination product. However, see Section 11 (Other Relevant Regulatory Issues) regarding the companion diagnostic test.

4. Nonclinical Pharmacology/Toxicology

Please refer to the Non-Clinical Pharmacology and Toxicology Review (signed by the primary and secondary reviewers on April 29, 2013) for detailed non-clinical aspects of the application. This section will summarize the key non-clinical properties of the drug and review findings. The EGFR family of receptors are present on normal cells and play important roles in many normal cellular activities, but overexpression or aberrant function of these receptors has been implicated in the development and pathogenesis of many tumor types.

The non-clinical reviewers noted that Afatinib is highly reactive and forms covalent adducts to cysteine-bound SH groups. As a result, it can form widespread adducts to endogenous proteins, including red blood cells (RBCs), which contained a significant proportion of drug-associated radioactivity in exposed animals. The reviewers also noted that the presence of covalent adducts is a concern for the overall safety of afatinib, since adduction of reactive small molecules to foreign proteins has been associated with adverse idiosyncratic drug reactions (IDRs), including serious reactions, with other drugs with these properties. Whether or not to convey this concern in the product labeling was discussed among the non-clinical and clinical reviewers. Because the concern is only a theoretical one, as no documented IDRs had been reported in association with afatinib, it was decided not to include it in the product labeling.

The weight of non-clinical evidence suggests that afatinib is not mutagenic at clinically relevant concentrations. Afatinib was embryotoxic and led to abortions at late gestational stages in rabbits showing overt toxicity at doses of 5 mg/kg (approximately 0.40.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater.

The Applicant submitted protocols for carcinogenicity studies in rat and mouse for review by the FDA's Executive Carcinogenicity Assessment Committee; however these studies are not required to support the development of drugs, such as this one, for patients with advanced cancer and were not been initiated for this development program following discussion with the Agency.

I concur with the recommendations of the reviewers that the application is approvable from a non-clinical pharmacology perspective. Note that the DHOT Division Director, John Leighton, Ph.D. provided concurrence with the reviewers' conclusion in a memo signed on April 30, 2013.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to the Clinical Pharmacology review (signed by the primary and secondary reviewers on April 22, 2013) and the ONDQA Biopharmaceutics review (signed by primary and secondary reviewers on April 22, 2013) for detailed clinical pharmacology and biopharmaceutical aspects of the application. This section will summarize the key clinical pharmacology properties of the drug and findings of the reviews.

Following oral administration, time-to-peak afatinib plasma concentrations (Tmax) is 2 to 5 hours. Mean maximum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞) values increased slightly more than dose proportional in the range of 20 to 50 mg. The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients. Steady-state plasma concentrations are achieved within 8 days of repeat dosing. The mean relative bioavailability of 20 mg of afatinib tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%. The major form of afatinib presented in human plasma is covalent adducts to plasma proteins and minor metabolites catalyzed by CYP450 enzymes. Fecal elimination of oral afatinib is approximately 85%, while 4% is eliminated in urine.

Mild to moderate hepatic impairment or mild renal impairment had no effect on afatinib exposure; moderate renal impairment increased afatinib exposure. The effect of severe hepatic impairment or severe renal impairment on afatinib exposure was not studied. Based on the submitted data, the PT reviewers recommended that patients with severe hepatic impairment or moderate to severe renal impairment should be monitored for toxicity and the dose should be reduced if not tolerated. The reviewers also noted that afatinib is a substrate and inhibitor of P-gp transporter. They also noted that exposure to afatinib was effected when it was administered with ritonavir (a P-gp inhibitor) or rifampicin (a P-gp inducer). For those patients who require therapy with an oral P-gp inhibitor, the daily dose of afatinib should be reduced by 10 mg if not tolerated. For patients who require a chronic oral P-gp inducer, the daily dose of afatinib should be increased by 10 mg based on tolerability.

Because of the findings that a high fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition, the label indicates that afatinib should be taken at least 1 hour before or 2 hours after a meal.

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

I concur with the conclusions in the Clinical Pharmacology reviewers and the ONDQA Biopharmaceutics reviewers that the application is acceptable from a clinical pharmacology and biopharmaceutics perspective, provided that the Applicant and the Agency come to a

mutually satisfactory agreement regarding the labeling language. The final product labeling will reflect the agreed upon labeling language.

6. Clinical Microbiology

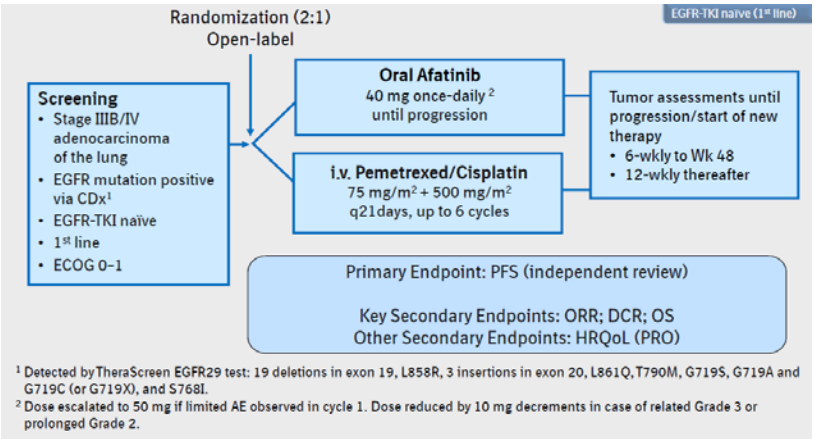
N/A

7. Clinical/Statistical- Efficacy

Please refer to the Clinical Review (signed by the clinical reviewer on April 22, 2013) and the Statistical Review (signed by the primary and secondary reviewers on April 19 and the biometrics division director on April 22, 2013). This review will provide the key clinical efficacy and safety aspects of the application and review findings.

The efficacy of afatinib in the first-line treatment setting was based on the results of the pivotal trial Study 1200.32 (LUX-Lung 3). This randomized, multicenter, open-label trial consisted of 345 patients with EGFR mutation-positive, metastatic NSCLC who were randomized (2:1) to receive afatinib 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). The trial design schema is shown in the figure below. Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The primary efficacy endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC). Key secondary efficacy endpoints 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 test was designed to detect 29 EGFR mutations against a background of wild-type genomic DNA, including deletions in exon 19 (Del 19), L858R substitution, insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. 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, for which a PMA has been submitted for CDRH review. Action on the PMA is pending at the time of this CDTL review; if approved, this companion diagnostic will be used for selection of patients for afatinib treatment.

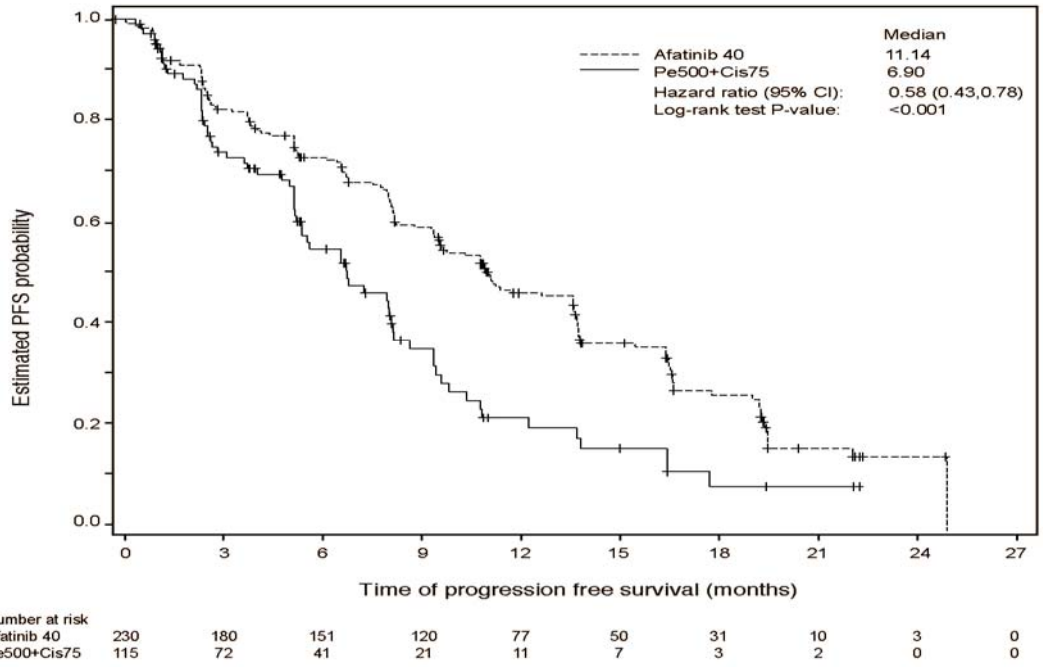
Pivotal Study 1200.32 (LUX-Lung 3) Design



The vast majority of patients had tumors with an EGFR mutation categorized as either exon 19 deletion (49%) or exon 21 L858R substitution mutations (40%), while the remaining 11% had other less common EGFR mutation types.

A statistically significant improvement in the primary endpoint PFS as determined by the IRC was demonstrated for patients randomized to afatinib compared to those randomized to chemotherapy (see figure below).

Kaplan-Meier Curve for PFS by Independent Review (ITT Population)



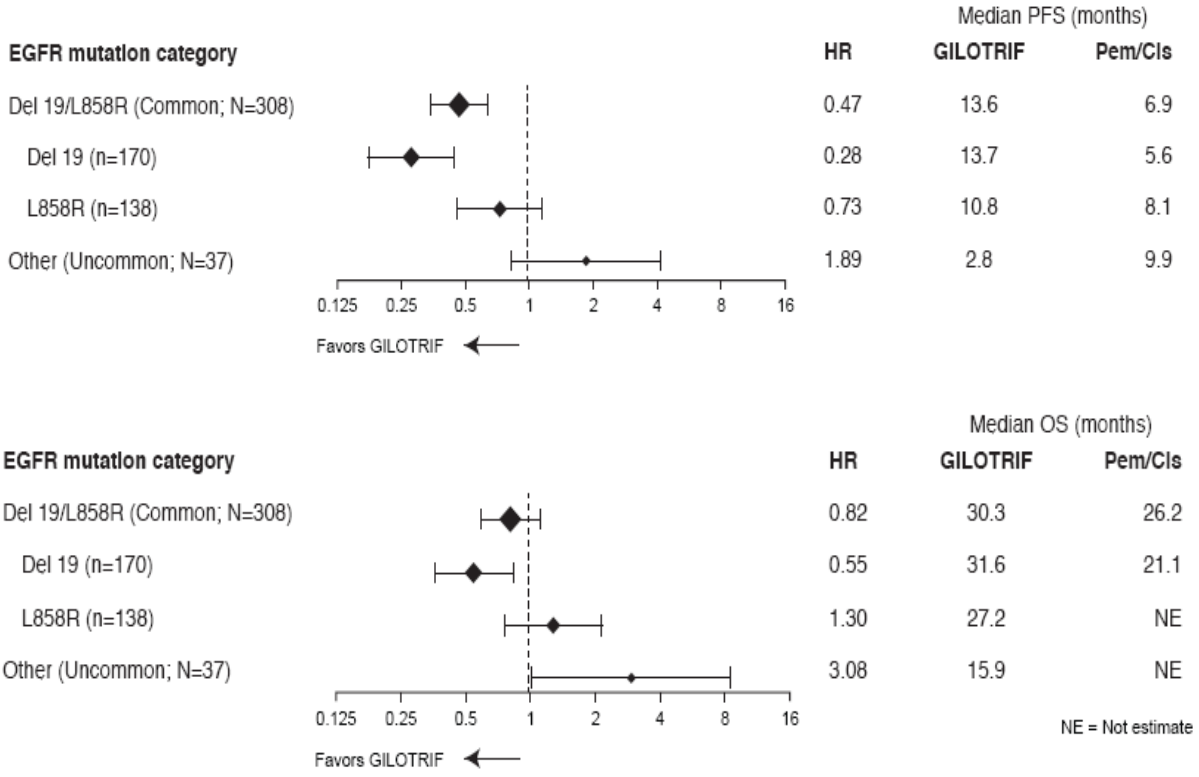
For patients with exon 19 deletion, median PFS was 13.7 months for afatinib-treated patients (n=113) vs. 5.6 months for chemotherapy-treated patients (n=57); HR 0.28 (95% CI 0.18 to 0.44). For patients with exon 21 (L858R) substitution, the median PFS was 10.8 months for afatinib-treated patients (n=91) vs. 8.1 months for chemotherapy-treated patients (n=47); HR 0.73 (95% CI 0.46 to 1.16).

For patients with other (uncommon) mutations, median PFS was 2.8 months for afatinib-treated patients (n=26) vs. 9.9 months for chemotherapy-treated patients (n=11); HR 1.89 (95% CI 0.84 to 4.28).

There was no statistically significant difference for overall survival between the treatment arms at the interim analysis conducted at 50% of the 345 randomized patients planned events for the final analysis (median 28.1 vs. 28.2 months in the afatinib and chemotherapy arms, respectively; HR 0.91 (95% CI 0.66, 1.25). The objective response (complete plus partial) rate was 50% in the afatinib arm and 19% in the chemotherapy arm; median duration of response was 12.5 months in the afatinib arm and 6.7 months in the chemotherapy arm.

As graphically demonstrated in the Forest Plot below, the improvement in PFS in the Common mutation group (i.e, exon 19 del + L858R) is clearly driven by the results in the del 19 group, and that the point estimates for HRs for PFS and OS in the Other (Uncommon) group favors the chemotherapy group.

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



"Supportive" studies

As noted above, the FDA review team determined that the results from three "supportive" studies (1200.22, 1200.23, 1200.42) are inadequate to support efficacy claims. Please refer to Clinical Review (pages 50-59) for detailed descriptions of these studies. Study 1200.23 (Lux Lung 1) did not support the applicant's proposed indication (b) (4) .

Study 1200.23 was a phase 2b/3 randomized double-blind trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients after failure of erlotinib or gefitinib and having previously received 1 or 2 lines of chemotherapy. The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg afatinib orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195). The trial population was "clinically enriched" for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. In the study, only 186/585 (32%) of the patients had tissue available for EGFR mutational status testing at either the local lab or central lab. Of the 141 patients with tissue test results, 68% were found to be positive for EGFR mutations.

Study 1200.23 failed its primary endpoint of OS; median OS for placebo was 12.0 months versus 10.8 months for afatinib (HR=1.08; 95% confidence interval: 0.86 to 1.35). At the Mid-Cycle teleconference and again at the Late-Cycle Face-Face Meeting (see Section 1 above), FDA conveyed that these study results do not support (b) (4) (b) (4) because the study failed its primary endpoint of OS, had at best a marginal benefit in the secondary endpoint of PFS (only 2 months), and because the patient population is poorly defined.

As noted in Section 1, above, the data from "supportive" Study 1200.22 do not support (b) (4)

8. Safety

Refer to Section 7 of the Clinical Review for a detailed description and an assessment of the results to support the safety profile of afatinib. The evaluation of clinical safety was based on the treated set of patients, i.e. all patients who received at least one dose of study medication (a total of 3865 patients).

The clinical review assessed the safety data for the individual studies as well as across studies. In regards to the pivotal efficacy trial 1200.32, 13 patients (5.7%) in the afatinib arm had adverse events (AEs) with fatal outcomes compared to 3 patients (2.7%) in the chemotherapy arm. The reported causes of death in the afatinib arm were progressive disease (6 patients), pulmonary toxicity (3 patients including 2 with Interstitial Lung Disease), sepsis (1 patient), pneumonia (1 patient) and 2 patients where cause of death was unknown. According to the reported preferred terms, all deaths during the on-treatment period were attributed to the underlying cancer by the PI and the applicant, except for 2 patients in the afatinib arm who died of infections and 3 patients (2 in the afatinib arm and 1 in the chemotherapy arm) who died of unknown causes. The frequencies of serious adverse events leading to discontinuation or death in Study 1200.32 are shown in the following table.

	Afatinib 40 mg N = 229 11.7 mo*	Pem/Cis N = 111 3.7 mo*
	All AEs, %	
Any AEs	100.0	98.2
Grade 3	51.1	44.1
Grade 4	3.9	9.9
AEs leading to dose reduction	57.2	16.2+
AE leading to discontinuation	14.0	15.3
Due to drug-related AEs	7.9	11.7
Serious AE	28.8	22.5
Drug-related SAEs	14.4	14.4
AE leading to death	5.7	2.7
Drug-related fatal AEs	1.7	0

The most frequently reported SOCs of drug-related AEs leading to treatment discontinuation in the afatinib arm were respiratory, thoracic and mediastinal disorders, gastrointestinal disorders (each 1.7% of patients), and infections and infestations (1.3%).

Diarrhea and rash of any grade were reported in 96% and 71% of patients, respectively, in the afatinib arm of Study 1200.32. In some patients, the diarrhea resulted in dehydration and renal failure. The rash can take the form severe bullous, blistering, and exfoliating lesions, which occurred in 0.15% of the patients in the afatinib arm. The following other adverse events reported in more than 10% of the patients in Study 1200.32: stomatitis, cheilitis, paronychia, cystitis, epistaxis, rhinorrhea, pyrexia and conjunctivitis.

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

- Interstitial lung disease (ILD) or ILD-like reactions (1.5%). See note below.
- Hepatic Toxicity (10.1%)
- Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in (0.8%).
- LVEF decrease, indicative of heart failure and/or cardiomyopathy (1.4%). See note below.

Note: The applicant wants to include the term ILD-like reactions in the labeling, whereas the reviewers do not. In addition, there was considerable discussion between the clinical review team and the applicant regarding the characterization of the cardiac events. The applicant argued (b) (4) ; the review team does not agree. At the time of this review, resolution of these two matters is still under negotiation.

Overall, most of the side effects reported were similar to those associated with EGFR inhibitors, including EGFR TKIs.

I concur with the conclusions in clinical reviewers and the statistical reviewers that the application is approvable, contingent on satisfactory resolution of outstanding issues (see Sections 11 and 12).

9. Advisory Committee Meeting

No advisory committee meeting was planned or held because there were no controversial issues that would benefit from advisory committee discussion. However, the clinical review team did confer with 3 special government employees (two subject matter experts and one patient representative) for an outside assessment and concurrence that benefit of afatinib treatment in the indicated patient population outweighs the risk.

10. Pediatrics

Safety and effectiveness of afatinib in pediatric patients have not been established. However, afatinib was granted orphan designation for this indication from the Office of Orphan Drug Products on December 3, 2012 and thus is exempt PREA requirements.

11. Other Relevant Regulatory Issues

Outstanding regulatory issues

Companion Diagnostic

Please refer to the Section 7 above for a description of the assay used in the clinical trial. In support of the US registration, experiments were submitted to demonstrate equivalence between the clinical trial assay and the TheraScreen EGFR RGQ PCR Kit (Qiagen Manchester Ltd, Manchester, UK), for which US Pre-market Approval (PMA) is sought. At the time of this CDTL review, CDRH was still in the process reviewing an Information Request response, which is necessary before completing their review and action on the PMA.

Manufacturing Site Inspection Deficiencies

As noted in Section 3, the OC had not yet completed the review of the applicant's response to the manufacturing facility inspection Warning Letter. The final disposition of this matter was pending at the time this CDTL review was completed.

12. Labeling

Proprietary Name

Division of Medication Error Prevention and Analysis issued a memo (signed April 19, 2013) concluding that the proprietary name "Gilotrif" is acceptable.

Physician Labeling

The review and development of the product label involved a multidisciplinary FDA team and multiple communications and negotiations with the applicant. This CDTL review makes particular note of a teleconference with the applicant held on June 5, 2013 to negotiate content in the product labeling, during which the applicants requested to include the Kaplan-Myer (K-M) plot of PFS for a subset of patients [those (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations] in addition to or instead of the K-M plot of the Intent-to-Treat (ITT) population requested by the FDA. FDA conveyed that only the ITT K-M plot, not the subset analysis, should be included in the package insert. Having two plots may be confusing. A summary of the analysis of the EGFR exon 19 deletions or exon 21 (L858R) substitution mutations subset can be included in the text. Given that this represents the approved indication and is based on substantial evidence of safety and effectiveness, the DOP2 reviewers have no objection to the sponsor including a K-M plot of the subset PFS analysis in the product label.

At this time, the product label is not finalized pending resolution of ongoing negotiations between the FDA and the applicant on exact wording in several different sections of the package insert.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Approval, contingent on satisfactory resolution of outstanding matters described in Sections 11 and 12, above.

- **Risk Benefit Assessment**

The pivotal Study 1200.32 met its primary endpoint, showing a statistically significant and clinically meaningful benefit of a 4.2-month improvement in median in PFS in patients treated with afatinib as compared to patients treated with chemotherapy. At the interim updated analysis of survival median OS was estimated to be approximately 28 months for both treatments. Of note, the results suggest that the magnitude of improvement in PFS in the Common mutation group (i.e, exon 19 del + L858R) is driven, in large part, by the results in the del 19 group; however, the HR point estimate for the L858R group was 0.73. In contrast, the point estimates for HRs for PFS and OS in the Other (Uncommon) mutation subgroup favors the control chemotherapy arm; but the results in this subgroup did not reach statistical significance, likely because of the small sample size.

In conclusion, the risk benefit assessment is favorable for the proposed indication for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety profile of afatinib is similar to that of other approved EGFR inhibitors. The risk benefit assessment is not considered favorable for the treatment of patients whose tumors have other EGFR mutations or for previously treated patients, because the safety and effectiveness of afatinib has not been established in those indications.

- **Postmarketing Risk Evaluation and Management Strategies**

REMS not recommended.

- **Postmarketing Commitment**

As noted previously, during the Late-Cycle meeting between the FDA and Boehringer Ingelheim (BI) held on May 7, 2013, the following Post-Marketing Commitment (PMC) was discussed and agreed on between the FDA and BI:

"BI will submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival." BI will submit the full final clinical trial report by 04/30/2014.

The applicant confirmed this PMC in writing on July 12, 2013.

Recommended comments to applicant:
Please include the PMC information above in the action letter.

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

/s/

ANTHONY J MURGO
06/20/2013