

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022059Orig1s007

Trade Name: TYKERB

Generic or Proper Name: lapatinib

Sponsor: SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline

Approval Date: January 29, 2010

Indication: TYKERB, a kinase inhibitor, is indicated in combination with:

- capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

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APPROVAL LETTER



NDA 022059/S-007

ACCELERATED APPROVAL

SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline
Attention: Richard Swenson, Ph.D., Senior Director
GlaxoSmithKline UP4110
1250 S. Collegeville Road, POB 5089
Collegeville, PA 19426-0989

Dear Dr. Swenson:

Please refer to your supplemental new drug application dated March 31, 2009, received March 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tykerb[®] (lapatinib) Tablets, 250 mg.

We acknowledge receipt of your submissions dated April 28, 2009; June 3, 2009; July 2, and 29, 2009; August 6, 2009; September 10, 11(2), 14, 18, 28, and 29, 2009; October 2, 7, 9, and 30, 2009; November 11, 2009; December 21, 2009; January 12, 14, 18, 21, 27(2), and 28, 2010.

Please also refer to our approval letter dated January 29, 2010, for supplements (S-003) and (S-006).

This supplemental new drug application provides for the use of Tykerb[®] (lapatinib) tablets in combination with letrozole tablets for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. Tykerb[®] in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

We completed the review of this supplemental application, as amended. It is approved under the provisions of accelerated approval regulations, 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

POSTMARKETING REQUIREMENTS UNDER 21 CFR 314.510 (SUBPART H)

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled trials to verify and describe clinical benefit. We remind you of the following post marketing requirements specified in your submission dated January 21, 2010. Submit clinical protocols for at least two trials to confirm the clinical benefit of treatment with

Tykerb[®] (lapatinib). These requirements, along with any completion dates, are listed below.

- 1586-1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3 randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and who had prior neo-adjuvant/adjuvant trastuzumab and endocrine therapy. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary efficacy endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

The timetable you submitted on January 21, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: May 31, 2010

Trial Completion Date: March 31, 2016

Final Report Submission Date: May 31, 2018

- 1586-2. EGF108919 is an ongoing collaborative trial between NCIC and GSK. It is a randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

The timetable you submitted on January 21, 2010, states that you will conduct this trial according to the following timetable:

Final Protocol Submission May 31, 2010

Trial Completion Date: June 15, 2011

Final Report Submission Date: PFS: April 30, 2013

Final Survival Report Submission: July 31, 2016

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirements.**"

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling text for the package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022059/S-007.**"

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure (label)

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYKERB safely and effectively. See full prescribing information for TYKERB.

TYKERB (lapatinib) tablets
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.
Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. [See Warnings and Precautions (5.2).]

-----**RECENT MAJOR CHANGES**-----

Indications and Usage. (1) Month Year
Dosage and Administration. (2) Month Year
Contraindications. (4) Month Year

-----**INDICATIONS AND USAGE**-----

TYKERB, a kinase inhibitor, is indicated in combination with: (1)
• capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
• letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
TYKERB in combination with an aromatase inhibitor has not been compared to trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

-----**DOSAGE AND ADMINISTRATION**-----

The recommended dosage of TYKERB for advanced or metastatic breast cancer is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. (2.1)
The recommended dose of TYKERB for hormone receptor positive, HER2 positive metastatic breast cancer is 1500 mg (6 tablets) given orally once daily continuously in combination with letrozole. When TYKERB is coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily. (2.1)
• TYKERB should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. (2.1)
• TYKERB should be taken once daily. Do not divide daily doses of TYKERB. (2.1, 12.3)
• Modify dose for cardiac and other toxicities, severe hepatic impairment, and CYP3A4 drug interactions. (2.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosing
- 2.2 Dose Modification Guidelines

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Decreased Left Ventricular Ejection Fraction
- 5.2 Hepatotoxicity
- 5.3 Patients with Severe Hepatic Impairment
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- 5.6 QT Prolongation
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6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems
- 7.2 Drugs that Inh bit or Induce Cytochrome P450 3A4 Enzymes
- 7.3 Drugs that Inh bit Drug Transport Systems

-----**DOSAGE FORMS AND STRENGTHS**-----

250 mg tablets (3)

-----**CONTRAINDICATIONS**-----

Known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Decreases in left ventricular ejection fraction have been reported. Confirm normal LVEF before starting TYKERB and continue evaluations during treatment. (5.1)
- Lapatinib has been associated with hepatotoxicity. Monitor liver function tests before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. Discontinue and do not restart TYKERB if patients experience severe changes in liver function tests. (5.2)
- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.3, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.4)
- Lapatinib has been associated with interstitial lung disease and pneumonitis. Discontinue TYKERB if patients experience severe pulmonary symptoms. (5.5)
- Lapatinib may prolong the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.6, 12.6)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.7)

-----**ADVERSE REACTIONS**-----

The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. The most common (≥20%) adverse reactions during treatment with TYKERB plus letrozole were diarrhea, rash, nausea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- TYKERB is likely to increase exposure to concomitantly administered drugs which are metabolized by CYP3A4 or CYP2C8. (7.1)
- Avoid strong CYP3A4 inhibitors. If unavoidable, consider dose reduction of TYKERB in patients coadministered a strong CYP3A4 inhibitor. (2.2, 7.2)
- Avoid strong CYP3A4 inducers. If unavoidable, consider gradual dose increase of TYKERB in patients coadministered a strong CYP3A4 inducer. (2.2, 7.2)

See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**.

Revised: Month Year

8 USE IN SPECIFIC POPULATIONS

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- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
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11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

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*Sections or subsections omitted from the full prescribing information are not listed.

1 FULL PRESCRIBING INFORMATION

2 **WARNING: HEPATOTOXICITY**

3 **Hepatotoxicity has been observed in clinical trials and postmarketing experience.**
4 **The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is**
5 **uncertain. [See Warnings and Precautions (5.2).]**

6 **1 INDICATIONS AND USAGE**

7 TYKERB[®] is indicated in combination with:

- 8 • capecitabine for the treatment of patients with advanced or metastatic breast cancer whose
9 tumors overexpress HER2 and who have received prior therapy including an anthracycline, a
10 taxane, and trastuzumab.
- 11 • letrozole for the treatment of postmenopausal women with hormone receptor positive
12 metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is
13 indicated.

14 TYKERB in combination with an aromatase inhibitor has not been compared to a
15 trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

16 **2 DOSAGE AND ADMINISTRATION**

17 **2.1 Recommended Dosing**

18 HER2 Positive Metastatic Breast Cancer: The recommended dose of TYKERB is
19 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine
20 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in
21 a repeating 21 day cycle. TYKERB should be taken at least one hour before or one hour after a
22 meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing
23 the daily dose is not recommended [see *Clinical Pharmacology (12.3)*]. Capecitabine should be
24 taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not
25 double the dose the next day. Treatment should be continued until disease progression or
26 unacceptable toxicity occurs.

27 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer: The
28 recommended dose of TYKERB is 1,500 mg given orally once daily continuously in
29 combination with letrozole. When coadministered with TYKERB, the recommended dose of
30 letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour
31 after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once);
32 dividing the daily dose is not recommended [see *Clinical Pharmacology (12.3)*].

33 **2.2 Dose Modification Guidelines**

34 Cardiac Events: TYKERB should be discontinued in patients with a decreased left
35 ventricular ejection fraction (LVEF) that is Grade 2 or greater by National Cancer Institute

36 Common Terminology Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF
37 that drops below the institution's lower limit of normal [*see Warnings and Precautions (5.1) and*
38 *Adverse Reactions (6.1)*]. TYKERB in combination with capecitabine may be restarted at a
39 reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at a reduced
40 dose of 1,250 mg/day after a minimum of 2 weeks if the LVEF recovers to normal and the
41 patient is asymptomatic.

42 **Hepatic Impairment:** Patients with severe hepatic impairment (Child-Pugh Class C)
43 should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to
44 750 mg/day (HER2 positive metastatic breast cancer indication) or from 1,500 mg/day to
45 1,000 mg/day (hormone receptor positive, HER2 positive breast cancer indication) in patients
46 with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the
47 normal range and should be considered. However, there are no clinical data with this dose
48 adjustment in patients with severe hepatic impairment.

49 **Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4
50 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir,
51 indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit
52 may also increase plasma concentrations of lapatinib and should be avoided. If patients must be
53 coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction
54 to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without
55 inhibitors and should be considered. However, there are no clinical data with this dose
56 adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is
57 discontinued, a washout period of approximately 1 week should be allowed before the lapatinib
58 dose is adjusted upward to the indicated dose. [*See Drug Interactions (7.2).*]

59 **Concomitant Strong CYP3A4 Inducers:** The concomitant use of strong CYP3A4
60 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin,
61 rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered a strong CYP3A4
62 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually
63 from 1,250 mg/day up to 4,500 mg/day (HER2 positive metastatic breast cancer indication) or
64 from 1,500 mg/day up to 5,500 mg/day (hormone receptor positive, HER2 positive breast cancer
65 indication) based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC
66 to the range observed without inducers and should be considered. However, there are no clinical
67 data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong
68 inducer is discontinued the lapatinib dose should be reduced to the indicated dose. [*See Drug*
69 *Interactions (7.2).*]

70 **Other Toxicities:** Discontinuation or interruption of dosing with TYKERB may be
71 considered when patients develop $\geq$ Grade 2 NCI CTCAE toxicity and can be restarted at
72 1,250 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then
73 TYKERB in combination with capecitabine should be restarted at a lower dose (1,000 mg/day)
74 and in combination with letrozole should be restarted at a lower dose of 1,250 mg/day.

75 **See manufacturer's prescribing information for the coadministered product dosage**

76 **adjustment guidelines in the event of toxicity and other relevant safety information or**
77 **contraindications.**

78 **3 DOSAGE FORMS AND STRENGTHS**

79 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one
80 side.

81 **4 CONTRAINDICATIONS**

82 TYKERB is contraindicated in patients with known severe hypersensitivity (e.g.,
83 anaphylaxis) to this product or any of its components.

84 **5 WARNINGS AND PRECAUTIONS**

85 **5.1 Decreased Left Ventricular Ejection Fraction**

86 TYKERB has been reported to decrease LVEF [*see Adverse Reactions (6.1)*]. In clinical
87 trials, the majority (>57%) of LVEF decreases occurred within the first 12 weeks of treatment;
88 however, data on long-term exposure are limited. Caution should be taken if TYKERB is to be
89 administered to patients with conditions that could impair left ventricular function. LVEF should
90 be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the
91 patient has a baseline LVEF that is within the institution's normal limits. LVEF should continue
92 to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the
93 institution's normal limits [*see Dosage and Administration (2.2)*].

94 **5.2 Hepatotoxicity**

95 Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin
96 >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and
97 postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.
98 Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after
99 initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase)
100 should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as
101 clinically indicated. If changes in liver function are severe, therapy with TYKERB should be
102 discontinued and patients should not be retreated with TYKERB [*see Adverse Reactions (6.1)*].

103 **5.3 Patients with Severe Hepatic Impairment**

104 If TYKERB is to be administered to patients with severe pre-existing hepatic impairment,
105 dose reduction should be considered [*see Dosage and Administration (2.2) and Use in Specific*
106 *Populations (8.7)*]. In patients who develop severe hepatotoxicity while on therapy, TYKERB
107 should be discontinued and patients should not be retreated with TYKERB [*see Warnings and*
108 *Precautions (5.2)*].

109 **5.4 Diarrhea**

110 Diarrhea, including severe diarrhea, has been reported during treatment with TYKERB
111 [*see Adverse Reactions (6.1)*]. Proactive management of diarrhea with anti-diarrheal agents is
112 important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes
113 and fluids, and interruption or discontinuation of therapy with TYKERB.

114 **5.5 Interstitial Lung Disease/Pneumonitis**

115 Lapatinib has been associated with interstitial lung disease and pneumonitis in
116 monotherapy or in combination with other chemotherapies [see *Adverse Reactions (6.1)*].
117 Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease or
118 pneumonitis. TYKERB should be discontinued in patients who experience pulmonary symptoms
119 indicative of interstitial lung disease/pneumonitis which are $\geq$ Grade 3 (NCI CTCAE).

120 **5.6 QT Prolongation**

121 QT prolongation was observed in an uncontrolled, open-label dose escalation study of
122 lapatinib in advanced cancer patients [see *Clinical Pharmacology (12.4)*]. Lapatinib should be
123 administered with caution to patients who have or may develop prolongation of QTc. These
124 conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT
125 syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT
126 prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or
127 hypomagnesemia should be corrected prior to lapatinib administration.

128 **5.7 Use in Pregnancy**

129 TYKERB can cause fetal harm when administered to a pregnant woman. Based on
130 findings in animals, TYKERB is expected to result in adverse reproductive effects. Lapatinib
131 administered to rats during organogenesis and through lactation led to death of offspring within
132 the first 4 days after birth [see *Use in Specific Populations (8.1)*].

133 There are no adequate and well-controlled studies with TYKERB in pregnant women.
134 Women should be advised not to become pregnant when taking TYKERB. If this drug is used
135 during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be
136 apprised of the potential hazard to the fetus.

137 **6 ADVERSE REACTIONS**

138 **6.1 Clinical Trials Experience**

139 Because clinical trials are conducted under widely varying conditions, adverse reaction
140 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
141 trials of another drug and may not reflect the rates observed in practice.

142 HER2 Positive Metastatic Breast Cancer: The safety of TYKERB has been evaluated
143 in more than 12,000 patients in clinical trials. The efficacy and safety of TYKERB in
144 combination with capecitabine in breast cancer was evaluated in 198 patients in a randomized,
145 Phase 3 trial. [See *Clinical Studies (14.1)*.] Adverse reactions which occurred in at least 10% of
146 patients in either treatment arm and were higher in the combination arm are shown in Table 1.

147 The most common adverse reactions ($>20\%$) during therapy with TYKERB plus
148 capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-
149 plantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse
150 reaction resulting in discontinuation of study medication.

151 The most common Grade 3 and 4 adverse reactions (NCI CTCAE v3) were diarrhea and
152 palmar-plantar erythrodysesthesia. Selected laboratory abnormalities are shown in Table 2.

153
154

Table 1. Adverse Reactions Occurring in ≥10% of Patients

Reactions	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day (N = 198)			Capecitabine 2,500 mg/m ² /day (N = 191)		
	All Grades ^a %	Grade 3 %	Grade 4 %	All Grades ^a %	Grade 3 %	Grade 4 %
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash ^b	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

155
156
157
158

^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

^b Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine group.

159 **Table 2. Selected Laboratory Abnormalities**

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day			Capecitabine 2,500 mg/m ² /day		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

160 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

161
 162 Hormone Receptor Positive, Metastatic Breast Cancer: In a randomized clinical
 163 trial of patients (N = 1,286) with hormone receptor positive, metastatic breast cancer, who had
 164 not received chemotherapy for their metastatic disease, patients received letrozole with or
 165 without TYKERB. In this trial, the safety profile of TYKERB was consistent with previously
 166 reported results from trials of TYKERB in the advanced or metastatic breast cancer population.
 167 Adverse reactions which occurred in at least 10% of patients in either treatment arm and were
 168 higher in the combination arm are shown in Table 3. Selected laboratory abnormalities are
 169 shown in Table 4.
 170

171 **Table 3. Adverse Reactions Occurring in ≥10% of Patients**

Reactions	TYKERB 1,500 mg/day + Letrozole 2.5 mg/day (N = 654)			Letrozole 2.5 mg/day (N = 624)		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Anorexia	11	<1	0	9	<1	0
Skin and subcutaneous tissue disorders						
Rash ^b	44	1	0	13	0	0
Dry skin	13	<1	0	4	0	0
Alopecia	13	<1	0	7	0	0
Pruritus	12	<1	0	9	<1	0
Nail Disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0

172 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

173 ^b In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional
 174 subjects in each treatment arm had rash under "Infections and infestations"; none were Grade
 175 3 or 4.

176

177 **Table 4. Selected Laboratory Abnormalities**

	TYKERB 1,500 mg/day + Letrozole 2.5 mg/day			Letrozole 2.5 mg/day		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
Hepatic Parameters	%	%	%	%	%	%
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0
Total Bilirubin	22	<1	<1	11	1	<1

178 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

179
 180 **Decreases in Left Ventricular Ejection Fraction:** Due to potential cardiac toxicity
 181 with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week
 182 intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular
 183 cardiac function that are ≥Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac
 184 ejection fraction relative to baseline which is below the institution's lower limit of normal.
 185 Among 198 patients who received TYKERB/capecitabine combination treatment, 3 experienced
 186 Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTCAE v3). [See Warnings and
 187 Precautions (5.1).] Among 654 patients who received TYKERB/letrozole combination
 188 treatment, 26 patients experienced Grade 1 or 2 and 6 patients had Grade 3 or 4 LVEF adverse
 189 reactions.

190 **Hepatotoxicity:** TYKERB has been associated with hepatotoxicity [see Boxed Warning
 191 and Warnings and Precautions (5.2)].

192 **Interstitial Lung Disease/Pneumonitis:** TYKERB has been associated with interstitial
 193 lung disease and pneumonitis in monotherapy or in combination with other chemotherapies [see
 194 Warnings and Precautions (5.5)].

195 **6.2 Postmarketing Experience**

196 The following adverse reactions have been identified during post-approval use of
 197 TYKERB. Because these reactions are reported voluntarily from a population of uncertain size,
 198 it is not always possible to reliably estimate their frequency or establish a causal relationship to
 199 drug exposure.

200 **Immune System Disorders:** Hypersensitivity reactions including anaphylaxis [see
 201 Contraindications (4)].

202 **Skin and Subcutaneous Tissue Disorders:** Nail disorders including paronychia.

203 **7 DRUG INTERACTIONS**

204 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport** 205 **Systems**

206 Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations.
 207 Caution should be exercised and dose reduction of the concomitant substrate drug should be
 208 considered when dosing lapatinib concurrently with medications with narrow therapeutic
 209 windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the

210 following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or
211 UGT enzymes in vitro, however, the clinical significance is unknown.

212 Lapatinib inhibits human P-glycoprotein. If TYKERB is administered with drugs that are
213 substrates of P-gp, increased concentrations of the substrate drug are likely, and caution should
214 be exercised.

215 Paclitaxel: In cancer patients receiving TYKERB and the CYP2C8 substrate paclitaxel,
216 24-hour systemic exposure (AUC) of paclitaxel was increased 23%. This increase in paclitaxel
217 exposure may have been underestimated from the in vivo evaluation due to study design
218 limitations.

219 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

220 Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration
221 of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly (*see*
222 *Ketoconazole and Carbamazepine sections, below*). Dose adjustment of lapatinib should be
223 considered for patients who must receive concomitant strong inhibitors or concomitant strong
224 inducers of CYP3A4 enzymes [*see Dosage and Administration (2.2)*].

225 Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at
226 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to
227 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

228 Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at
229 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to
230 lapatinib was decreased approximately 72%.

231 **7.3 Drugs that Inhibit Drug Transport Systems**

232 Lapatinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If
233 TYKERB is administered with drugs that inhibit P-gp, increased concentrations of lapatinib are
234 likely, and caution should be exercised.

235 **8 USE IN SPECIFIC POPULATIONS**

236 **8.1 Pregnancy**

237 **Pregnancy Category D** [*see Warnings and Precautions (5.7)*].

238 Based on findings in animals, TYKERB can cause fetal harm when administered to a
239 pregnant woman. Lapatinib administered to rats during organogenesis and through lactation led
240 to death of offspring within the first 4 days after birth. When administered to pregnant animals
241 during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits)
242 at maternally toxic doses. There are no adequate and well-controlled studies with TYKERB in
243 pregnant women. Women should be advised not to become pregnant when taking TYKERB. If
244 this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the
245 patient should be apprised of the potential hazard to the fetus.

246 In a study where pregnant rats were dosed with lapatinib during organogenesis and
247 through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical
248 exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine), 91% of the

249 pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The
250 highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human
251 clinical exposure based on AUC).

252 Lapatinib was studied for effects on embryo-fetal development in pregnant rats and
253 rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects;
254 however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification)
255 occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the
256 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine).
257 In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day
258 (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC
259 following 1,250 mg dose of lapatinib plus capecitabine) and abortions at 120 mg/kg/day.
260 Maternal toxicity was associated with decreased fetal body weights and minor skeletal
261 variations.

262 **8.3 Nursing Mothers**

263 It is not known whether lapatinib is excreted in human milk. Because many drugs are
264 excreted in human milk and because of the potential for serious adverse reactions in nursing
265 infants from TYKERB, a decision should be made whether to discontinue nursing or to
266 discontinue the drug, taking into account the importance of the drug to the mother.

267 **8.4 Pediatric Use**

268 The safety and effectiveness of TYKERB in pediatric patients have not been established.

269 **8.5 Geriatric Use**

270 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in
271 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were
272 75 years of age and older. Of the total number of hormone receptor positive, HER2 positive
273 metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole
274 (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No
275 overall differences in safety or effectiveness were observed between elderly subjects and
276 younger subjects, and other reported clinical experience has not identified differences in
277 responses between the elderly and younger patients, but greater sensitivity of some older
278 individuals cannot be ruled out.

279 **8.6 Renal Impairment**

280 Lapatinib pharmacokinetics have not been specifically studied in patients with renal
281 impairment or in patients undergoing hemodialysis. There is no experience with TYKERB in
282 patients with severe renal impairment. However, renal impairment is unlikely to affect the
283 pharmacokinetics of lapatinib given that less than 2% (lapatinib and metabolites) of an
284 administered dose is eliminated by the kidneys.

285 **8.7 Hepatic Impairment**

286 The pharmacokinetics of lapatinib were examined in subjects with pre-existing moderate
287 (n = 8) or severe (n = 4) hepatic impairment (Child-Pugh Class B/C, respectively) and in 8
288 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose

289 increased approximately 14% and 63% in subjects with moderate and severe pre-existing hepatic
290 impairment, respectively. Administration of TYKERB in patients with severe hepatic
291 impairment should be undertaken with caution due to increased exposure to the drug. A dose
292 reduction should be considered for patients with severe pre-existing hepatic impairment [see
293 *Dosage and Administration (2.2)*]. In patients who develop severe hepatotoxicity while on
294 therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB
295 [see *Warnings and Precautions (5.2)*].

296 **10 OVERDOSAGE**

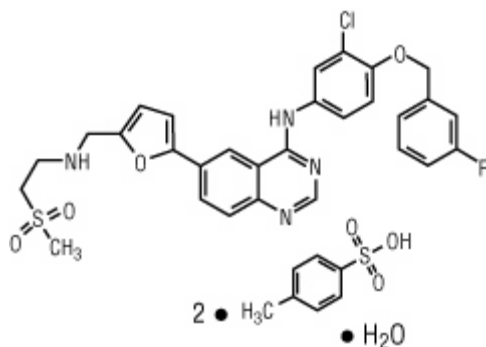
297 There is no known antidote for overdoses of TYKERB. The maximum oral doses of
298 lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent
299 ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical
300 trials and could result in increased toxicity. Therefore, missed doses should not be replaced and
301 dosing should resume with the next scheduled daily dose.

302 There has been a report of one patient who took 3,000 mg of TYKERB for 10 days. This
303 patient had Grade 3 diarrhea and vomiting on Day 10. The event resolved following IV hydration
304 and interruption of treatment with TYKERB and letrozole.

305 Because lapatinib is not significantly renally excreted and is highly bound to plasma
306 proteins, hemodialysis would not be expected to be an effective method to enhance the
307 elimination of lapatinib.

308 **11 DESCRIPTION**

309 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase
310 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-
311 chloro-4-{{(3-fluorophenyl)methyl}oxy}phenyl)-6-[5-({[2-
312 (methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-
313 methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$
314 $(C_7H_8O_3S)_2 H_2O$ and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the
315 following chemical structure:



316

317 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is
318 0.001 mg/mL at 25°C.

319 Each 250 mg tablet of TYKERB contains 405 mg of lapatinib ditosylate monohydrate,
320 equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base.

321 The inactive ingredients of TYKERB are: **Tablet Core:** Magnesium stearate,
322 microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat:
323 FD&C yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400,
324 polysorbate 80, titanium dioxide.

325 **12 CLINICAL PHARMACOLOGY**

326 **12.1 Mechanism of Action**

327 Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase
328 domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal
329 Receptor Type 2 (HER2 [ErbB2]) receptors (estimated K_i^{app} values of 3nM and 13nM,
330 respectively) with a dissociation half-life of ≥ 300 minutes. Lapatinib inhibits ErbB-driven tumor
331 cell growth in vitro and in various animal models.

332 An additive effect was demonstrated in an in vitro study when lapatinib and 5-FU (the
333 active metabolite of capecitabine) were used in combination in the 4 tumor cell lines tested. The
334 growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines.
335 Lapatinib retained significant activity against breast cancer cell lines selected for long-term
336 growth in trastuzumab-containing medium in vitro. These in vitro findings suggest non-cross-
337 resistance between these two agents.

338 Hormone receptor positive breast cancer cells (with ER [Estrogen Receptor] and/or PgR
339 [Progesterone Receptor]) that coexpress the HER2 tend to be resistant to established endocrine
340 therapies. Similarly, hormone receptor positive breast cancer cells that initially lack EGFR or
341 HER2 upregulate these receptor proteins as the tumor becomes resistant to endocrine therapy.

342 **12.3 Pharmacokinetics**

343 Absorption: Absorption following oral administration of TYKERB is incomplete and
344 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to
345 1.5 hour). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours
346 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to
347 7 days, indicating an effective half-life of 24 hours.

348 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)
349 values of C_{max} were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.hr/mL (23.4
350 to 56 mcg.hr/mL).

351 Divided daily doses of TYKERB resulted in approximately 2-fold higher exposure at
352 steady state (steady state AUC) compared to the same total dose administered once daily.

353 Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC
354 values were approximately 3- and 4-fold higher (C_{max} approximately 2.5- and 3-fold higher)
355 when administered with a low fat (5% fat-500 calories) or with a high fat (50% fat-1,000
356 calories) meal, respectively.

357 Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid

358 glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast
359 cancer resistance protein (BCRP, ABCG2) and P-glycoprotein (P-gp, ABCB1). Lapatinib has
360 also been shown in vitro to inhibit these efflux transporters, as well as the hepatic uptake
361 transporter OATP 1B1, at clinically relevant concentrations.

362 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and
363 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated
364 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or
365 10% of lapatinib concentration in plasma.

366 Elimination: At clinical doses, the terminal phase half-life following a single dose was
367 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

368 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with
369 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of
370 27% (range 3 to 67%) of an oral dose.

371 Effects of Age, Gender, or Race: Studies of the effects of age, gender, or race on the
372 pharmacokinetics of lapatinib have not been performed.

373 **12.4 QT Prolongation**

374 The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-
375 label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses
376 of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and
377 Day 14 to evaluate the effect of lapatinib on QT intervals. Analysis of the data suggested a
378 consistent concentration-dependent increase in QTc interval.

379 **13 NONCLINICAL TOXICOLOGY**

380 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

381 Two-year carcinogenicity studies with lapatinib are ongoing.

382 Lapatinib was not clastogenic or mutagenic in the Chinese hamster ovary chromosome
383 aberration assay, microbial mutagenesis (Ames) assay, human lymphocyte chromosome
384 aberration assay or the in vivo rat bone marrow chromosome aberration assay at single doses up
385 to 2,000 mg/kg. However, an impurity in the drug product (up to 4 ppm or 8 mcg/day) was
386 genotoxic when tested alone in both in vitro and in vivo assays.

387 There were no effects on male or female rat mating or fertility at doses up to
388 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times
389 the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus
390 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,
391 when female rats were given oral doses of lapatinib during breeding and through the first 6 days
392 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and
393 in the fetal body weights at ≥ 60 mg/kg/day (approximately 6.4 times and 3.3 times the expected
394 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine,
395 respectively).

396 **14 CLINICAL STUDIES**

397 **14.1 HER2 Positive Metastatic Breast Cancer**

398 The efficacy and safety of TYKERB in combination with capecitabine in breast cancer
 399 were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2
 400 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic
 401 breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and
 402 trastuzumab.

403 Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously)
 404 plus capecitabine 2,000 mg/m²/day on Days 1-14 every 21 days, or to receive capecitabine alone
 405 at a dose of 2,500 mg/m²/day on Days 1-14 every 21 days. The endpoint was time to progression
 406 (TTP). TTP was defined as time from randomization to tumor progression or death related to
 407 breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was
 408 discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The
 409 median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were
 410 Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+
 411 (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH
 412 confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes,
 413 and trastuzumab.

414 Efficacy analyses 4 months after the interim analysis are presented in Table 5, Figure 1,
 415 and Figure 2.

416

417 **Table 5. Efficacy Results**

	Independent Assessment ^a		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
Number of TTP events	82	102	121	126
Median TTP, weeks (25 th , 75 th , Percentile), weeks	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)
Hazard Ratio (95% CI) <i>P</i> value	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
Response Rate (%) (95% CI)	23.7 (18.0, 30.3)	13.9 (9.5, 19.5)	31.8 (25.4, 38.8)	17.4 (12.4, 23.4)

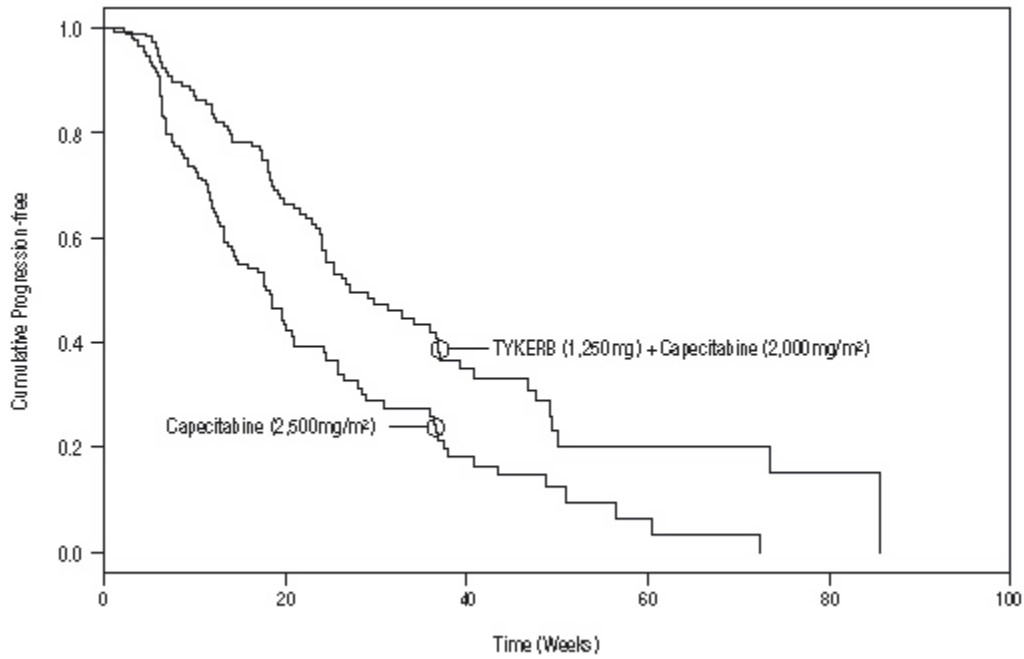
418 TTP = Time to progression.

419 ^a The time from last tumor assessment to the data cut-off date was >100 days in approximately

420 30% of patients in the independent assessment. The pre-specified assessment interval was 42
421 or 84 days.

422

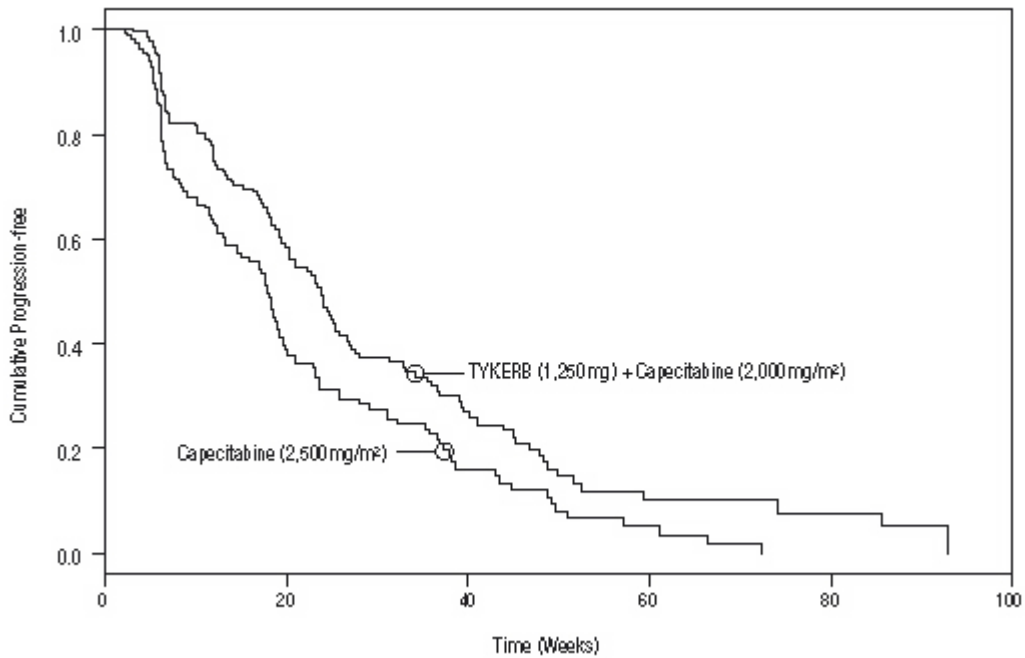
423 **Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to**
424 **Progression**



425

426

427 **Figure 2. Kaplan-Meier Estimates for Investigator Assessment Time to Progression**



428
429

430 At the time of above efficacy analysis, the overall survival data were not mature (32%
431 events). However, based on the TTP results, the study was unblinded and patients receiving
432 capecitabine alone were allowed to cross over to TYKERB plus capecitabine treatment. The
433 survival data were followed for an additional 2 years to be mature and the analysis is
434 summarized in Table 6.

435
436

Table 6: Overall Survival Data

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m²/day (N = 207)	Capecitabine 2,500 mg/m²/day (N = 201)
Overall Survival		
Died	76%	82%
Median Overall Survival (weeks)	75.0	65.9
Hazard ratio, 95% CI (<i>P</i> value)	0.89 (0.71, 1.10) 0.276	

437 CI = confidence interval
438

439 **14.2 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer**

440 The efficacy and safety of TYKERB in combination with letrozole were evaluated in a

441 double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women
 442 with hormone receptor positive (ER positive and/or PgR positive) metastatic breast cancer, who
 443 had not received prior therapy for metastatic disease, were randomly assigned to receive either
 444 TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg
 445 once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had
 446 tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH)
 447 ≥ 2 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2 negative
 448 and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective
 449 was to evaluate and compare progression-free survival (PFS) in the HER2 positive population.
 450 Progression-free survival was defined as the interval of time between date of randomization and
 451 the earlier date of first documented sign of disease progression or death due to any cause.

452 The baseline demographic and disease characteristics were balanced between the two
 453 treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-
 454 four percent (84%) of the patients were White. Approximately 50% of the HER2 positive
 455 population had prior adjuvant/neo-adjuvant chemotherapy and 56% had prior hormonal therapy.
 456 Only 2 patients had prior trastuzumab.

457 In the HER2 positive subgroup (n = 219), the addition of TYKERB to letrozole resulted
 458 in an improvement in PFS. In the HER2 negative subgroup, there was no improvement in PFS of
 459 the TYKERB plus letrozole combination compared to the letrozole plus placebo. Overall
 460 response rate (ORR) was also improved with the TYKERB plus letrozole combination therapy.
 461 The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor
 462 positive, HER2 positive and HER2 negative subgroups are presented in Table 7 and Figure 3.
 463

464 **Table 7. Efficacy Results**

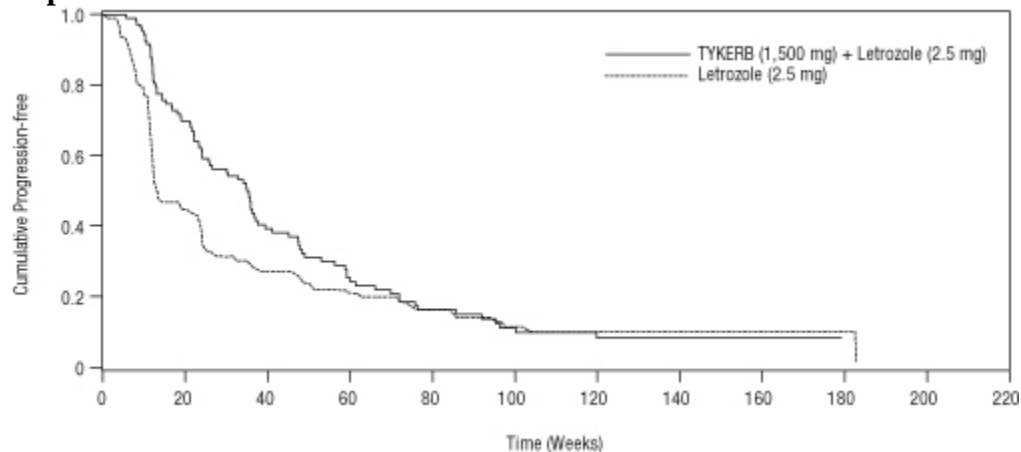
	HER2(+) Population		HER2(-) Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
Median PFS^a, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
Hazard Ratio (95% CI) P value	0.71 (0.53, 0.96) 0.019		0.90 (0.77, 1.05) 0.188	
Response Rate (%) (95% CI)	27.9 (19.8, 37.2)	14.8 (8.7, 22.9)	32.6 (28.4, 37.0)	31.6 (27.5, 36.0)

465 PFS = progression-free survival; CI = confidence interval.

466 ^a Kaplan-Meier estimate.

467

468 **Figure 3. Kaplan-Meier Estimates for Progression-Free Survival for the HER2 Positive**
469 **Population**



470
471

472 **16 HOW SUPPLIED/STORAGE AND HANDLING**

473 The 250 mg tablets of TYKERB are oval, biconvex, orange, and film-coated with
474 GS XJG debossed on one side and are available in:

475 Bottles of 150 tablets: NDC 0173-0752-00

476 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP
477 Controlled Room Temperature].

478 **17 PATIENT COUNSELING INFORMATION**

479 *See FDA-approved patient labeling (17.2).*

480 **17.1 Information for Patients**

481 Patients should be informed of the following:

- 482 • TYKERB has been reported to decrease left ventricular ejection fraction which may result in
483 shortness of breath, palpitations, and/or fatigue. Patients should inform their physician if they
484 develop these symptoms while taking TYKERB.
- 485 • TYKERB often causes diarrhea which may be severe in some cases. Patients should be told
486 how to manage and/or prevent diarrhea and to inform their physician if severe diarrhea
487 occurs during treatment with TYKERB.
- 488 • TYKERB may interact with many drugs; therefore, patients should be advised to report to
489 their healthcare provider the use of any other prescription or nonprescription medication or
490 herbal products.
- 491 • TYKERB may interact with grapefruit. Patients should not take TYKERB with grapefruit
492 products.
- 493 • TYKERB should be taken at least one hour before or one hour after a meal, in contrast to
494 capecitabine which should be taken with food or within 30 minutes after food.
- 495 • The dose of TYKERB should be taken once daily. Dividing the daily dose is not
496 recommended.

497 **17.2 FDA-Approved Patient Labeling**

498 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing
499 information.

500
501 TYKERB is a registered trademark of GlaxoSmithKline.
502



503
504 GlaxoSmithKline
505 Research Triangle Park, NC 27709

506
507 ©Year, GlaxoSmithKline. All rights reserved.

508
509 Month YEAR
510 TKB:XPI

514 **PATIENT INFORMATION**

515
516 **TYKERB (TIE-curb)**
517 **(lapatinib) tablets**
518

519 Read this leaflet before you start taking TYKERB[®] and each time you get a refill. There may be
520 new information. This information does not take the place of talking with your doctor about your
521 medical condition or treatment.

522
523 **What is TYKERB?**

524 TYKERB is used with the medicine capecitabine for the treatment of patients with advanced or
525 metastatic breast cancer that is HER2 positive (tumors that produce large amounts of a protein
526 called human epidermal growth factor receptor-2), and who have already had certain other breast
527 cancer treatments.

528
529 TYKERB is also used with a type of medicine called letrozole for the treatment of
530 postmenopausal women with hormone receptor positive, HER2 positive metastatic breast cancer
531 for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor
532 has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of
533 metastatic breast cancer.

534
535 **Who should not take TYKERB?**

536 Do not take TYKERB if you are allergic to any of its ingredients. See the end of this leaflet for a
537 list of ingredients in TYKERB.

538
539 **Before you start taking TYKERB**, tell your doctor about all of your medical conditions,
540 including if you:

- 541 • ever had a severe allergic (hypersensitivity) reaction to TYKERB. Check with your doctor if
542 you think this applies to you. Don't take TYKERB.
- 543 • have heart problems.
- 544 • have liver problems. You may need a lower dose of TYKERB.
- 545 • are pregnant or may become pregnant. TYKERB may harm an unborn baby. If you become
546 pregnant during treatment with TYKERB, tell your doctor as soon as possible.
- 547 • are breast-feeding. It is not known if TYKERB passes into your breast milk or if it can harm
548 your baby. If you are a woman who has or will have a baby, talk with your doctor about the
549 best way to feed your baby.

551 Tell your doctor about all the medicines you take, including prescription and nonprescription
552 medicines, vitamins, and herbal and dietary supplements. TYKERB and many other medicines
553 may interact with each other. Your doctor needs to know what medicines you take so he or she
554 can choose the right dose of TYKERB for you.

555

556 Especially tell your doctor if you take:

- 557 • antibiotics and anti-fungals (drugs used to treat infections)
- 558 • HIV (AIDS) treatments
- 559 • anticonvulsant drugs (drugs used to treat seizures)
- 560 • calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- 561 • antidepressants
- 562 • drugs used for stomach ulcers
- 563 • St. John's Wort or other herbal supplements

564

565 Know the medicines you take. Keep a list of your medicines with you to show your doctor. Do
566 not take other medicines during treatment with TYKERB without first checking with your
567 doctor.

568

569 Because TYKERB is given with other drugs called capecitabine or letrozole, you should also
570 discuss with your doctor or pharmacist any medicines that should be avoided during treatment.

571

572 **How should I take TYKERB?**

- 573 • Take TYKERB exactly as your doctor tells you to take it. Your doctor may change your dose
574 of TYKERB if needed.
- 575 • For patients with advanced or metastatic breast cancer, TYKERB and capecitabine are
576 taken in 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by
577 mouth all at once, **one time a day on days 1 to 21**. Your doctor will tell you the dose of
578 capecitabine you should take and when you should take it.
- 579 • For patients with hormone receptor positive, HER2 positive breast cancer, TYKERB and
580 letrozole are taken daily. The usual dose of TYKERB is 1,500 mg (6 tablets) taken by
581 mouth all at once, **one time a day**. Your doctor will tell you the dose of letrozole you
582 should take and when you should take it.
- 583 • TYKERB should be taken at least one hour before, or at least one hour after food.
- 584 • Do not eat or drink grapefruit products while taking TYKERB.
- 585 • If you forget to take your dose of TYKERB, do not take two doses at one time. Take your
586 next dose at your scheduled time.

587

588 **What are the possible side effects of TYKERB?**

589 **Serious side effects** include:

- 590 • **heart problems** including, decreased pumping of blood from the heart and an abnormal
591 heartbeat. Signs and symptoms of an abnormal heartbeat include:
 - 592 • feeling like your heart is pounding or racing
 - 593 • dizziness
 - 594 • tiredness
 - 595 • feeling lightheaded
 - 596 • shortness of breath
 - 597 • Your doctor should check your heart function before you start taking TYKERB and
598 during treatment.
- 599 • **liver problems.** Signs and symptoms of liver problems include:
 - 600 • itching
 - 601 • yellow eyes or skin
 - 602 • dark urine
 - 603 • pain or discomfort in the right upper stomach area
 - 604 • death
 - 605 • Your doctor should do blood tests to check your liver before you start taking
606 TYKERB and during treatment.
- 607 • **diarrhea**, which may cause you to become dehydrated. Follow your doctors instructions for
608 what to do to help prevent or treat diarrhea.
- 609 • **lung problems.** Symptoms of a lung problem with TYKERB include a cough that will not
610 go away or shortness of breath.

611
612 **Call your doctor right away if you have any of the signs or symptoms of the serious side**
613 **effects listed above.**

614
615 **Common side effects** of TYKERB in combination with capecitabine or letrozole include:

- 616 • diarrhea
- 617 • red, painful hands and feet
- 618 • nausea
- 619 • rash
- 620 • vomiting
- 621 • tiredness or weakness
- 622 • mouth sores
- 623 • loss of appetite
- 624 • indigestion
- 625 • unusual hair loss or thinning
- 626 • nose bleeds
- 627 • headache
- 628 • dry skin
- 629 • itching

630 • nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles.

631

632 Tell your doctor about any side effect that gets serious or that does not go away.

633

634 These are not all the side effects with TYKERB. Ask your doctor or pharmacist for more
635 information.

636

637 Call your doctor for medical advice about side effects. You may report side effects to FDA at
638 1-800-FDA-1088.

639

640 **You may also get side effects from the other drugs taken with TYKERB.** Talk to your doctor
641 about possible side effects you may get during treatment.

642

643 **How should I store TYKERB tablets?**

644 • Store TYKERB tablets at room temperature at 59° to 86°F (15° to 30°C). Keep the
645 container closed tightly.

646 • Do not keep medicine that is out of date or that you no longer need. Be sure that if you
647 throw any medicine away, it is out of the reach of children.

648 • **Keep TYKERB and all medicines out of the reach of children.**

649

650 **General information about TYKERB**

651 Medicines are sometimes prescribed for conditions that are not mentioned in patient information
652 leaflets. Do not use TYKERB for any other condition for which it was not prescribed. Do not
653 give TYKERB to other people, even if they have the same condition that you have. It may harm
654 them.

655

656 This leaflet summarizes the most important information about TYKERB. If you would like more
657 information, talk with your doctor. You can ask your doctor or pharmacist for information about
658 TYKERB that is written for health professionals. For more information, you can call toll-free 1-
659 888-825-5249 or by visiting the website www.tykerb.com.

660

661 **What are the ingredients in TYKERB?**

662 **Active Ingredient:** Lapatinib.

663 **Inactive Ingredients: Tablet Core:** Magnesium stearate, microcrystalline cellulose, povidone,
664 sodium starch glycolate. **Coating:** Orange film-coat: FD&C yellow #6/sunset yellow FCF
665 aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

666

667 TYKERB tablets are oval, biconvex, orange, film-coated with GS XJG printed on one side.

668



669

670

671 TYKERB is a registered trademark of GlaxoSmithKline.

672



673

674 GlaxoSmithKline

675 Research Triangle Park, NC 27709

676

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678

679 Revised: Month Year

680 TKB:XPIL

681

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22059

SUPPL-7

SMITHKLINE
BEECHAM CORP
DBA
GLAXOSMITHKLIN
E

TYKERB TABLETS

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

/s/

ANN T FARRELL

01/29/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Deputy Division Director
Subject	Division Director Summary Review
NDA/BLA #	022059 #007 and SLR-003 and SLR-006
Supplement #	
Applicant Name	Glaxo-Smith Kline
Date of Submission	March 31, 2009
PDUFA Goal Date	January 29, 2010
Proprietary Name / Established (USAN) Name	Tykerb/lapatinib
Dosage Forms / Strength	250 mg oral tablet
Proposed Indication(s)	(b) (4)
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Jennie Chang, Pharm. D.
Statistical Review	Qiang Xu, Ph.D./ Shenghui Tang, Ph.D.
Pharmacology Toxicology Review	Kimberly Benson, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	Jean Tang, Ph.D./Liang Zhou Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Gene Williams, Ph.D./Q. Liu, Ph.D.
DDMAC	Keith J. Olin and Stephanie L. Victor
DSI	Anthony Orenca, M.D.
CDTL Review	Patricia Cortazar, M.D.
OSE/DMEPA	Felicia Duffy, R.N., B.S.N., M.S.Ed.
OSE/DRISK	Steve L. Morin, R.N., B.S.N., O.C.N.
OSE/DSRCS	
Other	Suchitra M. Balakrishnan, M.D. – QT review for SLR 003

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK= Division of Risk Management

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

GlaxoSmithKline has submitted a supplemental New Drug Application (sNDA) #22059-0028 for the following indication:

TYKERB[®] is indicated in combination with [REDACTED] (b) (4)

The support for this indication is based on a single, multinational, randomized, placebo-controlled phase 3 study (EGF30008) testing the combination of lapatinib plus letrozole versus placebo plus letrozole in patients with hormone receptor-positive metastatic breast cancer supported by a phase 1 open-label study (EGF10030) of the safety, tolerability and pharmacokinetics of lapatinib in combination with letrozole [REDACTED] (b) (4) in cancer patients.

2. Background

Lapatinib is a small molecule, dual ErbB1 and ErbB2 receptor inhibitor initially developed to treat patients with breast cancers that overexpressed ErbB2 (by immunohistochemistry and confirmed by FISH) and had already received treatment with anthracyclines, taxanes, and trastuzumab.

On March 13, 2007 Tykerb[®] received full approval for the use of TYKERB[®] in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane and trastuzumab based on an improvement in time-to-progression results from a randomized phase 3 trial. The Warnings and Precautions section of the labeling described the following as potential complications associated with Tykerb[®] use: decreased left ventricular function, diarrhea, QT prolongation, fetal harm and increased toxicity if administered to patients with severe hepatic impairment. Less serious adverse reactions seen with lapatinib include: dermatologic (rash, radiation dermatitis and mucositis), ocular (squamous blepharitis, dysfunctional tear syndrome, and corneal epithelial defects), and pulmonary (interstitial pneumonitis).

This submission is based on a single, multinational, randomized, placebo-controlled phase 3 study (EGF30008) testing the combination of lapatinib plus letrozole versus placebo plus letrozole in patients with hormone receptor-positive metastatic breast cancer.

The sponsor initially wished to develop lapatinib for use in (b) (4) whose metastatic breast cancer is HER2+. However, the sponsor revised the study protocol in order to demonstrate an improvement in progression-free survival (PFS) for patients whose metastatic breast cancer expresses ER+/PgR+ and ErbB2+.

3. CMC/Device

N/A

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

From Dr. William's review:

A single pharmacokinetic study was submitted. The study results show that a single dose of (b) (4) has little or no effect on steady-state lapatinib pharmacokinetics, and conversely, a single dose of TYKERB does not alter steady-state letrozole pharmacokinetics. As both drugs are administered continuously, the single dose design is not adequate to assess the potential for pharmacokinetic changes, and (b) (4)

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Study EGF30008 randomized 1286 patients with hormone receptor-positive advanced or metastatic breast cancer to two arms: (1) lapatinib plus letrozole or (2) placebo plus letrozole. Lapatinib was dosed at 1500 mg daily and letrozole was dose at 2.5 mg daily. Enrollment began in December 2003 and ended in December 2006. Nearly 50% of the patients enrolled in this study were from Europe.

The final primary endpoint was PFS (investigator assessment) and the primary analysis population was the population of patients with HER2+ status. Only 17% of enrolled patients had HER2+ disease. Only 3 patients enrolled in the study had received prior treatment with trastuzumab. Only 2 patients with HER2+ disease enrolled in the study had received prior treatment with trastuzumab, which is the standard of care in the United States at this time.

From the clinical reviewer’s review:

Although Study EGF30008 enrolled all patients with hormone receptor-positive breast cancer, efficacy was observed only in patients with overexpressing HER2. The results of the pivotal study showed that median PFS was 35.4 weeks in the letrozole plus lapatinib group compared to 13.0 weeks in the letrozole plus placebo group, with a hazard ratio of 0.71 (95% CI: 0.53, 0.96; stratified log-rank p-value=0.019) in the HER2-positive subgroup.

From Dr. Xu’s statistical review, her analyses of PFS:

Table 3.1.4.1		Summary of Investigator-Evaluated PFS Analyses				
	HER2-Positive		HER2-Negative		ITT	
	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)	Letrozole (N=478)	Letrozole (N=474)	Letrozole (N=642)	Letrozole (N=644)
Events (%)	88 (79)	89 (82)	294 (62)	342 (72)	413 (64)	476 (74)
Median in weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)
Log-rank p-value	0.019		0.188		0.026	
Hazard Ratio (95% CI)	0.71 (0.53, 0.96)		0.90 (0.77, 1.05)		0.86 (0.76, 0.98)	

Dr. Xu’s table

Dr. Xu further commented in her review:

The sponsor used a hierarchical ordered hypothesis testing procedure to control the overall type I error for tests in the primary HER2-positive population and the secondary ITT population. However, this proposed testing procedure is not truly “closed” in the sense that the rejection of the second level null in the ITT population does not necessarily lead to the rejection of the first level null in HER2-positive population, contradicting with the basic characteristic of a closed test procedure. Therefore, from the statistical aspect, the proposed method may not strictly protect overall type I error.

Moreover, as presented in Tables 3.1.4.1 and 3.1.4.2, the study results failed to demonstrate a clinically relevant benefit of the combined treatment in HER2-negative subset (74% of the ITT population) in PFS and OS endpoints. The median PFS in tested group improved only 1.4 weeks compared with the placebo+letrozole group with a hazard ratio of 0.9. The median OS in lapatinib group was approximately 5 weeks less than the placebo arm with a hazard ratio of 1.15, in favor of the placebo group. As a result, the small effect of 4.7 weeks in PFS seen in the ITT population is most likely driven by the HER2-positive population.

There was no improvement in Overall Survival in the intent-to-treat population nor in the HER2+ subgroup.

Several issues are raised by this trial. First are the trial results for the HER-2+ and ITT populations correct? The statistical reviewer and statistical team leader reviews concur that treatment with lapatinib resulted in an improvement in investigator-determined progression-free survival for patients with advanced or metastatic hormone positive breast cancer which expresses HER-2. However, the statistical review team stated that the sponsor's proposed method of statistical testing to preserve the type 1 error rate for the ITT analysis based on the investigator-determined PFS does not necessarily preserve so it is not certain that the results are significant. No evidence exists to suggest that Second are the trial results relevant to patients who would be receiving the standard of care in United States? Only 2 patients with HER2+ disease in the study had received prior treatment with trastuzumab, which is the standard of care in the United States at this time. No, based on the prior treatment characteristics for the enrolled patients the results demonstrate a benefit for those who have not had prior trastuzumab.

From the clinical reviewer's review of the data: *The clinical reviewer recommends accelerated approval on the basis of its review of the supplemental NDA 22,059. The basis for this recommendation is the review of the results of the. This pivotal study met its primary endpoint of progression-free survival (PFS); however, questions remain as the applicability of the results in the United States population is unknown. In the U.S., trastuzumab, a HER2-antagonist, is given to patients with HER2-overexpressing breast cancer. Only three patients in the pivotal study had prior exposure to trastuzumab. Hence, more studies are needed to fully determine whether lapatinib is effective and safe to use in this patient population.*

The CDTL reviewer concurred with the above statements.

8. Safety

From the primary clinical review: *The safety population for this review comprises 1278 patients who received lapatinib 1500 mg daily plus letrozole 2.5 mg daily or placebo daily plus letrozole 2.5 mg daily. The safety profile of lapatinib in this combined study population appears unchanged from the previous safety review of the initial application of lapatinib.*

After reading the primary review, the statistical review, the statistical team leader's review, and the CDTL review, I concur that this information should be incorporated into the labeling. I also agree that additional studies should be required to demonstrate the benefit of this agent using standard of care treatment in the United States so that the labeling can be relevant.

9. Advisory Committee Meeting

This product is not a NME.

10. Pediatrics

Pediatric waiver granted due to the fact that breast cancer is extremely rare in the pediatric population.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Information on the current submission was incorporated into the labeling. In addition, safety information from 2 additional labeling supplements were incorporated. Prior approval supplement (SLR-003) revised the QT information presented in the labeling. Prior approval supplement (SLR-006) added information concerning hypersensitivity to the Contraindications and Adverse Reactions sections and nail disorders to the Adverse Reactions section.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Accelerated Approval
- Risk Benefit Assessment

Approval of this supplement allows incorporation of information from this study into the labeling; however, since the trial results do not reflect current US practice, the sponsor should conduct studies which will reflect usage in the United States.

- Recommendation for Postmarketing Risk Management Activities
Continued post marketing surveillance

- Recommendation for other Postmarketing Study Commitments (Subpart H)

#1- A randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor. This will be a Phase 3, randomized clinical trial designed to demonstrate superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane. Secondary endpoints include progression-free survival.

#2- A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor. This will be a Phase 3, randomized clinical trial designed to demonstrate superiority in overall survival. The secondary efficacy endpoint will be

overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-3	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-6	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

ANN T FARRELL
01/29/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 22-059/S-007

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Kimberly Benson
Qi Liu
Zhe J. Tang
Liang Zhou
Shenghui Tang
Qiang (Casey) Xu
Keith Olin
Steve Morin
Sarah Simon
Felicia Duffy
Robert Justice
Patricia Cortazar

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 15, 2010
DDOP Clinical Team Leader	Patricia Cortazar, MD
NDA Supplement#	22-059 SE-007
Applicant	SmithKline Beecham (Cork) Ltd d/b/a GlaxoSmithKline
Date of Submission	March 31, 2009
PDUFA Goal Date	January 31, 2010
Proprietary Name / Established (USAN) names	Tykerb®/Lapatinib
Dosage forms / Strength	Tykerb is supplied in a (b) (4) tablets
Proposed Indication(s)	"Tykerb in combination with (b) (4) (D) (4)
Recommended:	<i>Accelerated Approval</i>

1. Introduction

GlaxoSmithKline submitted a supplemental New Drug Application (NDA) to support marketing approval of Tykerb in combination with (b) (4). This document summarizes the reviews and conclusions of each review discipline. Most importantly, this review will focus on the reasons for accelerated-approval. This document also addresses the review of SLR 002 and 006.

2. Background

Tykerb® (lapatinib) is a kinase inhibitor, FDA approved in 2007 for use in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. This approval was for a refractory population, as 2nd-3rd line setting. Table 1 summarizes the study results. The basis of approval was an improvement in TTP in the range of 5 to 8 weeks, in patients treated with the lapatinib plus capecitabine combination with a hazard ratio of 0.57 and 0.72 per independent and investigator reviewed assessments, respectively. The magnitude of the treatment benefit was different between the independent radiology review and the investigator assessments.

The study was stopped early based on an interim analysis of TTP. At the time of approval, the survival data were not mature.

Table 1 Lapatinib Approval Efficacy Results

	Independent radiology Review		Investigator	
	Lap +Cap	Cap	Lap +Cap	Cap
TTP # events	82	102	121	126
Median (weeks)	27.1	18.6	23.9	18.3
Hazard ratio	0.57		0.72	
95% CI	(0.43, 0.77)		(0.56, 0.92)	
P-value	0.00013		0.00762	
ORR %	23.7	13.9	31.8	17.4

The pivotal trial for this supplemental NDA is the EGF30008 Trial which was conducted in 1286 patients and sponsored by the Applicant. The trial was a Phase III multicenter, multinational, randomized, double-blind, placebo-controlled trial in 1286 postmenopausal women with hormone receptor positive, previously untreated, advanced or metastatic breast cancer. Patients were randomized 1:1 to lapatinib (1500 mg once daily) with letrozole (2.5 mg once daily), or letrozole (2.5 mg once daily) with placebo. Randomization was stratified by sites of disease (visceral/soft tissue versus bone only) and prior adjuvant hormonal therapy (< 6 months vs. ≥ 6 months from prior endocrine therapy or no prior endocrine therapy).

The primary endpoint was initially time to progression (TTP) in the intent-to-treat population (ITT), but this was later changed to investigator-assessed progression-free survival (PFS) in the HER2 positive population. The secondary endpoints were overall survival, overall response rate, and duration of response.

The EGF30008 trial was not conducted under a Special Protocol Assessment (SPA) agreement and was not prospectively designed as a registration study. Discussions with the Agency started at the time of Amendment #3 in 2005 when the study had 97% of the pre-planned accrual. The amendment consisted of an increase to the sample size from 760 to 1280 patients in order to have sufficient power for analysis in the HER2-positive subgroup. FDA stated: “ If the primary analysis in the ITT (original) population does not achieve a statistical significance level, no further efficacy claim will be granted in the HER2 positive subgroup”. Additionally, the protocol was changed to restrict the study to Stage IV disease as investigators were enrolling patients with neoadjuvant intent as a bridge to surgery.

The Agency also expressed concerns with the HER2 status which was determined retrospectively therefore was not a stratification factor. The potential for imbalances in baseline prognostic factors may exist and the p-value for comparing TTP between the 2 arms in the HER2-subgroup may not be interpretable. For this reason, DDOP reviewers recommended GSK to conduct another study to focus on the HER2 positive population.

CDTL

Patricia Cortazar, MD

NDA 22059

In October 2007, Amendment 4 was submitted when 100% of the patients were accrued into the trial. The amendment consisted in the change of the primary endpoint from time to progression to progression free survival as evaluated by the investigator, in the HER2-positive population. DDOP review team stated that PFS will be reviewed in the ITT population as originally designed before considering the subgroup results.

The main problems with the study design are the patient population and the treatment control arm.

Patient population:

Enrollment to the EGF30008 trial was open to all patients regardless of the HER2 status. HER2 status was assessed retrospectively and patients were not prospectively stratified by HER2 status which could potentially have led to an imbalance in important risk factors. Patients with non-measurable disease were eligible, which is very problematic when PFS is the primary endpoint.

Treatment control arm:

Letrozole is an acceptable control arm for 1st line MBC. It is approved for first-line treatment of postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer. The letrozole trial that supported the approval showed a 3 month improvement in time to progression (HR 0.72, $p < 0.0001$) when compared to tamoxifen. The median overall survival was 35 months for the letrozole group and 32 months for the tamoxifen group, with a P-value of 0.5136. The trial design allowed patients to cross over upon progression to the other therapy (approximately 50%). In patients who did not cross over to the opposite treatment arm, median survival was 35 months with letrozole (n=219, 95% CI 29 to 43 months) vs 20 months with tamoxifen (n=229, 95% CI 16 to 26 months).

Although letrozole is an acceptable control arm for patients with hormone receptor positive MBC, endocrine monotherapy for the treatment of 1st line metastatic breast cancer in patients who overexpress HER2, could be considered suboptimal when patients have symptomatic visceral disease, are rapidly progressing or have visceral crisis. Even though the applicant claims that this patient population was excluded in the EGF30008 trial, it is unclear from the data submitted by the applicant, whether some of the patients with visceral metastasis and disease progression < 6 months from last hormonal therapy, could have benefited from a trastuzumab chemotherapy regimen combination. Trastuzumab combination regimens provide clinical benefit in the 1st line MBC setting in women with HER2 positive disease. In 1998, the Agency approved trastuzumab in combination with paclitaxel for first line treatment of patients with HER2 positive metastatic breast cancer. The study that supported the trastuzumab approval was a randomized clinical trial in 469 women who had not received chemotherapy for metastatic disease. Patients were randomized to receive chemotherapy alone or chemotherapy in combination with trastuzumab. Table 2 summarizes the trial results, trastuzumab when added to chemotherapy showed a statistically significant prolongation on time to progression and a survival benefit of 5 months.

Table 2 Trastuzumab 1st line MBC Efficacy Results

	Trastuzumab+Chemotherapy N=235	Chemotherapy N=234
Median TTP (months)	7.2	4.5
Hazard ratio (95% CI)	0.53 (0.43, 0.65)	
P-value (log-rank test)	<0.0001	
Median Survival (months)	25.1	20.3
Hazard ratio (95% CI)	0.80 (0.64, 1.0)	
P-value (log-rank test)	0.046	

3. CMC/Device

There is no new data submitted with this supplement.

4. Nonclinical Pharmacology/Toxicology

There is no new data submitted with this supplement.

5. Clinical Pharmacology/Biopharmaceutics

There is no new data submitted with this supplement.

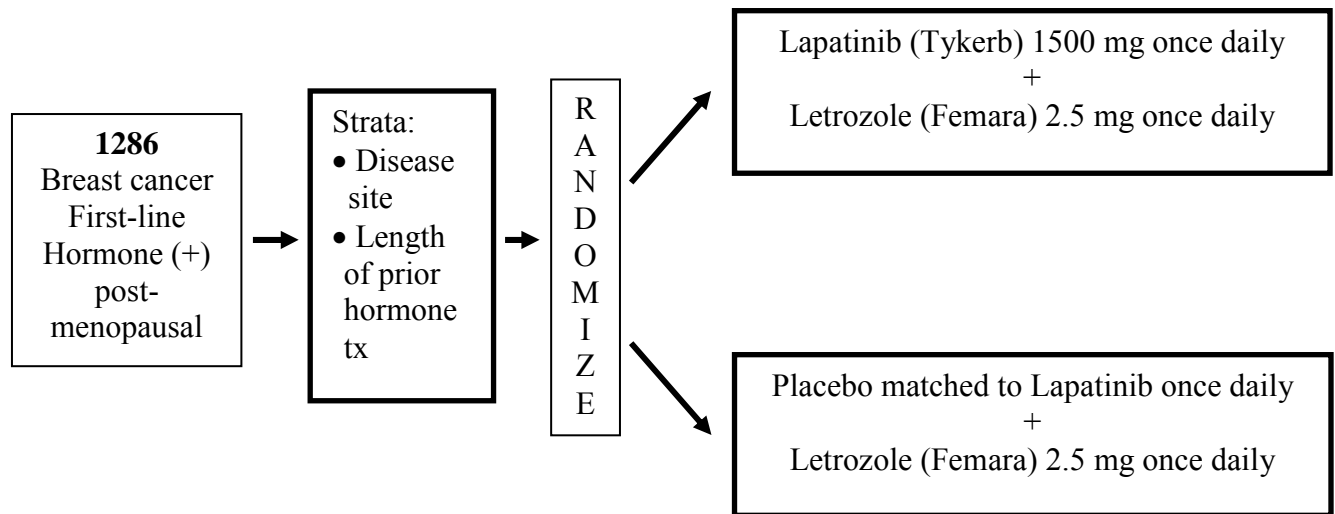
6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Study Design:

The pivotal trial for this supplemental NDA is the EGF30008 Trial which was conducted in 1286 patients and sponsored by the Applicant. The trial was a Phase III multicenter, multinational, randomized, double-blind, placebo-controlled trial in 1286 postmenopausal women with hormone receptor positive, previously untreated, advanced or metastatic breast cancer. Patients were randomized 1:1 to lapatinib (1500 mg once daily) with letrozole (2.5 mg once daily), or letrozole (2.5 mg once daily) with placebo. Randomization was stratified by sites of disease (visceral/soft tissue versus bone only) and prior adjuvant hormonal therapy (< 6 months vs. ≥ 6 months from prior endocrine therapy or no prior endocrine therapy).



The primary endpoint was initially time to progression (TTP) in the intent-to-treat population (ITT), but this was later changed to investigator-assessed progression-free survival (PFS) in the HER2 positive population. The secondary endpoints were overall survival, overall response rate, and duration of response.

Statistical Plan:

The protocol was to target a sample size of 1280 patients. The study provided 90% power to detect a median PFS of 13 months in the lapatinib plus letrozole arm versus 10 months in the placebo plus letrozole arm. The statistic for sample size calculation was the log rank statistic.

The study planned to target a sample size of 218 HER2-positive patients. The study provided 80% power to detect a median PFS of 15.5 months in the lapatinib plus letrozole arm versus 10 months in the placebo plus letrozole arm. The number of events required for the final analysis was at least 173 events (progression or death) for analysis of PFS. The statistic for sample size calculation was log-rank statistic. No interim analyses were done.

There were major protocol amendments on the primary endpoint after the patient accrual was completed. The primary endpoint was changed from TTP to PFS. PFS should be prospectively planned and properly assessed to be considered an acceptable primary endpoint for a registration trial.

The primary analysis population was changed from the intent-to-treat population to the HER2-positive subgroup.

Study Results:

Results of the EGF30008 trial were based on the database-lock date of June 3, 2008. A total of 1286 patients with hormone-sensitive metastatic breast cancer at primary diagnosis or relapse after neoadjuvant or adjuvant therapy were enrolled. Six hundred forty-four patients were

randomized to the lapatinib plus letrozole arm and 642 patients were randomized to the placebo plus letrozole arm. A total of 212 centers in 29 countries across 5 regions (North America, Latin America, Western Europe, Eastern Europe and Asia Pacific) accrued subjects in this multicenter study.

Of the 1286 patients randomized in the trial, only 17% were HER2-positive. Most of the patient population was HER2-negative and in 9% of the patients, the HER2 status was unknown. Although it appears that the HER2 status was balanced between treatment arms, there is potential for an imbalance between treatment groups since 9% of the data is missing. In addition, 20 % of the patients were hormone receptor negative, which is inadequate considering the trial is designed to treat patients in both arms with endocrine therapy.

Table 3 Patient Population (ITT)

Population	Lapatinib + Letrozole	Placebo + Letrozole	Total
Randomized	642 (100)	644 (100)	1286 (100)
HER2-positive	111 (17)	108 (17)	219 (17)
HER2-negative	478 (74)	474 (74)	952 (74)
HER2-missing	53 (8)	62 (10)	115 (9)
ER or PgR-positive ¹	515 (80)	492 (77)	1007 (78)
ER or PgR-negative ¹	129 (20)	132 (20)	261 (20)

¹ ER=estrogen receptor, PgR=progesterone receptor

Prior breast cancer therapies in the EGF30008 trial do not reflect the U.S. standard of care. The available information on prior breast cancer chemotherapy in the HER2+ subgroup is shown in Table 4. Only 2 patients with HER2 positive breast cancer were treated with prior trastuzumab. Approximately 55% of the patients had prior hormonal therapy and only half of the patients had prior chemotherapy, including 36% treated with prior anthracyclines and 8% with prior anthracyclines plus a taxane.

Table 4 Prior Breast Cancer Therapy (HER2 positive subgroup)

Prior Therapy	Lapatinib + Letrozole	Placebo + Letrozole
Neoadjuvant/adjuvant	111 (%)	108 (%)
Hormone therapy	60 (54)	62 (57)
Tamoxifen or Toremifene	59 (53)	60 (55)
Aromatase Inhibitor	1 (1)	1 (1)
Trastuzumab	1 (<1)	1 (<1)
Chemotherapy	61 (55)	51 (47)
Anthracycline only	41 (37)	38 (35)
Anthracyclines + taxanes	9 (8)	9 (8)
Hormone + chemotherapy	44 (40)	43 (40)

Progression-Free Survival

The applicant’s analysis of PFS in the ITT population shows that the combination of lapatinib plus letrozole has a median PFS of 51.7 weeks compared to 47.0 weeks for the placebo plus lapatinib arm, a median difference of 4.7 weeks. The Hazard Ratio was 0.86. These results are shown in Table 5 and Figure 1. Sixty-nine percent of the patients had an event and 36% were censored.

Table 5 Applicant's PFS results (ITT)

	Lapatinib + Letrozole 642 (%)	Placebo + Letrozole 644 (%)
PFS Events (%)	413 (64)	476 (74)
Death	11 (2)	18 (3)
PD	402 (63)	458 (71)
Censored (%)	229 (36)	168 (26)
Median PFS in Weeks (95% CI)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)
P-value	0.026	
Hazard Ratio (95% CI)	0.86 (0.76, 0.98)	

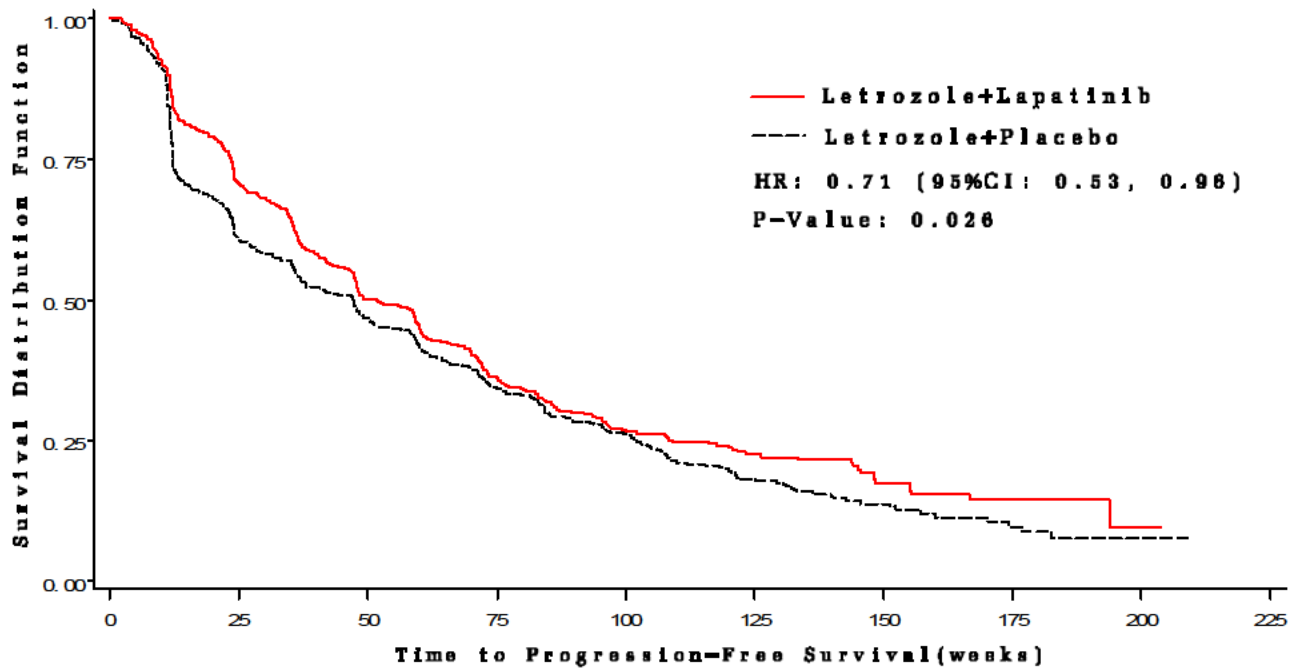


Figure 1 PFS in the ITT population

The primary efficacy analysis of PFS is based on investigator’s assessment of disease progression using radiological imaging data and symptomatic assessment in the HER2-positive, hormone receptor-positive advanced or metastatic breast cancer patients. As depicted in Table 6 and Figure 2, the combination of lapatinib plus letrozole has a median PFS of 35.4 weeks compared to 13.0 weeks for the placebo plus letrozole arm, a median difference of 22 weeks, hazard ratio of 0.71 and p value of 0.019, in favor of the combination arm.

Table 6 PFS results (HER2 positive subgroup)

	Lapatinib + Letrozole 111 (%)	Placebo + Letrozole 108(%)
PFS Events (%)	88 (79)	89 (82)
Death	3 (3)	2 (2)
PD	85 (77)	87(81)
Censored (%)	23 (21)	19 (18)
Median PFS in Weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)
P-value	0.019	
Hazard Ratio (95% CI)	0.71 (0.53, 0.96)	

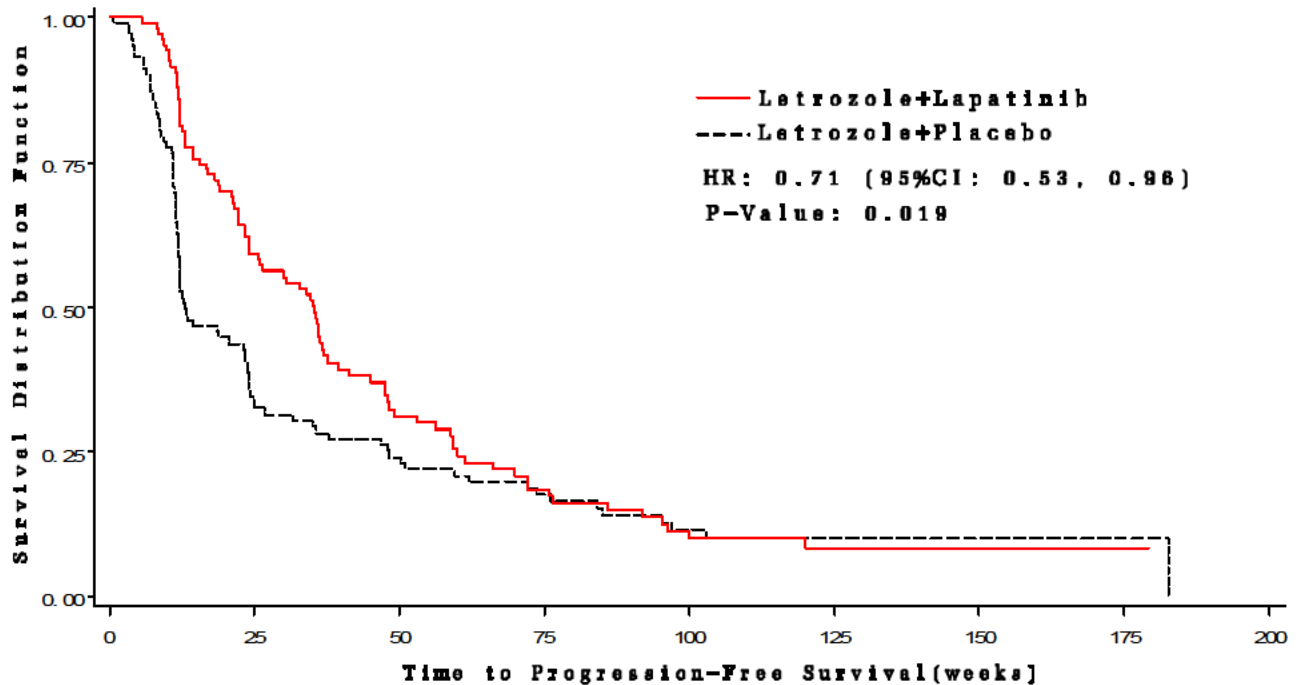


Figure 2 PFS in the HER2 positive subgroup

A comparison of the PFS analysis in the HER2 negative and the HER2 positive subsets, show there is no effect of the lapatinib plus letrozole combination compared to the letrozole plus placebo combination in patients who are HER2 negative. Therefore, the small effect of 4.7 weeks in PFS seen in the ITT population reflects the PFS effect in the HER2 positive population.

Table 7 PFS Results in HER2 positive and HER2 negative subsets (INV)

	HER2-negative		HER2-positive	
	Letrozole + Lapatinib 478 (%)	Letrozole + Placebo 474 (%)	Letrozole + Lapatinib 111 (%)	Letrozole + Placebo 108 (%)
PFS events	294 (62)	342 (72)	88 (79)	89 (82)
Median PFS weeks	59.7	58.3	35.4	13
p-value	0.189		0.019	
Hazard ratio (95% CI)	0.90 (0.77, 1.05)		0.71 (0.53, 0.96)	

In this pivotal trial, PFS could be determined by symptomatic progression or clinical disease assessments for palpable or visual lesions. The use of this method for PFS assessment in a registration study is problematic because it is not precise, is subject to bias and can not be confirmed by independent reviewers or the FDA. Table 8 below shows several sensitivity analyses performed by FDA to explore the PFS effect with different assessments such as symptomatic progressions excluded, bone disease only at baseline excluded or combining both categories. The PFS results still demonstrate improvement with the combination of lapatinib plus letrozole treatment, with a difference in median PFS of 3 to 4 months.

Table 8 PFS sensitivity analyses (FDA)

	Median PFS difference (weeks)	Hazard Ratio
1) Excluding symptomatic progressions	12.5	0.76
2) Excluding only bone disease at baseline	21.4	0.73
Excluding 1 and 2	12.3	0.78

The interim survival analysis results are shown in Table 9 and figures below. The difference in OS between treatment arms is very small, with a median OS difference between 4 to 6 weeks. The study was not powered for survival.

Table 9 Overall Survival

	HER2-positive		ITT	
	Letrozole + Placebo 108 (%)	Lapatinib + Letrozole 111 (%)	Letrozole + Placebo 474 (%)	Lapatinib + Letrozole 478 (%)
OS events (%)	54 (50)	50 (45)	234 (36)	240 (37)
Median OS (weeks)	140.3	144.7	176.3	170.9
p-value	0.113		0.915	
Hazard ratio (95% CI)	0.73 (0.5, 1.1)		1.01 (0.8, 1.2)	

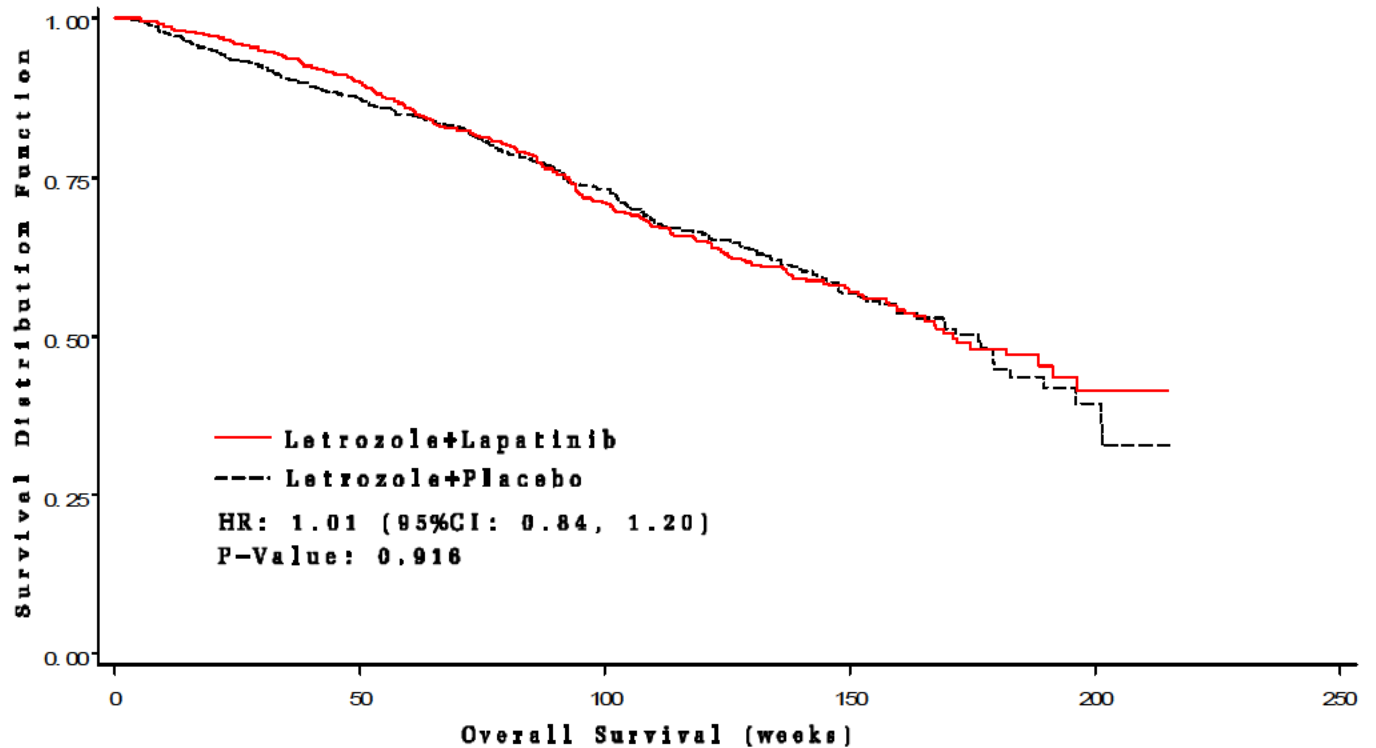


Figure 3 Overall Survival (ITT)

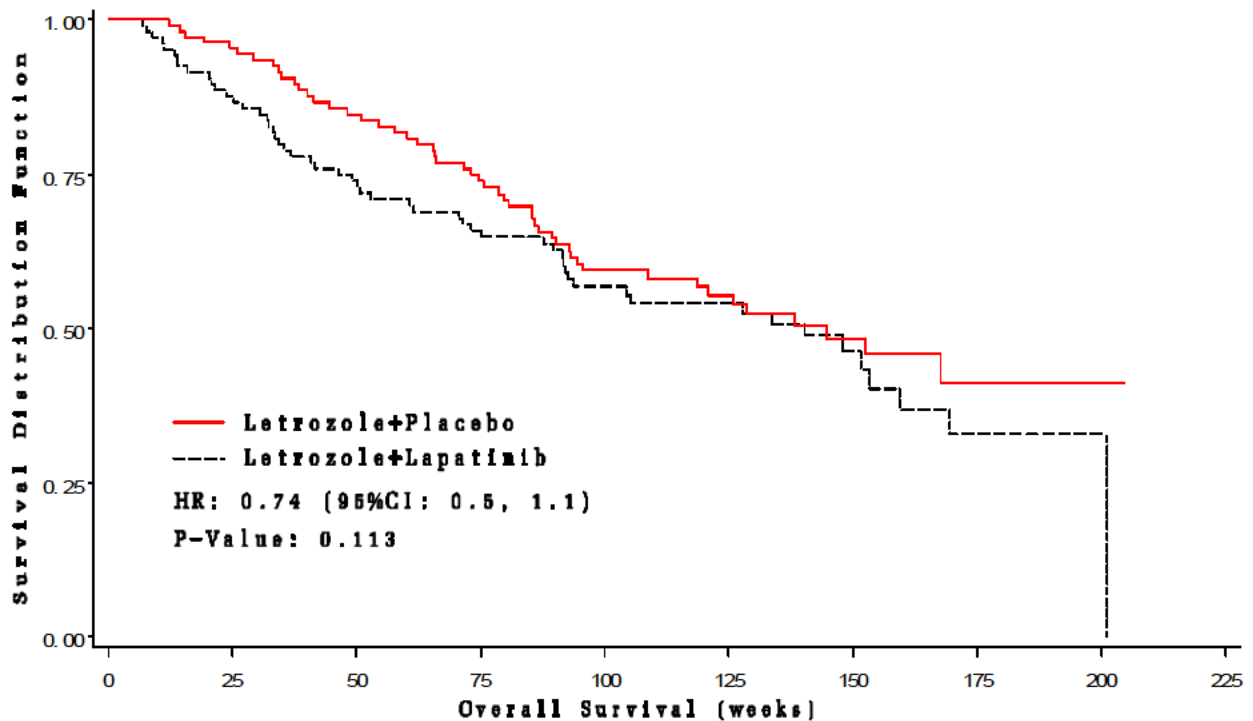


Figure 4 Overall Survival (HER2 positive subgroup)

8. Safety

The safety profile of lapatinib has been previously described in the Tykerb label. This trial did not have additional safety signals. Using National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, the adverse events occurring in at 10% of patients in EGF30008 trial included: diarrhea, rash, nausea and fatigue occurred in decreasing order at $\geq 20\%$ frequency in the lapatinib plus letrozole arm. Diarrhea occurred in the greatest frequency of grade 3-4 severity in patients in the lapatinib plus letrozole arm. These adverse events are consistent with the initial approval of lapatinib.

Cardiac Adverse Events

Study EGF30008 excluded patients with a known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure. Patients randomized to the study were required to have cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive). Measurement of LVEF was to be performed every 8 weeks.

FDA analysis of cardiac events consisted of a MedDRA search including a definition of cardiac events that included: cardiac failure, cardiac failure congestive, cardiomyopathy, decreased

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ejection fraction, left ventricular dysfunction, left ventricular failure, and ventricular dysfunction. Table 10 shows the number of patients and cardiac events in the treatment arm was twice higher than the placebo arm including the number of patients with left ventricular dysfunction. However, the number of cases of congestive heart failure was about the same.

Table 10 Cardiac adverse events (FDA analysis)

	Letrozole + Placebo N=624		Letrozole + Lapatinib n= 654	
Number of subjects with cardiac events	19		39	
Preferred Term	All Grades	Grade 3-4	All Grades	Grade3-4
Cardiac Failure, Congestive, Cardiomyopathy	3	1	4	0
Ejection Fraction Decreased	10	1	25	5
Ventricular Dysfunction	4	0	10	1
LV Failure	2	1	0	0
Withdrawal due to Cardiac AE	2 LV Dysfunction		2 Cardiac Failure, LV Dysfunction	
Cardiac Deaths	0		0	

Table 11 LVEF Assessments (FDA analysis)

Event	Lapatinib + Letrozole, N=599, (%)	Placebo + Letrozole, N=581 (%)
Protocol-defined LVEF decrease (absolute) ¹	13 (2)	13 (2)
Absol. decrease >20%	7 (1)	9 (2)
LLN + absol. decrease >20%	6 (1)	4 (1)
LVEF decrease (relative) ¹	62 (10)	42 (7)
Relative decrease >20%	40 (7)	35 (6)
LLN + relative decrease >20%	22 (4)	7 (1)
No baseline EF	5 (<1)	5 (<1)
No follow-up and/or conclusive EF	412 (63)	402 (64)

Although it appears that a cardiac safety signal may not exist for patients in the lapatinib plus letrozole arm, in 64% of the patients had no follow up or conclusive measurement of ejection fraction. Therefore, an adequate cardiac evaluation can not be done due to missing data in a high percentage of the patients.

Hepatotoxicity:

Hepatotoxicity is a well know side effect of Lapatinib and is labeled as a black box warning. It has been observed in clinical trials and postmarketing experience. Hepatotoxicity observed in

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Study EGF30008 is consistent with what has been observed in the pre-marketing clinical trials. One subject experienced a fatal outcome due to hepatotoxicity in the lapatinib plus letrozole arm.

9. Advisory Committee Meeting

This application was scheduled to be presented at the December 17, 2009 ODAC meeting. The ODAC presentation was cancelled because the important issues that the initial issues that FDA initially had with the application were properly addressed by the applicant in the ODAC Briefing Document or were no longer relevant since the PFS improvement were still robust. The Agency had a T-con with GSK in November 2009, was very productive in providing the applicant with a good understanding of the issues with the application and GSK got the opportunity to rethink about their approach.

The following are the issues that have been resolved:

1) The indication submitted on March 2009 is too broad:

“Tykerb[®] in combination with [REDACTED] (b) (4)

(b) (4)

In the ODAC briefing document, the applicant proposed a modified indication that better reflected the results from the pivotal trial:

“Tykerb in combination with [REDACTED] (b) (4)

(b) (4)

2) [REDACTED] (b) (4)

(b) (4)

3) The benefit from chemotherapy treatment has been demonstrated in patients with metastatic breast cancer with visceral metastasis, rapidly progressing disease or who are symptomatic. The applicant states that this population was excluded from the pivotal trial. (b) (4)

(b) (4)

4) The methods for PFS assessments in the pivotal trial, which included clinical measurements of the lesions and symptomatic progressions were problematic because they were not precise and could not be confirmed. However, several sensitivity analyses that FDA performed still showed a solid PFS improvement in the range of 3 to 5 months.

10. Pediatrics

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

The following sections were changed:

INDICATIONS AND USAGE

From:

TYKERB®, a kinase inhibitor, is indicated in combination with

(b) (4)

To:

TYKERB®, a kinase inhibitor, is indicated in combination with

- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. Tykerb in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

DOSAGE AND ADMINISTRATION

The following text was added to section 2.1:

The recommended dose of TYKERB

(b) (4)

(b) (4) is 1500 mg (b) (4) given orally once daily

continuously in combination with (b) (4) When TYKERB is

coadministered with letrozole, the recommended dose of letrozole is 2.5 mg

once daily. (2.1)

ADVERSE REACTIONS

- The following text was added to section 6.1. The most common ($\geq 20\%$) adverse reactions during treatment with TYKERB plus letrozole were diarrhea, rash, nausea, and fatigue. (b) (4)

(b) (4)

CLINICAL STUDIES

Sections 14.1 and 14.2 were updated to include the efficacy update from the HER2 positive metastatic breast cancer from the original approval. See review by Clinical reviewer Jennie Chang.

CONTRAINDICATIONS

This refers to SLR 006. In section 4, the following text was added:

Known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components.

WARNINGS AND PRECAUTIONS

GSK wanted to remove the following text (b) (4) “Lapatinib may prolong the QT interval in some patients. Consider ECG and electrolyte monitoring”. FDA did not agree on removing this text. Please see review of SLR 003 by Balacinchra Suchitra.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The FDA reviewers recommend accelerated approval for this supplemental NDA. The following summarizes the most important issues with this application.

The **first issue** is that EGF30008 trial is not a well designed trial for a regulatory submission. This study was not prospectively designed as a registration study. Discussions with the Agency started in 2005, at the time Amendment # 3 was submitted to the Agency, when the study had completed 97% of the pre-planned accrual. The trial started with 1286 patients with hormone receptor-positive, advanced or metastatic breast cancer, regardless of HER2/neu status. The applicant changed the primary analysis population to the HER2+ subgroup, which constitutes of only 219 patients, 17% of the randomized population. The PFS results from a pre-specified HER2+ subgroup analysis are positive, but this study did not powered for overall survival.

In general, for consideration of regulatory submissions, the Agency has required two well-designed, well-controlled studies. The current submission is based on a subgroup analysis of a very small population in a single study.

The Agency has previously accepted PFS as the primary endpoint for approval in the first-line MBC setting. Avastin received accelerated approval based on a statistically significant improvement in PFS, with a difference in median PFS of over 5 months. The median PFS in the combination arm was 11.3 months compared to 5.8 months with a HR of 0.48 indicating that the risk of progression or death was less than half in patients treated with Avastin and paclitaxel combination. There was no improvement in overall survival. However, because Avastin was already approved in multiple disease settings and because of the magnitude of the PFS improvement, PFS was considered to be of clinical benefit. This was corroborated by a doubling of response rate from (22% to 49%) and preliminary data from a second trial, the AVADO trial.

The **second issue** is the applicability of the EGF30008 trial results to the US population of patients with HER2+ hormone positive metastatic breast cancer. The population in this trial is not a representative sample of the US population with HER2+, hormone-positive metastatic breast cancer. The EGF30008 trial was conducted mostly in foreign countries; only 2 of the 219 patients with HER2+ breast cancer had prior trastuzumab, 50% of the patients were treatment-naïve, 36% received prior anthracyclines and none of the patients had prior taxanes. It is possible that since the EGF30008 trial population did not receive prior aromatase inhibitors and were more chemotherapy naïve than what is expected for a US population, the magnitude of the PFS benefit in the US population might not be as impressive as in the EGF30008 trial. It is concerning that the magnitude of PFS effect on patients that received prior adjuvant trastuzumab and an aromatase inhibitor is unknown. Study EGF30008 was not designed to answer this question.

The **third issue** is the risk of cardiac toxicity which has not been properly studied in the EGF30008 trial. The risk for cardiac toxicity in the US population, most of whom will likely have received prior trastuzumab, is unknown.

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The **fourth issue** relates to the indication proposed by the applicant which is broad and does not reflect the population studied in the pivotal trial. The following is the indication submitted with the supplemental NDA on March 2009:

“Tykerb® in combination with [REDACTED] (b) (4)
[REDACTED] (b) (4)

As stated in the applicant’s ODAC briefing document, GSK is proposing a modified indication that better reflects the studied population:

"Tykerb in combination with [REDACTED] (b) (4)
[REDACTED] (b) (4)

The indication should be further modified to better define the applicability of the pivotal trial results to the US patient population: The following is FDA’s proposed wording of the Tykerb indication:

Tykerb in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. Tykerb in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

Recommendation for Postmarketing Requirements:

The following trials will be necessary in order to fulfill the postmarketing requirement of the accelerated approval.

1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab [REDACTED] (b) (4)

[REDACTED] The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor. [REDACTED] (b) (4)

[REDACTED] (b) (4)

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2. A randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

(b) (4)

Supplemental Labeling Requests 003 and 006

On December 5, 2008, the Applicant submitted supplemental labeling request (SLR) 006 to change the Tykerb labeling and patient information leaflet to include nail disorders in the *Adverse Reactions* section and hypersensitivity to the *Contraindications* and *Adverse Reactions* sections.

Nail Disorders

Nail disorders has been reported in clinical trials, 1-4%. There were: 49 postmarketing reports of nail disorder, 11 included information on positive dechallenge and 3 reports of positive rechallenge. Time to onset in these 14 reports ranges from 4 to 363 days with a mean of approx. 69 days or 10 weeks which is consistent with the literature. All reports occurred in females.

Hypersensitivity

There were 21 cases in overall dataset, 16 cases were found unassessable or confounded. The remaining five cases have been further reviewed. There was one positive rechallenge and 4 positive dechallenges. Two were spontaneous and three were from clinical trials.

In 24% (5/21) of the reports an association between the use of lapatinib and the HS/anaphylaxis is possible due to:

- Positive dechallenge data of event resolution within 30 days of lapatinib was reported in 4 of 5 patients.
- Positive rechallenge data was reported in one patient.

Time to onset was 5-10 days with a median of 7 days. None were fatal. Symptoms were rash, SOB, facial and tongue swelling, mouth sores, rhinitis, fever,

Based on disproportionality analysis, the EB05 values for this AE is not considered a signal, however, given the seriousness of hypersensitivity/anaphylaxis, it will be added to the label.

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Labeling for other agents in this class:

- Sunitinib: under postmarketing AE section (b) (4): Hypersensitivity reactions, including angioedema, have been reported.
- Sorafenib: Under Contraindications: NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-6	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-3	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

PATRICIA CORTAZAR
01/25/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	022059
Priority or Standard	Standard
Submitted Date(s)	March 31, 2009
Received Date(s)	March 31, 2009
PDUFA Goal Date	January 29, 2010
Division / Office	DDOP
Reviewer Name(s)	Jennie Chang, Pharm.D.
Team Leader Name	Patricia Cortazar, M.D.
Review Completion Date	January 11, 2010
Established Name	Lapatinib
(Proposed) Trade Name	Tykerb
Therapeutic Class	Tyrosine kinase inhibitor
Applicant	GlaxoSmithKline
Formulation(s)	Oral
Dosing Regimen	1500 mg daily
Indication	Breast cancer
Intended Population(s)	Postmenopausal women with hormone receptor-positive metastatic breast cancer whose tumors overexpress HER2

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APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

GlaxoSmithKline has submitted a supplemental New Drug Application (sNDA) #22059-0028 for the following indication:

"Tykerb in combination with

(b) (4)

(b) (4)

The clinical reviewer recommends accelerated approval on the basis of its review of the supplemental NDA 22,059. The basis for this recommendation is the review of the results of the multinational, randomized, placebo-controlled phase 3 study EGF30008 of lapatinib plus letrozole versus placebo plus letrozole in patients with hormone receptor-positive metastatic breast cancer. This pivotal study met its primary endpoint of progression-free survival (PFS); however, questions remain as the applicability of the results in the United States population is unknown. In the U.S., trastuzumab, a HER2-antagonist, is given to patients with HER2-overexpressing breast cancer. Only three patients in the pivotal study had prior exposure to trastuzumab. Hence, more studies are needed to fully determine whether lapatinib is effective and safe to use in this patient population.

Study EGF30008 randomized treatment in 1286 patients with hormone receptor-positive advanced or metastatic breast cancer to two arms: (1) lapatinib plus letrozole or (2) placebo plus letrozole. The primary endpoint had undergone several revisions during the course of the study. The original primary endpoint of the protocol was TTP in the ITT population. The protocol was amended on October 27, 2005 to change the primary endpoint to the ErbB2-positive subgroup, after 760 patients had already been randomized. The amendment also included a provision to include additional patients to ensure adequate power to see a difference in both the original population as well as ErbB2-positive population. The protocol was further amended on October 31, 2007 to revise the statistical plan for the primary endpoint, after 1286 had already been randomized. The primary endpoint was changed from TTP to PFS in the ErbB2-positive population. Assessment of primary endpoint was based on investigator determination.

Although Study EGF30008 enrolled all patients with hormone receptor-positive breast cancer, efficacy was observed only in patients with overexpressing HER2. The results of the pivotal study showed that median PFS was 35.4 weeks in the letrozole plus lapatinib group compared to 13.0 weeks in the letrozole plus placebo group, with a hazard ratio of 0.71 (95% CI: 0.53, 0.96; stratified log-rank p-value=0.019) in the HER2-positive subgroup.

The safety population for this review comprises 1278 patients who received lapatinib 1500 mg daily plus letrozole 2.5 mg daily or placebo daily plus letrozole 2.5 mg daily. The safety profile of lapatinib in this combined study population appears unchanged from the previous safety review of the initial application of lapatinib.

1.2 Risk Benefit Assessment

Based on the review of the clinical data in support of this application, the benefit of the treatment of metastatic breast cancer with lapatinib plus letrozole outweighs the risk. Although the risks associated with lapatinib treatment include potentially life-threatening hepatotoxicity, decreases in left ventricular ejection fraction, diarrhea, the benefit of lapatinib in combination with letrozole in HER2-positive metastatic breast cancer patients is demonstrated by the superiority of progression-free survival compared to letrozole alone.

Safety of lapatinib was assessed initially during the review of NDA 22-059 with the comparison of adverse reactions in patients with previously treated, HER2-overexpressing, advanced or metastatic breast cancer with lapatinib and capecitabine and capecitabine alone. For this supplemental application, safety assessment did not reveal any unexpected toxicities of lapatinib that would hinder the approval of lapatinib.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No new post-marketing risk management activities have been recommended since the approval of lapatinib. The Applicant should continue to provide periodic safety reporting and continue post-marketing surveillance activities.

1.4 Recommendations for Postmarket Requirements and Commitments

Because the population studied in Study EGF30008 does not adequately reflect the U.S. population, accelerated approval will be granted for this sNDA. As a condition of accelerated approval, the Applicant has agreed to conduct more studies to further evaluate the efficacy and safety of lapatinib in patients with prior exposure to trastuzumab.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Lapatinib

Proprietary Name: Tykerb

Applicant: GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Pharmacological Class: Tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR [ErbB2]) and human epidermal receptor type 2 (HER2[ErbB2])

Chemical Class: Multi-targeted antineoplastic small molecule

Proposed Indication: "TYKERB in combination with (b) (4)
(b) (4)

Reviewer's comment: The proposed indication was later amended in the Applicant's regulatory briefing document in November 17, 2009:

*"Tykerb in combination with (b) (4)
(b) (4)*

Proposed Dosage and Administration: The recommended dose of Tykerb (b) (4) (b) (4) is 1500 mg (b) (4) given orally once daily continuously in combination with (b) (4). When Tykerb is coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily.

2.2 Currently Available Treatments for Proposed Indications

The proposed indication for lapatinib is in combination with letrozole (b) (4)
(b) (4)

Patients with metastatic breast cancer can be divided into two groups, those with metastatic disease at presentation and those that develop metastases after primary treatment. Patients who develop metastases present with either low-risk or intermediate-high-risk, depending on the biologic aggressiveness of the disease. Low-risk disease consists of long disease-free interval, tumors that are positive for hormone receptors (estrogen and progesterone), or bone-only disease, as well as those without extensive visceral involvement. Intermediate- or high-risk include those with rapidly progressive disease, visceral involvement, hormone-refractory disease, or tumors that are negative for hormone receptors.

Low-risk patients are usually treated with hormone therapy and first-line hormonal therapy consists of third-generation aromatase inhibitors. Aromatase inhibitors inhibit the peripheral and intra-tumoral enzyme, p450 aromatase, which catalyzes the final step in the estrogen synthesis. In a double-blind, Phase III study, 907 post-menopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer received treatment with either letrozole or tamoxifen as first-line therapy. Letrozole showed superior median time to progression (TTP) compared to tamoxifen (9.4 months versus 6.0 months).ⁱ

Lapatinib is a dual ErbB1 and ErbB2 receptor inhibitor and was approved in 2007 for HER2-positive metastatic breast cancer in combination with capecitabine on the basis of a phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab. Patients were randomized to receive either lapatinib 1250 mg once daily plus capecitabine 2,000 mg/m²/day on days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m²/day on days 1-14 every 21 days. Endpoint was TTP. Per independent assessment at the interim analysis, the median TTP was 27.1 weeks in the lapatinib + capecitabine arm versus 18.6 weeks in the capecitabine alone arm (HR 0.57).

Several lines of pre-clinical and clinical evidence demonstrate an inverse functional relationship between estrogen receptors (ER) and ErbB signaling pathways. ER-negative tumors are more likely to express ErbB1 and/or ErbB2 and behave more aggressively. ER-positive breast cancer cells initially inhibited by an anti-estrogen can use an autocrine ErbB signaling network to re-establish their growth.ⁱⁱ Estrogen acts to suppress ErbB1 expression in estrogen-responsive breast cancer cells, and conversely, estrogen depletion has been found to upregulate ErbB1 expression.ⁱⁱⁱ Treatment of tamoxifen-resistant breast cancer cells with small molecule ErbB1 TKIs or trastuzumab leads to significant growth inhibition, indicating that this inverse relationship may have therapeutic consequences.^{iv}

Additionally, serum ErbB2 levels are relatively resistant to aromatase inhibitors as well as to tamoxifen, compared to breast cancers with normal serum ErbB2 levels.^v A proposed mechanism for hormone resistance is due to the increase of ErbB2 and activation of its downstream pathways. In a study comparing serum ErbB2 at the time of disease progression in metastatic breast cancer patients treated with letrozole versus tamoxifen, approximately one-fourth (26%) of patients treated with 1st-line hormone therapy converted from serum ErbB2 negative to ErbB2 positive at the time of disease progression. This increase of serum ErbB2 occurred with equal frequency in patients treated with either tamoxifen or letrozole.^{vi} Thus, combination therapy with an aromatase inhibitor and a dual ErbB1 and ErbB2 TKI, such as lapatinib, may prevent or delay the development of hormone-resistant progressive disease and provide greater growth inhibition than would occur with aromatase inhibitor therapy alone.

Table 1. Currently available hormonal treatment regimens for metastatic breast cancer

Drug/combination	Dose and schedule
Pre-menopausal	
Tamoxifen	20 mg by mouth once daily
Leuprolide	7.5 mg intramuscular depot every 28 days 22.5 mg intramuscular every 3 months 30 mg intramuscular every 4 months
Goserelin	3.6 mg subcutaneous depot every 28 days 10.8 mg subcutaneous every 3 months
Megestrol	40 mg by mouth 4 times daily
Fluoxymesterone	10 mg by mouth 3 times daily
Post-menopausal hormonal therapy	
Tamoxifen	20 mg by mouth once daily
Letrozole	2.5 mg by mouth once daily
Exemestane	25 mg by mouth once daily
Anastrozole	1 mg by mouth once daily
Toremifene	60 mg by mouth once daily
Fulvestrant	250 mg intramuscularly every month
Megestrol	40 mg by mouth 4 times daily
Fluoxymesterone	10 mg by mouth 3 times daily
Aminoglutethimide	250 mg by mouth 4 times daily
Monoclonal antibody	
Trastuzumab	Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions (as tolerated)

Source: Table adapted from *Cancer Management: A Multidisciplinary Approach*, Pazdur R, et al. 2008.

2.3 Availability of Proposed Active Ingredient in the United States

Lapatinib is marketed in the United States. Regular approval occurred on March 13, 2007.

2.4 Important Safety Issues with Consideration to Related Drugs

Lapatinib

Lapatinib is a tyrosine kinase inhibitor that affects EGFR and HER2. Toxicities associated with EGFR inhibitors are dermatologic, ocular, and pulmonary. Dermatologic effect includes rash, radiation dermatitis, and mucositis. Although observed less frequently than the dermatologic reactions, ocular toxicities can cause significant discomfort due to changes in the eyelids, such as squamous blepharitis, dysfunctional tear syndrome, corneal epithelial defect. Severe or lethal pulmonary

toxicity, such as interstitial pneumonitis, and treatment-acquired resistance has been reported in non-small cell lung patients treated with other small molecule EGFR inhibitors, gefitinib and erlotinib.

Trastuzumab

Cardiomyopathy manifesting as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF), and pulmonary toxicity has been observed in patients receiving trastuzumab, a HER2/neu receptor antagonist. Interstitial pneumonitis and acute respiratory distress syndrome have been reported.

Table 2 illustrates the per-patient incidence of new onset of myocardial dysfunction as measured by LVEF in studies 1, 2, 3, and 4. Study 1 and 2 consisted of patients who were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC→paclitaxel) also or paclitaxel plus trastuzumab (AC→paclitaxel + trastuzumab). Study 3 involved patients who were randomized (1:1) to receive adjuvant trastuzumab or no additional treatment after completion of definitive surgery and at least four cycles of chemotherapy. In study 4, patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC-TH), or docetaxel and carboplatin plus trastuzumab (TCH).

Table 2. Per-patient incidence of new onset myocardial dysfunction (by LVEF) studies

	LVEF <50% and Absolute Decrease from Baseline		Absolute LVEF Decrease		
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
Studies 1 & 2^b					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
Study 3					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4^c					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

^a For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization.

^b Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)

^c Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH)

Source: Herceptin package labeling, revision date March 2009. Genentech, Inc.)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

July 17, 2003: IND submission

October 30, 2006: End-of-phase 2 (EOP2) meeting

The FDA advised the sponsor that the ITT population should be all randomized patients, regardless of treatment received. FDA also recommended that the treatment effect on TTP should be tested first in the ITT population since this is the originally selected patient population. If treatment effect is significant in the ITT population, then efficacy can be evaluated in subgroups.

The Sponsor proposed that the Hochberg method as a decision rule to control for multiplicity while preserving the experimental-wide alpha level at 0.025 (two-sided). The Hochberg decision rule would be applied to the primary endpoint of TTP at the final analysis to allow testing in both ITT and HER2 populations. The Sponsor believed that the proposed primary analysis incorporated the an appropriate decision rule for controlling the overall type I error at 0.05 alpha level, but the Agency did not agree because the Hochberg method does not always maintain the type I error at 0.05 for all types of dependency among p-values. The Hochberg method generally applies to comparing multiple mutually excluded groups, or multiple endpoint, and doesn't apply to testing ITT and subgroup simultaneously.

Since the Agency did not agree to the statistical proposal mentioned above, the Sponsor asked if the Agency would consider the following decision rule: to ensure that the pre-defined type I alpha error rate of 0.05 is preserved, a closed testing hierarchical procedure would be employed whereby the effect of the TTP would be initially tested in the HER2 population at an alpha level of 0.05. Testing would be performed in the ITT population at the 0.05 alpha level only if statistical significance was achieved in the HER2 population. FDA informed the Sponsor the treatment effect on TTP should be tested first in the ITT population since this was the originally selected patient population. If the treatment effect is significant in the ITT population, then efficacy can be evaluated in subgroups. Because HER2 status was not a randomization stratification factor, subgroup population is not a randomized group and potential imbalances could arise in baseline known and unknown prognostic factors. In the discussion with the Sponsor, we stated that a positive result in the ErbB2 subpopulation and negative results in ITT may be problematic and was a review issue. Furthermore, FDA stated that p-value for comparing TTP between two treatment arms in HER2+ population may not be interpretable given the small subgroup of patients and other concerns aforementioned. *Conducting another study to focus on a HER2+ population was recommended.* Alternatively, splitting alpha between the two populations was also recommended.

Additionally, FDA suggested that the Sponsor submit a statistical analysis plan for review.

January 12, 2009: Pre-sNDA meeting with Sponsor

- FDA stated the revised Statistical Analysis Plan submitted 11 December 2007 (Serial No 1371) appears acceptable, but the differences between investigator and independent review of progression (primary endpoint) should be investigated; Applicant should provide a “high-level” explanation for these differences.
- FDA stated that the indication will be likely limited to the ErbB2-positive patient population, but this will be a review issue. FDA stated that the findings in (b) (4)

- Treatment arms appear reasonably balanced with respect to pre-specified stratification factors. However, as potential imbalances are inherent characteristics of subgroup analyses, more explorations, such as those on ECOG performance status, baseline serum, number of metastatic sites and other possible prognostic factors, are strongly recommended.

In addition, there are 9% patients missing in HER2 status. Appropriate sensitivity analyses regarding the HER2 missingness issue should be incorporated in the statistical analysis plan.

It was suggested that Applicant provide the reasons for HER2 missingness and three sensitivity analysis: 1) Include all 115 patients in HER2 positive group; 2) Include all 115 in HER2 negative group; 3) Simulations with randomly selecting 20% patients from the 115 and including them in the HER2 positive group. The FDA suggests that the sponsor perform logistic regression with PFS and reasons for missingness as covariates in the model.

- FDA agreed that the proposed censoring rules on PFS were acceptable and recommended that additional sensitivity analyses of PFS irrespective of subsequent anti-cancer therapy be considered in the later submission. The Sponsor stated that it will perform two sensitivity analyses which will ignore subsequent anti-cancer therapy and include the date of patient's death as an event, as well as the censoring the patient at the last assessment date.
- FDA agreed that PFS was to be tested in the ITT following significance in the ErbB2-positive population at an alpha level of 0.05, according to the proposed rules of the hierarchical analysis. These rules are that the effect of study treatment on PFS was initially tested in the ErbB2-positive population at an alpha level of 0.05. Testing was then performed for the ITT population at the 0.05 alpha level only if statistical significance was achieved in the ErbB2-positive population.

Reviewer's comment: This is an extremely important issue as it establishes the basis of the Sponsor's submission.

- FDA informed the Sponsor that the approvability will be a review issue with the consideration of both clinical efficacy and safety, as to whether lapatinib + letrozole produces a clinically meaningful and highly statistically significant reduction in the risk of disease progression in patients with hormone-sensitive metastatic breast cancer. The Sponsor stated that the study was not powered to show a statistically significant difference in overall survival. Despite this and the immaturity of the data, with only 50% of the events, there was a trend in overall survival in favor of the combination of lapatinib plus letrozole with a hazard ratio of 0.77 (95% CI: 0.52, 1.14, p=0.185) in the HER2 positive population.

- Based on the design of the pivotal study EGF30008 and the pre-planned analysis contained in the Statistical Analysis Plan submitted, the Sponsor believes the data support the following indication:



In response, FDA did not believe the results of EGF30008 supported the proposed indication.

Reviewer's comment: In the regulatory briefing document, the Applicant narrowed the indication to  (b) (4)

2.6 Other Relevant Background Information

Hormonal therapy plays an important role in the management of hormone-receptor positive breast cancer. It is indicated as adjuvant hormonal therapy in women with primary, stage I/II breast cancer. Patients with metastatic disease also receive treatment with hormonal therapy to obtain clinical benefit. Research in therapeutic targeting at the molecular level has led to the development of the monoclonal antibody, trastuzumab, directed at human epidermal growth factor receptor-2 (HER2, neu or c-erbB2) due to the amplification of HER2 in breast cancer. Trastuzumab was approved in September 1998 to be used in combination with chemotherapy for the first-line treatment of HER2-positive metastatic breast cancer.

Recent data from *in vitro* studies demonstrate the existence of a potential interaction or cross-talk between HER2 and ER pathways. Estrogen down-regulates HER2 expression and anti-estrogen produces a partial reversal of this effect.^{vii} Estrogen response appears to negatively regulate the HER2 transcription when estrogen binds to ER.^{viii} This negative feedback relationship between ER expression and HER2 overexpressing in breast cancer has been well-established in clinical studies.^{ix}

The use of trastuzumab in combination with another aromatase inhibitor, anastrozole, in women with metastatic breast cancer was approved in Europe on May 5, 2007. The approval was based on data from the international phase III TAnDEM study which showed that the addition of trastuzumab to hormonal therapy doubled the median progression-free survival from 2.4 months to 4.8 months (p=0.0016).^x TAnDEM was an international, multicenter, randomized phase III trial which evaluated trastuzumab in

combination with hormonal therapy anastrozole versus anastrozole alone as first-line therapy (or second-line hormonal therapy) in postmenopausal women with advanced (metastatic) HER2-positive and hormone receptor-positive (ER-positive and/or PR-positive) breast cancer. Two hundred seven of 208 patients were treated. In the 147 evaluable patients with measurable disease, the ORR was significantly higher in the combination group than in the anastrozole group (20.3% versus 6.8%; $p=0.018$). Patients in the combination arm responded significantly better to treatment (overall response rate was 20.3% versus 6.8%; $p=0.018$). Patients in the combination arm had a longer PFS (4.8 versus 2.4 months; $p=0.0016$) and TTP was doubled (4.8 vs. 2.4 months; $p=0.0007$) in the combination arm. There was also a positive trend in median overall survival (28.5 months versus 23.9 months; $p=0.325$), despite the fact that in the hormonal therapy alone arm, more than half of patients (58/104) crossed over to receive trastuzumab during the trial when their disease had progressed.

Furthermore, overall survival benefit has been observed in treatment of women with metastatic breast cancer with overexpression of HER2 in a randomized, controlled clinical trial in combination with chemotherapy ($n=469$ patients), and an open-label single agent clinical trial ($n=222$ patients). A multicenter, randomized, open-label clinical trial was conducted in 469 women with previously untreated metastatic breast cancer. Only patients with 2+ or 3+ tumors tested using immunohistochemistry (IHC) were eligible. Patients were randomized to receive chemotherapy alone or in combination with trastuzumab. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel; for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received Herceptin at the time of disease progression as part of a separate extension study. Patients randomized to Herceptin and chemotherapy also had a longer median survival. These treatment effects were observed both in patients who received Herceptin plus paclitaxel and in those who received trastuzumab plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup. Looking at combined results (trastuzumab and all chemotherapy, $n=235$) versus all chemotherapy, the median overall survival was 25.1 months (95% CI 22, 30, $p=0.05$) versus 20.3 months (95% CI 17, 24), respectively.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Table 3. Inspection sites

Inspected entity	City/ Country	Inspection Dates	EIR Received date	Field Classification
François Pivot	Bensançon, France	September 14- 18, 2009	November, 11, 2009	VAI ^a
Michael Lichnitser	Moscow Russia	September 21- 24, 2009	November, 21, 2009	VAI
Henry Gomez	Lima, Peru	September 14- 18, 2009	October 2, 2009	VAI

^aVAI = Voluntary action indicated
 Source: Reviewer's table

DSI inspections were conducted prior to the initial NDA approval for the following reasons:

1. Progression-free survival, not overall survival was the primary endpoint of interest.
2. This was a multicenter, international study and there are concerns of data integrity.
3. Concern for scientific misconduct at several sites based on review of financial disclosures, protocol violations, and safety and efficacy results.

Although minor regulatory deficiencies were noted during the inspections as denoted by VAI in Table 3, the deviations from regulations and data are acceptable. Data from these clinical sites inspected in support of sNDA 22,059 are acceptable.

3.2 Compliance with Good Clinical Practices

The study was conducted under US IND 61,362 'in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, and, the guiding principles of the Declaration of Helsinki.' Prior to initiation of the study, the protocol, any amendments, the informed consent form, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center institutional ethics committees (IEC) or institutional review boards (IRB).

3.3 Financial Disclosures

Conflicts of interest by investigator would be under consideration if valid. There are four potential claims concerning conflicts for study EGF30008 from four different geographical locations

(b) (6)

These investigators in study EGF30008 had payments that exceeded the \$25,000 threshold for Significant Payments of Other Sorts. The sponsor relied upon payments of other sorts of data provided by the clinical investigators through questionnaires that were completed at the end of the study or as of the clinical cut-off date. Altogether, these investigators enrolled a total of 60 patients (<5%, n=1286). Although no analysis was conducted to explore the impact of these sites on the data, the likelihood of potential bias introduced by the patients from four different study sites in 1286 patients is low. (b) (6)

(b) (6) The investigators are as follows:

1. (b) (6) (center (b) (6)), principal investigator at (b) (6) (b) (6) in study EGF30008. No analysis was conducted to explore the effect of this site's data on the results of study EGF30008, as this site enrolled (b) (6) of 1286 patients in the ITT population used in the analysis of this study; therefore, the data does not have the potential to bias the outcome and/or conclusions of the study.

2. (b) (6) (center (b) (6)), principal investigator at (b) (6) (b) (6) in study EGF30008. No analysis was conducted to explore the effect of this site's data on the results of study EGF30008, as this site enrolled (b) (6) (b) (6) of 1286 patients in the ITT population used in the analysis of this study; therefore, the data does not have the potential to bias the outcome and/or conclusions of the study.

3. (b) (6) (center (b) (6) investigator (b) (6)), principal investigator at (b) (6) (b) (6) No analysis was conducted to explore the effect of this site's data on the results of study EGF30008, as this site enrolled (b) (6) of 1286 patients in the ITT population used in the analysis of this study; therefore, the data does not have the potential to bias the outcome and/or conclusions of the study.

4. (b) (6) (center (b) (6)), principal investigator at (b) (6) (b) (6) No analysis was conducted to explore the effect of this site's data on the results of study EGF30008, as this site enrolled (b) (6) of 1286 patients in the ITT population used in the analysis of this study; therefore, the data does not have the potential to bias the outcome and/or conclusions of the study.

Additionally, (b) (6) had significant equity interest in the Applicant that exceeded the \$50,000 threshold.

Reviewer's comment: The Applicant appears to have done due diligence with regard to conflicts of interest due to financial disclosures. The results of the pivotal study do not appear to be impacted by these conflicts. (b) (6) financial interest does not appear

to impact the study results had his site enrolled only (b) (6) even if these patients were excluded from the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The Applicant states that they have cross-referenced their initial lapatinib application (22-059) for the CMC and non-clinical modules. However, new pharmacology and toxicology information is proposed in the product label.

4.1 Chemistry Manufacturing and Controls

No new data submitted for review. Please refer to the review for NDA 22-059.

4.2 Clinical Microbiology

No new data submitted for review. Please refer to the review for NDA 22-059.

4.3 Preclinical Pharmacology/Toxicology

No new data submitted for review. Please refer to the review for NDA 22-059.

4.4 Clinical Pharmacology

Minor proposed changes to the label regarding clinical pharmacology were submitted. Please refer to the clinical pharmacologist's review.

4.4.1 Mechanism of Action

No new data submitted for review. Please refer to the review for NDA 22-059.

4.4.2 Pharmacodynamics

No new data submitted for review. Please refer to the review for NDA 22-059.

4.4.3 Pharmacokinetics

No new data submitted for review. Please refer to the review for NDA 22-059.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies submitted in support of sNDA 22,059 are shown below:

Table 4. Studies submitted for sNDA 22,059

Study	Protocol Title	Drug Regimen/s	Number of Subjects
Pivotal Study			
EGF30008	A randomized, double-blind, placebo-controlled, multicenter, phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer	Letrozole 2.5 mg once daily + lapatinib 1500 mg once daily OR Letrozole 2.5 mg once daily + placebo	Total: 1286 Letrozole + lapatinib: 642 Letrozole + placebo: 644
Supportive Study			
EGF10030	A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib in combination with letrozole (Femara) in cancer patients	Cohort 1 (optimal treatment regimen) Starting doses of letrozole (2.5 mg once daily) + lapatinib (1250 mg once daily). The letrozole dose remained at 2.5 mg at all dose levels. Lapatinib dose escalated in 3 subjects/dose level. Cohort 2 (OTR expanded): Letrozole 2.5 mg/day and lapatinib 1500 mg/day. Cohort 3 (PK): Letrozole 2.5 mg/day and lapatinib 1500 mg/day	Total: 39 Cohort 1: 12 Cohort 2: 7 Cohort 3: 20

5.2 Review Strategy

This review focuses on the pivotal, randomized, placebo-controlled, multicenter phase 3 clinical study, EGF30008. No Special Protocol Assessment request was submitted. During the review process, study EGF30008 was reviewed in detail, including study reports, raw datasets, derived datasets, case report forms (CRFs) and narratives.

Major efficacy and safety analyses were reproduced or audited using JMP datasets submitted electronically under the NDA. The analyses included the following:

- A survey of the current literature on diagnosis, classification, and treatment of metastatic breast cancer, using published literature, internet, and references submitted by the Applicant;
- Review of all correspondence and meeting minutes between the Applicant and the Agency;
- Review of datasets submitted as SAS transport files;
- Review of patient narratives in selected cases;
- Review of previous clinical review completed for the original NDA approval;
- Review of the current product labeling;
- Requests for additional information from the Sponsor;
- Evaluation of proposed labeling and revision of labeling.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Study Protocol EGF30008

Study title

EGF30008: A randomized, double-blind, placebo-controlled, multicenter, phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer

Principal investigator

Dr. Stephen R.D. Johnston, Consultant Medical Oncologist
The Royal Marsden NHS Foundation Trust
Fulham Road
London SW3 6JJ
United Kingdom

Protocol milestones

Table 5. Protocol milestones

Milestone	Date	# Patients Entered
Protocol Original Version	July 17, 2003	0
Amendment 1 Protocol Version 2	May 25, 2004	24
Amendment 2 Protocol Version 3	January 11, 2005	264
Amendment 3 Protocol Version 4	October 27, 2005	740
Amendment 4 Protocol Version 5	October 31, 2007	1286
Amendment 5 Protocol Version 6	May 27, 2008	1286
First Patient recruited	December 9, 2003	1286
Last Patient recruited	December 29, 2006	1286
Study closed to accrual	December 29, 2006	1286
Database lock	June 3, 2008	
NDA submission	March 31, 2009	
Clinical study report and datasets submission	March 31, 2009	

Source: Reviewer's table extracted for Applicant's Study EGF30008

5.3.2 Protocol Amendments for Study EGF30008

Amendment 1: May 25, 2004

Number of subjects enrolled: 24, first randomized patient on December 9, 2003

Several major and minor changes were made to improve protocol clarity. The following were the major changes:

- Remove the requirement for measurable disease at study entry. Since the primary endpoint of the study is time to progression (TTP), it was considered unnecessary to require subjects to have measurable disease or assessable disease. This change was made in Protocol Summary Key Eligibility Criteria #5 (original version) and Section 4.2.1, Inclusion Criteria #6. Patients could have measurable or non-measurable disease per RECIST.

Reviewer's comment: Enrolling patients with nonmeasurable disease may make it difficult to assess PFS which is based on disease progression. Additionally, patients with nonmeasurable disease were not evaluable using the independent radiology review.

- Revised the eligibility criteria for stage III, IV breast cancer patients to reflect the most current version of the staging criteria from the American Joint Committee on Cancer, Version 6.

Reviewer's comment: Change in criteria. As of February 2006, only 44 (6%) of 688 subjects had stage III disease. The Applicant revised the criteria as many investigators were attempting to use the treatment as neoadjuvant therapy as a bridge to surgery for the primary breast cancer, which was not the intent of the protocol. Additionally, the treatment at this stage was not thought to be adequate therapy for such patients. As the primary endpoint was TTP, treating patients in this setting would result in the patient coming off study at that juncture and other untenable outcomes or biases.

- Subjects with extensive symptomatic visceral disease or the disease are considered by the investigator to be rapidly progressing or life threatening was added as an exclusion criteria. This change was implemented to be more consistent with the standards of clinical practice, as this patient population would be more appropriate for treatment with chemotherapy rather than with an aromatase inhibitor.

Reviewer's comment: There is concern that this exclusion of these patients may select for a more favorable treatment population, but this is the standard of care as these patients would receive chemotherapy.

- The statistical plan corrected the null hypothesis. The study design was modified to provide evidence to support the null hypothesis $H_0: \lambda \geq 1$ or to reject it in favor of the alternative hypothesis $H_A: \lambda < 1$, where λ is the hazard ratio: LAPATINIB plus letrozole/letrozole alone. The prior version stated that the null hypothesis $H_0: \lambda = 1$.
- In the statistical plan, the sponsor expanded on the definition of TTP, "All deaths other than due to breast cancer will be regarded as competing risks. A competing risk is the occurrence of a secondary event that precludes the possibility of the primary event occurring; death other than from breast cancer is a competing risk for disease progression. Furthermore, the Sponsor removed clinical deterioration from the definition of TTP.

Reviewer's comment: Protocol amended later to PFS as the primary endpoint. In the TTP definition, the Sponsor only included deaths due to breast cancer. Noncancer deaths were considered a competing risk.

Additional changes:

- A potential proteomic analysis was added as an additional serum biomarker test in order to further identify novel candidate biomarkers/profiles, which may help

predict which patients respond to lapatinib, which patients are more likely to experience certain adverse events, or predict the markers that are affected by the action of lapatinib.

- Modified the definition for radiological assessments once a subject withdraws from treatment without progressive disease (e.g., discontinues due to an adverse event and has a partial response or stable disease). Previously stated that subjects will have radiological assessments performed every 12 weeks until disease progression or death. This amendment states that subjects will have radiological assessments performed every 12 weeks until disease progression, *until the subject begins a new anti-cancer therapy*, or death.
- In the inclusion criteria, bilateral oophorectomy for the initial treatment of premenopausal women with metastatic breast cancer is not permitted as the Sponsor states that this would constitute a first-line hormonal treatment.
- Clarification of the prior use of aromatase inhibitor and trastuzumab. Treatment must have ended more than 1 year prior (>12 months) to the first dose of randomized therapy, not study entry.
- Revised the washout period for termination of hormone replacement therapy (HRT), from two months to at least 1 month (30 days) prior to receiving the first dose of randomized therapy in the inclusion criteria.
- Modified the treatment criterion for radiation therapy. Radiation to a limited area for palliative treatment is acceptable and should be allowed prior to the first dose of randomized therapy, provided that the subject has recovered from all toxicities.

Reviewer's comment: This is standard.

- For baseline laboratory criteria, the allowance for subjects with a transfusable hemoglobin level ≥ 9 g/dl was deleted to prevent potential hematologic toxicity and criteria for subjects with Gilbert's syndrome were included.

Reviewer's comment: This is acceptable as this may be a safety issue.

- In the eligibility criteria, clarification on bisphosphonate therapy was provided. Bisphosphonate therapy for bone metastases is allowed; however, treatment must be initiated prior to the first dose of randomized therapy.
- Clarified that subjects must have recovered from all prior adjuvant therapies not just those which were investigational in the eligibility criteria.
- New exclusion criteria pertaining to prior anthracycline therapy was added. Limitations as to the amount of anthracycline exposure were added, given that

cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines.

Reviewer's comment: This appears appropriate given the cardiotoxicity observed with lapatinib. Exposure to anthracycline may be important when assessing cardiac dysfunction in patients receiving lapatinib.

- The language for echocardiogram assessment was modified to include a MUGA if echocardiogram cannot be performed or if the investigator feels it is not conclusive to evaluate left ventricular cardiac ejection fraction.

Reviewer's comment: This is acceptable as the tool used to measure LVEF would remain consistent on a per patient level.

- In Section 5.2.1, Safety Assessment Schedule, Every 8 Weeks, the option of a MUGA scan was added if the investigator feels the echocardiogram could not be performed or was not conclusive to evaluate left ventricular cardiac ejection fraction. Additionally, a window of up to 7 days was included for performing cardiac tests to allow for flexibility in scheduling.

Reviewer's comment: This is acceptable.

- In the efficacy assessment, clinical deterioration was removed from the definition of TTP as this may introduce bias. Furthermore, the sponsor added, "Radiological scans will be collected until disease progression. If a subject discontinues randomized therapy (lapatinib or placebo) before disease progression is noted, radiological scans done after discontinuation of randomized therapy, will also be collected until disease progression is confirmed, until the subject begins new anti-cancer therapy, or death."

Reviewer's comment: This is acceptable as the Agency does not consider clinical deterioration as an objective measurement of response.

- In the definition of assessable disease, subjects are no longer required to have bone lesions with at least 50% lytic component to be eligible for the study.

Reviewer's comment: As stated previously, enrolling patients with nonmeasurable disease may make it difficult to assess PFS which is based on disease progression. Additionally, patients with nonmeasurable disease would not be evaluable using an independent radiology review.

- In Section 6.2.1, Randomized Therapy (lapatinib or placebo), Sponsor added that grapefruit and grapefruit juice is not permitted for the duration of the study.

- In Section 6.2.3, Criteria for Continuing Treatment, the sponsor added that subjects with an NCI CTCAE Grade 3 or 4 interstitial pneumonitis must be withdrawn from randomized therapy.
- The wording in Section 6.2.3.1, Criteria for Evaluating Cardiac Events was changed to correct > 20% decrease in LVEF to $\geq$ 20% decrease in LVEF.
- Section 7.2, Prohibited Medications was revised such that the list was expanded to provide clarification and to include only significant CYP3A4 inhibitors and inducers.
- The protocol was revised such that baseline disease assessment had to be performed within 2 weeks before the start of the study, including CA-125 measurement (previously assessment needed to be within 4 weeks of study initiation).
- In Section 10.7.2.4, Duration of Response, language was added: “All deaths other than due to breast cancer will be regarded as competing risks.” Sponsor stated that death other than due to breast cancer is a competing risk for disease progression (a competing risk is the occurrence of a secondary event that precludes the possibility of the primary event occurring).

Reviewer’s comment: Modification is more comprehensive as radiological assessments will still need to be performed on subjects who discontinue the study without progressive disease.

Amendment 2: January 11, 2005

Number of subjects enrolled: 264

The protocol was amended to have pharmacogenetic research to be conducted on blood samples collected from consenting subjects. This amendment applied only in Italy to comply with the “Italian Proposed Guideline for Evaluation of Pharmacogenetic Research”. This document was finalized by a multidisciplinary group of experts and APPLICANT Italy has decided to use the guideline as a reference document when performing pharmacogenetic research.

Amendment 3: October 27, 2005

Number of subjects enrolled: 740

Revisions to the protocol mostly focused on increasing the study population to change the eligibility criteria to include only subjects with Stage IV disease, to increase the sample size by 520 patients to a total of 1280 in order to include more ErbB2-positive subjects and ensure adequate power to see a difference in this population, and remove the interim analyses. The following were the major changes:

- Wording was added as a secondary objective, “To evaluate and compare TTP in subjects with ER+/PR+, ErbB2 positive advanced or metastatic breast cancer treated with lapatinib and letrozole versus placebo and letrozole. Purpose was to evaluate and compare of TTP between treatment arms in ErbB2 positive advanced or metastatic breast cancer will be performed.

Reviewer’s comment: FDA informed the Sponsor that claiming efficacy on a subgroup analysis is problematic. Refer to response from statistical reviewer below.

- Increased the study population to an additional 520 subjects approximately which including the initially planned 760 subjects. This will give a total of 1280 subjects. The reason was to better understand the role of ErbB2.

Reviewer’s comment: The reason for the increase in the ITT population is to claim subgroup analysis. Refer to response from statistical reviewer below.

- The eligibility criteria for stage of breast cancer was revised such that only subjects with histologically confirmed invasive breast cancer with stage IV disease at primary diagnosis or at relapse after curative-intent surgery could be enrolled. This was amended to ensure that patients with Stage IIIb/IIIc disease who are eligible or potentially eligible for surgery are not enrolled in this study.

Reviewer’s comment: Acceptable as only a small number of stage III patients were enrolled at the time of the amendment. Stage III patients enrolled in the study were less than 10% (44/688).

- Include fluorescence *in situ* hybridization (FISH) testing from the central lab. As the complicated pathophysiology of breast cancer is continually elucidated, the role of ErbB2 amplification is increasingly being recognized as an important poor prognostic marker as well as the driver of the disease.

Reviewer’s comment: The FISH testing is related to the change in the primary endpoint.

- In the Assessments at Study Conclusion or Withdrawal, Section 5.3.1., there was clarification on the radiographic disease assessments at withdrawal with regard to bone scans, “For subjects with measurable and/or non-measurable disease as well as bone disease at baseline, bone scans do not need to be repeated at withdrawal unless it is greater than 6 months since their last bone scan.” Additionally, information about clinical disease assessments were added, “Clinical disease assessments for palpable or visual lesions (for visual skin lesions, documentation of target lesions by color photography- including a ruler to estimate the size of the lesion(s) is required). For details regarding documentation of skin lesions see Section 5.3.2.2.”

Reviewer's comment: PFS may be difficult to assess if patients have nonmeasurable and bone-only disease.

- Sections 10.1, Hypotheses, through section 10.4.3, Sample Reestimation, were revised as the plan for the two interim analyses was removed. The Sponsor stated that the safety of this drug is monitored routinely on a quarterly basis by an IDMC that oversees the majority of Phase II and Phase III breast cancer trials in which lapatinib is being studied. Additionally, the sponsor stated this study has been expanded to provide sufficient power for analysis of the subgroup of subjects who have hormone receptor positive ErbB2 positive breast cancer or ErbB2 negative tumors that convert to ErbB2 positive.

Reviewer's comment: The Sponsor stated that there was no unblinded or blinded review of the safety or efficacy data.

- Sections 10.5, Analysis Populations, and 10.7.1.1, Time to Progression, were revised to add a subgroup analysis of ErbB2-positive subjects. In Section 10.7.1.1, the following language was added, "All secondary analyses will either be performed on both the ITT and the ErbB2-positive subgroup or, where appropriate, the analyses will be stratified by ErbB2 status. Both populations will be used in the case of key efficacy analyses, including the survival and progression-free survival analyses."

Reviewer's comment: ErbB2 status was not a pre-specified stratification factor, so this may be problematic.

Statistical review dated March 20, 2006 and conveyed to the Sponsor on April 3, 2006:

The FDA statistical reviewer evaluated the submission and had the following comments to the Sponsor in a review dated March 20, 2006 and conveyed to the Sponsor on April 3, 2006:

-No further efficacy claim can be made if the primary analysis on the ITT (original) population doesn't achieve significance level even though the test for ErbB2-positive subgroup appears to be "significant". If a claim on the ErbB2-positive subgroup is made when the drug effect cannot be demonstrated in the ITT population, then a decision rule of controlling overall type I error at 0.05 and an allocation of α should be proposed.

-ITT population should consist of all randomized patients.

-The timing of analysis should be based on event time rather than calendar time since the power of primary test depends on the number of events.

-The decision to include only stage IV patients only appears to be acceptable because stage III patients enrolled in the study are less than 10% (44/688). With targeted sample size expansion to 1280 patients, the proportion of stage III patients will be < 5%.

End-of-phase 2 (EOP2) meeting between Sponsor and FDA on October 30, 2006

The following messages were conveyed:

-The treatment effect on PFS should be tested first in the ITT population since this is the original selected patient population. Only if the treatment effect is significant in the ITT population, then efficacy can be evaluated in subgroups.

-Considering that no proper stratified randomization was done with ErbB2 status as stratum, there is a potential for imbalances in baseline prognostic factors between the treatment arms in the relatively small subgroup of ErbB2+ patients and the p-value for comparing PFS between the two treatment arms in ErbB2+ population may not be interpretable.

Additional changes:

- Language was added to discuss the rationale for continuing enrollment of subjects, particularly as the complicated pathophysiology of breast cancer is continually elucidated, and the role of ErbB2 amplification is increasingly being recognized as an important poor prognostic marker as well as the driver of the disease in Section 1.2, Rationale.
- PET scans are not acceptable methods for evaluating tumors per RECIST.
- Language was added to Criteria for Evaluating Cardiac Events, Section 6.2.3.1 to clarify that relative rather than absolute decreases are used in determining decreases in cardiac ejection fraction.
- Include Grade 4 cardiac dysfunction in the additional protocol defined criteria as an SAE for SAE, Section 9.2.

Reviewer's comment: Amendment 3 is a significant amendment as the primary analysis has been changed from TTP in ITT population to ErbB2-positive population. Furthermore, the sample size was increased to ensure adequate statistical power for an analysis of PFS in the ErbB2-positive population. Statistical review has captured FDA's concerns. Cannot claim subgroup without first demonstrating effect in ITT.

October 31, 2007: Amendment 4

Number of subjects enrolled: 1286

Amendment 4 consisted of changes to the statistical analysis plan for the primary endpoint. The following were the highlights:

- Revision to the Protocol Summary and Section 2.1 Objective(s), Primary Objectives consisted of changing primary endpoint to "evaluate and compare progression-free survival (PFS) in subjects with ER+/PgR+, ErbB2-positive advanced or metastatic breast cancer..." The Sponsor's rationale was that PFS was preferred because it included all deaths (including those due to causes other than breast cancer) and is correlated with OS. The study population was changed because the Sponsor stated that lapatinib has promising efficacy in

ErbB2-amplified breast cancer, confirmed in other studies. These changes were also made in Section 5.3, Efficacy.

Reviewer's comment: The change is significant because the primary endpoint was modified from TTP to PFS in subjects with ER+/PgR+, ErbB2-positive advanced or metastatic breast cancer. PFS is the preferred endpoint in ITT, but not in a subgroup population, as iterated in Amendment 3.

- In Section 10.1, Data Analysis and Statistical Considerations, Hypotheses, the statistical analysis was changed to evaluate PFS to support $H_0: \lambda \geq 1$ or to reject it in favor of $H_A: \lambda < 1$ in ErbB2-positive population as primary endpoint and in ITT as the secondary endpoint. A total of 173 events are required in ErbB2-positive population to provide 80% power to detect an HR of 0.645 corresponding to a 55% increase in median PFS in subjects who receive lapatinib + letrozole (15.5 months) compared to letrozole alone (10 months). Hierarchical closed testing will be used, with an alpha level of 0.05. About 218 with ErbB2-positive disease would need to be enrolled to achieve 173 events. A maximum of 173 subjects with disease progression or death will be required.

Reviewer's comment: This is a very important amendment because the primary endpoint has changed from TTP to PFS when all patients in the study have already been randomized (last patient 12/29/2006). Per ODAC discussion on December 5, 2007, OS was recommended as the primary endpoint for measuring clinical benefit; however, the initial protocol was not reviewed by FDA statisticians and the study was not sized for OS. The Agency continued to recommend OS as the primary endpoint.

Statistical review dated January 6, 2008 and conveyed to the Sponsor on January 21, 2008:

-Per ODAC discussion on 12/05/2007, PFS alone without a demonstration of survival advantage may not be considered as a measure of direct clinical benefit in the initial treatment of metastatic breast cancer. OS is recommended to be the primary endpoint for this first-line study.

-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 PFS assessments depend on frequency, accuracy, reproducibility, and completeness of tumor assessments, it is important the observed magnitude of effect is robust.

-Considering the randomization principle is violated that there could be imbalances in prognostic factors between treatment arms in the ErbB2+ subgroup with only 17% of patients, the PFS results will be reviewed based on all randomized patients with consideration of total results prior to reviewing the subgroup results. We note that this study was not stratified by ErbB2 status at randomization and that the study was originally designed to evaluate efficacy only in the ITT population.

-PFS as assessed by independent reviews will be reviewed together with the investigator determined PFS. Discrepancy between investigators and independent review assessments should be examined.
-The ITT population should include all randomized patients, regardless of dosing.

Additional changes:

- Six-month PFS was removed as a secondary objective. Additionally, the incidence of brain metastases was added. Sponsor also wanted to compare and characterize the patients who convert to ErbB2 status using serum ErbB2 collections to look at time to conversion and relationship to disease progression due to scientific and clinical evidence of cross-talk of these receptors with ER. Lapatinib was shown in another study to have activity in brain metastases.
- For subjects who have been on study for ≥ 108 weeks, safety and efficacy assessments will be performed at 12-week intervals starting week 108, instead of 4-week intervals for safety and 8 week intervals for cardiac monitoring. Changes were based on the long-term safety data of lapatinib. These changes were implemented in Section 3, Study Design, Section 5.2.1, Safety assessment Schedule, Section 5.3.1, Efficacy Assessment Schedule.
- Clarifications on definitions of study completion and study treatment completion were made in Section 8.1, Study Completion. For study completion, "A subject is considered to have completed the study when the subject has died, is lost to follow-up, or another reason exists that prevents additional data to be collected on the subject.

Reviewer's comment: Efficacy assessment at every 12 weeks was not modified, only safety.

May 27, 2008: Amendment 5

Number of subjects enrolled: 1286

Amendment 5 consisted of enhancements to monitoring of hepatobiliary events throughout the protocol. The Sponsor has concluded a causal relationship between hepatobiliary disorders and lapatinib.

Reviewer's comments: The improved safety monitoring of hepatic toxicities will provide more information for safety analysis of lapatinib.

5.3.3 Overview of Protocol for Study EGF30008

Study objectives

Primary: To evaluate and compare PFS in subjects with ER+/PR+ ErbB2-positive advanced or metastatic breast cancer.

Secondary:

- To evaluate and compare PFS in subjects with ER+/PgR+ advanced or metastatic breast cancer treatment with lapatinib and letrozole versus placebo and letrozole.
- To evaluate and compare the 2 treatment arms with respect to:
 - Overall response rate (complete and partial responses);
 - Clinical benefit (complete response, partial response, or stable disease for at least 6 months);
 - Time to response;
 - Duration of response;
 - Time to progression;
 - Overall survival;
 - Incidence of brain metastases;
 - To determine the qualitative and quantitative toxicities associated with oral lapatinib when administered with letrozole.
 - To evaluate and compare the 2 treatment arms with respect to change in quality of life (QOL) status, the change of QOL relative to baseline, and quality adjusted survival.
 - To compare and correlate tumor response rates following lapatinib and letrozole therapy, with respect to baseline and on-treatment serum concentrations of ErbB1 and ErbB2. Potentially, proteomic analysis will also be performed to detect other shed tumor proteins and identify changes in the protein profile, which correlate to treatment response and adverse events.
 - To characterize the patient population by determination of intra-tumoral expression levels of relevant biomarkers from archived tumor tissue such as ErbB1, ErbB2, and potentially other biomarkers that are downstream of ErbB1 or ErbB2 receptors.
 - To compare and characterize the patient population who convert to ErbB2 status using the serum ErbB2 collections every 4 weeks of serum data. To specifically look at the time to conversion and the relationship to disease progression.

Reviewer's comment: Clinical benefit is not considered an evaluable endpoint. The treatment effect on PFS should be tested first in the ITT population since this is the original selected patient population. Only if the treatment effect is significant in the ITT population, then efficacy can be evaluated in subgroups.

Study design

EGF30008 was a pivotal, randomized, double-blind, placebo-controlled, parallel group, international, multicenter, phase III study to evaluate and compare the efficacy and tolerability of lapatinib and letrozole versus placebo and letrozole in approximately 1280 post-menopausal female subjects (ITT population) with estrogen and/or progesterone

receptor-positive (ER+/PR+) previously untreated advanced or metastatic breast cancer. Randomization was 1:1 ratio to letrozole + lapatinib or letrozole arms. Subjects were stratified based on site of disease (soft tissue/visceral or bone only disease), prior adjuvant anti-estrogen (e.g., tamoxifen or raloxifene) therapy (interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is ≥ 6 months or subject never received adjuvant anti-estrogen therapy versus interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is < 6 months).

The protocol primary endpoint as per Protocol Amendment 4, dated on October 31, 2007 was PFS in the ER+/PR+, ErbB2-positive population. The secondary endpoint was overall survival, PFS in the ITT population, time to progression, overall response rate, duration of response, and incidence of brain metastases in patients with ER+PR+ advanced or metastatic breast cancer (ITT population). No interim analysis was performed. The analysis of the primary endpoint, PFS, was to be conducted after at least 173 subjects with disease progression or death occurred in the ErbB2-positive subgroup.

Randomized therapy (lapatinib or placebo) was administered daily until disease progression or withdrawal from therapy (e.g., due to unacceptable toxicity, withdrawal of consent). Safety and efficacy assessments were performed on all subjects at 4-week and 12-week intervals respectively, as well as at the end of treatment. For subjects who had been on study treatment for ≥ 108 weeks, safety and efficacy assessments were performed at 12-week intervals starting at week 108. Subjects withdrawn from treatment without progressive disease (e.g., discontinuation due to an adverse event of a subject with a partial response or stable disease) had radiological assessments performed every 12 weeks until disease progression, until the subject began a new anti-cancer therapy, or death. All subjects were followed for survival information until death.

The study was to be designated as complete when 173 subjects with disease progression or death were observed in subjects with ErbB2-positive disease.

Eligibility criteria

Inclusion criteria

The study population consisted of post-menopausal females ≥ 18 years with histologically confirmed invasive breast cancer with stage IV disease at primary diagnosis or at relapse after curative intent surgery:

- Subjects must have had either measurable or non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST).
- If the disease was restricted to a solitary lesion, its neoplastic nature should have been confirmed by cytology or histology.
- Tumors that were ER+ and/or PgR+;

- Subjects were considered ER+ or PgR+ if any assay [cytochemical, immunochemical, immunohistochemistry (IHC), or radioimmunoassay] of primary or secondary tumor tissue is positive;
- Adjuvant therapy with an aromatase inhibitor was allowed; however, treatment must have ended more than 1 year prior (>12 months) to the first dose of randomized therapy;
- Adjuvant therapy with trastuzumab is allowed; however, treatment must have ended more than 1 year prior (>12 months) to the first dose of randomized therapy;
- Post-menopausal female subjects ≥ 18 years of age;
 - Post-menopausal as defined by any of the following:
 - Subjects at least 60 years of age;
 - Subjects under 60 years of age and amenorrheic for at least 12 months, and/or follicle-stimulating hormone (FSH) values ≥ 40 IU/L;
 - Prior bilateral oophorectomy or prior radiation castration with amenorrhea for at least 6 months. Bilateral oophorectomy for the initial treatment of pre-menopausal women with metastatic breast cancer is not permitted as this would constitute a first-line hormonal treatment.
- ECOG Performance Status of 0 or 1;
- Subjects must have had archived tumor tissue available to compare tumor response with intra-tumoral expression of ErbB1 and ErbB2. Archived tumor tissue will also be used to confirm estrogen receptor (ER) and/or progesterone receptor (PgR) positivity. Results were not be used to determine subject eligibility for the study.

Additional inclusion criteria:

- Subjects who received neo-adjuvant/adjuvant therapy and now present with newly relapsed advanced or metastatic disease are eligible; however, prior neo-adjuvant/adjuvant therapy is not required for study entry;
- Subjects must have ended hormone replacement therapy (HRT) (e.g., conjugated estrogens tablets, USP, [Premarin]), at least 1 month (30 days) prior to receiving the first dose of randomized therapy;
- Radiotherapy prior to initiation of randomized therapy is allowed to a limited area (e.g., palliative treatment for painful bone metastases), if it is not the sole site of disease. Subject must have completed treatment and recovered from all treatment-related toxicities, in particular bone marrow suppression;
- Able to swallow and retain oral medication;
- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive);
- Subjects must complete all screening assessments as outlined in the protocol;
- Adequate organ function as defined below:
 - Hematologic

- ANC (absolute neutrophil count) $\geq 1.5 \times 10^9/L$
- Hemoglobin ≥ 9 g/dL
- Platelets $\geq 100 \times 10^9/L$
- Hepatic
 - Albumin ≥ 2.5 g/dL
 - Serum bilirubin $\leq 1.5 \times$ ULN or $\leq 2.5 \times$ ULN with Gilbert's syndrome
 - AST and ALT $\leq 3 \times$ ULN without liver metastases and $\leq 5 \times$ ULN if documented liver metastases
- Renal
 - Serum creatinine ≤ 1.5 mg/dl
 - Calculated creatinine clearance ≥ 40 ml/min

Exclusion criteria

Subjects who met any of the following were excluded from study participation:

- Pre-menopausal, pregnant, or lactating;
- Received prior chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or anti-ErbB1/ErbB2 therapy for advanced or metastatic disease;
- Bisphosphonate therapy for bone metastases is allowed; however, treatment must be initiated prior to the first dose of randomized therapy. Prophylactic use of bisphosphonates in subjects without bone disease, except for the treatment of osteoporosis, is not permitted;
- Malabsorption Syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. Subjects with ulcerative colitis are also excluded;
- History of other malignancy. Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible;
- Concurrent disease or condition that would make the subject inappropriate for study participation, or any serious medical disorder that would interfere with the subject's safety;
- Subjects who have not recovered from toxicities related to prior adjuvant therapy (e.g., surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy, biologic therapy, and investigational agents);
- Subjects who have received anthracyclines in the neo-adjuvant and/or adjuvant setting, which exceeded the following doses: 360 mg/m^2 of doxorubicin, 720 mg/m^2 of epirubicin, and 72 mg/m^2 of mitoxantrone;
- Subjects with extensive symptomatic visceral disease including hepatic involvement and pulmonary lymphangitic spread of tumor, or the disease is considered by the investigator to be rapidly progressing or life threatening;
- Active or uncontrolled infection;
- Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent;

- Known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure;
- Known history of, or clinical evidence of, central nervous system (CNS) metastases or leptomeningeal carcinomatosis;
- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, hormonal therapy, targeted therapy, biologic therapy, or tumor embolization) other than letrozole;
- Concurrent treatment with an investigational agent or participation in another clinical trial;
- Used an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of randomized therapy (lapatinib or placebo);
- The subject has a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to randomized therapy (lapatinib or placebo) or to excipients of randomized therapy (lapatinib or placebo);
- Subject has known hypersensitivity to letrozole or excipients of letrozole.

Reviewer's comment: Note in the inclusion criteria, subjects must have had tumor tissue that is positive for ER+ or PR+ assay method was not specified in the protocol. It is a concern that in the U.S. population HER2-positive patients are treated with trastuzumab, which has clearly shown clinical benefit. Patients may have also had prior exposure to anthracyclines and mitoxantrone, which may affect LVEF.

Additionally, it is significant that no prior trastuzumab was required in the adjuvant setting as an inclusion criteria because this was not approved at the time of initiation of EGF30008.

Randomization and blinding

Subjects received treatment according to a 1:1 randomization schema. Subjects were identified by a unique subject number. Investigators or designated staff telephoned the interactive voice response (IVR) system called RAMOS (Registration And Medication Ordering System) to register and record subject activity. Randomization was stratified according to the following stratification factors in order to obtain a randomization number and treatment group assignment:

1. Sites of disease
 - Soft tissue/visceral disease (may also have metastases to the bone)
 - Bone only disease
2. Prior adjuvant anti-estrogen therapy (e.g. tamoxifen or raloxifene)
 - Interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is ≥ 6 months, or subject has never received adjuvant anti-estrogen therapy.

- Interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is < 6 months.

Subjects were supplied randomized therapy (lapatinib or placebo) using a double-blind technique, in which the subjects and investigators were blinded to the trial therapy codes.

Reviewer's comment: Note that no stratification was made for HER2 status prior to randomization and no adjustment could have been made as the study had already commenced.

Study Treatment

Table 6: Treatment plan

Medication	Treatment Arm	
	Lapatinib + Letrozole Combination	Letrozole + Placebo
Lapatinib	1500 mg once daily (qd)	None
Letrozole	2.5 mg qd	2.5 mg qd
Placebo	None	Matching placebo to lapatinib

Concomitant Medications

All concomitant medications taken during the study were recorded in the CRF with information regarding indication, route of administration, and dates of administration. Bisphosphonate therapy initiated prior to first dose of randomized therapy was permitted. Antacids were to be given at least one hour before or after dosing of randomized therapy. Subjects should have received full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Dose Reduction

One dose reduction for a randomized therapy related toxicity is permitted. If a NCI CTCAE Grade 3 or 4 drug-related event, (other than left ventricular systolic dysfunction, interstitial pneumonitis, or hepatotoxicity), occurred, the investigator must have discussed with Sponsor whether a reduction of dose is appropriate. The reduced dose of randomized therapy was 5 tablets (1250 mg of lapatinib) daily.

No dose reductions were allowed for letrozole.

Dose Delay

Treatment with randomized therapy could be delayed, up to 2 weeks, to allow for resolution of toxicity except in the event of left ventricular cardiac dysfunction, interstitial pneumonitis, or hepatotoxicity. If treatment was delayed for reasons other than toxicity

(i.e., unplanned travel or vacation, or lack of transportation to the site) and the subject had insufficient investigational product available, the subject should have resumed the usual dosing schedule once drug supply was made available.

Criteria for Hematologic and Non-Hematologic Toxicity

Lapatinib was delayed if:

Non-hematologic toxicity	Any grade 3 or 4 drug-related toxicity
Hematology	ANC < 1.0 x 10 ⁹ /L Platelet count < 75.0 x 10 ⁹ /L Hemoglobin < 9.0 g/dL
Chemistry	Unresolved grade 3 or 4 toxicity (except liver chemistry)
Serum creatinine	≥ 1.5 mg/dL or calculated creatinine clearance ≤ 40 mL/min

Source: Applicant's table, Study EGF30008 Protocol, Amendment 5, p. 50

Respiratory events:

Subjects with an NCI CTCAE Grade 3 or 4 interstitial pneumonitis were to be withdrawn from randomized therapy.

Criteria for Cardiac Toxicity

Asymptomatic cardiac events:

- Subjects who had a ≥20% relative decrease from baseline in left ventricular cardiac ejection fraction (LVEF), and the LVEF is below the institution's lower limit of normal, should have had a repeat evaluation of ejection fraction 1-2 weeks later while still receiving randomized therapy (lapatinib or placebo).
- If the repeat ejection fraction evaluation confirmed a ≥20% relative decrease from baseline in LVEF, and the ejection fraction was below the institution's lower limit of normal, then randomized therapy was temporarily discontinued.
- If the LVEF recovered during the next 3 weeks, after consultation and approval of the medical monitor, the subject might have been restarted on randomized therapy at a reduced dose (5 tablets or 1250 mg/day). For such subjects, monitoring of left ventricular ejection fraction was then performed 2 weeks and 4 weeks after re-challenge, and then every 4 weeks thereafter.
- If the repeat ejection fraction evaluation still showed a relative decrease ≥20% from baseline in LVEF and the value was below the institution's lower limit of normal, then the subject were to be withdrawn from randomized therapy.

- Ejection fraction was monitored every 4 weeks for at least 16 weeks or until resolution.

Symptomatic cardiac events:

Subjects with an NCI CTCAE Grade 3 or 4 LVEF were to be withdrawn from randomized therapy.

Reviewer's comment: In asymptomatic subjects, it is ambiguous whether LVEF must return to baseline to qualify as "recovered". Additionally, it is unclear if subjects with a relative decrease $\geq 20\%$ from baseline in LVEF and still above the institution of lower limit of normal could be continued on therapy. The Tykerb labeling recommends drug discontinuation with Grade 2 LVEF dysfunction.

Criteria for Liver Chemistry Stopping and Follow-up

If a subject experiences ALT $>3 \times$ ULN and total bilirubin $>2.0 \times$ ULN ($>35\%$ direct; bilirubin fractionation required*), then the following actions must be taken:

- immediately and permanently discontinue investigational product;
- monitor every week until liver chemistries resolve, stabilize or return to within baseline values;
- do not re-challenge with investigational product.

***NOTE:** bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin $>2.0 \times$ ULN, then the aforementioned actions must still be performed.

If a subject experiences:

- ALT $>8 \times$ ULN or
- ALT $>5 \times$ ULN persisting for ≥ 2 weeks: retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists or
- ALT $>3 \times$ ULN with signs or symptoms of hepatitis or hypersensitivity (the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia), then hold investigational product for 2 weeks, repeat liver chemistry testing in 2 weeks, and then call the Medical Monitor to discuss the possibility of re-challenging with investigational product.
- If the treatment is exhibiting efficacy **and** the subject wants to continue for potential benefit of investigational product (lapatinib therapy or placebo) after being informed of the results of liver chemistry testing, then the investigational product may be re-started at the reduced dose agreed upon by the investigator and the Medical Monitor. The liver event CRF should be completed and liver chemistries and aforementioned signs and symptoms should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

- If a subject experiences ALT $>3 \times$ ULN **but** $<5 \times$ ULN **and** total bilirubin $\leq 2 \times$ ULN, without signs or symptoms of hepatitis or hypersensitivity, **and** who can be monitored weekly, then the following actions should be taken:
 - continue investigational product;
 - monitor weekly until liver chemistries resolve, stabilize, or return to within baseline, then monitor liver chemistries as per protocol assessment schedule;
- if ALT >3 and $< 5 \times$ ULN for > 4 weeks , discontinue the treatment;
- if at any time this subject meets any of the aforementioned liver chemistry stopping criteria, then proceed as described above.

Discontinuation or Withdrawal from Study

A subject might have been voluntarily discontinued participation in this study at any time. The investigator might have also, at his/her discretion; discontinued the subject from participating in this study at any time. In addition, randomized therapy (lapatinib or placebo) might have been discontinued if unmanageable toxicity is documented, or the sponsor discontinued the study.

Subject withdrawal from investigational product: A subject was considered to have withdrawn from randomized therapy if the principle reason for ending treatment fell into 1 of the following categories:

- Adverse event (including intercurrent illness, unacceptable toxicity);
- Insufficient therapeutic effect (lack of efficacy/progressive disease);
- Deviation from protocol (including non-compliance);
- Lost to follow-up;
- Subject's own request for reasons other than those above

Compliance Assessment

Randomized Therapy (lapatinib or placebo)

A record of the number of tablets dispensed to and taken by each subject was maintained and reconciled with the 'Investigational Product' page in the CRF. Compliance with randomized therapy dosing was assessed through querying the patient during the monthly site visit and documented in the source documents and recorded in the CRF.

Letrozole

Letrozole prescriptions were documented in the physician's order sheets or by retention of a copy of the prescription. Compliance with letrozole dosing was assessed through querying the patient during the monthly site visit and documented in the source documents and recorded in the CRF.

Concomitant medications

Subjects received full supportive care during the study, including transfusion of blood and blood products, as appropriate:

- Bisphosphonate therapy initiated prior to first dose of randomized therapy is permitted.

Prohibited medications

The following medications were prohibited from 2 weeks before the first dose of lapatinib or placebo through lapatinib or placebo discontinuation unless indicated otherwise below.

- Anti-cancer therapy should not be given until disease progression or withdrawal from lapatinib or placebo. Subjects who receive concurrent anti-cancer therapy (e.g., cytotoxic or biologic) will not be allowed to continue to receive treatment with lapatinib or placebo;
- Hormonal therapy (e.g., anti-estrogen therapy, hormone replacement therapy (HRT), and aromatase inhibitors other than letrozole). Adjuvant therapy with an aromatase inhibitor is allowed; however, treatment must have ended more than 1 year prior (>12 months) to the first dose of randomized therapy;
- Subjects may have received anti-estrogen therapy (e.g., tamoxifen) within 2 weeks before the first dose of randomized therapy, however; no anti-estrogen therapy or aromatase inhibitors, other than letrozole are allowed once the subject begins randomized therapy. Subjects are not permitted to be treated with HRT during study participation and treatment with HRT must be discontinued 1 month prior to the first dose of randomized therapy.
- Any other investigational drugs from 30 days or 5 half lives prior to the first dose of lapatinib or placebo until 30 days after the last dose of lapatinib or placebo.

Lapatinib is a substrate for CYP3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of lapatinib. The following list of CYP3A4 inducers and inhibitors in Table 7 were prohibited from screening through discontinuation from study. Antacids that modify gastric pH, while not prohibited, were restricted. Histamine H₂-antagonists (H₂RAs) and proton pump inhibitors (PPIs) are allowed.

Certain herbal supplements were prohibited because it is not known what effects they might have had on lapatinib's pharmacokinetics or pharmacodynamics.

Table 7. Prohibited medications, CYP3A4 inhibitors and inducers

Drug Class	Agent	Wash-out ¹
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine	
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg) ²	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	atazanavir, delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	grapefruit, grapefruit juice	
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennie's	1 hour before and after dosing
Herbal or dietary supplements ³	Ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil.	14 days

1. At the time of screening, if a patient is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of GW572016 and throughout the study period in order for the patient to be eligible to participate in the study.
2. Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed. Glucocorticoid conversions are provided in parentheses.
3. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact the GSK Medical Monitor or Clinical Scientist.

Source: Study EGF30008 protocol, amendment 5

Patient evaluations

The study had screening, treatment, and post-treatment phases. The study calendars are shown in Table 8.

Screening phase

All screening and baseline evaluations were completed prior to initiating treatment. Four weeks prior to first dose, the subject signed an informed consent form and obtained archived tumor tissue for analysis of ErbB1 and ErbB2 expression by IHC and/or FISH and confirmation of estrogen receptor and/or progesterone receptor positivity. Two week prior to first dose, the following evaluations had to be completed: physical examination, medical history and ECOG performance status, 12-lead electrocardiogram, vital signs, hematology, chemistry, calculated creatinine clearance if serum creatinine > 1.5 mg/dl, echocardiogram (if echocardiogram could not be

performed or if the investigator felt it was not conclusive to evaluate left ventricular cardiac ejection fraction, then a MUGA scan should have been done).

Treatment phase

Studies during this phase include hematology and chemistry, bilirubin fractionation if total bilirubin > 2 x ULN when testing was available, ECOG performance status, vital signs, record of any nonserious and serious AEs, record of all concomitant medications, and assessment of treatment compliance. Every eight-week interval, an echocardiogram was to be performed. Echocardiograms may be performed up to 7 days before the actual 8-week visit. If the investigator felt the echocardiogram could not be performed or was not conclusive to evaluate left ventricular cardiac ejection fraction, a MUGA scan should have been done.

Post-treatment phase

When a subject was withdrawn from treatment for any reason, the following must be captured: physical examination, vital signs, ECOG performance status, 12-lead electrocardiogram, record of any AEs, record of all concomitant medications, assessment of compliance, hematology, chemistry, and echocardiogram (or MUGA) if the last cardiac assessment was > 12 weeks from the date the last assessment was performed.

Table 8. Time and events table (subjects that have been on study treatment for < 108 weeks)

Procedures	Screening	Day 1 Pre-Dose	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks	Every 6 Months	Withdrawal/Study Conclusion
Informed Consent	✓						
Archived Tumor Tissue for Biomarkers	✓ ¹						
Inclusion/Exclusion Criteria	✓	✓					
Medical, Surgical, & Treatment History	✓ ²						
Physical Exam	✓	✓	✓				✓
ECOG Performance Status	✓	✓	✓				✓
FACT-B QOL Questionnaire		✓			✓		✓
Vital Signs	✓	✓	✓				✓
Body Weight (& Height at baseline only)	✓	✓	✓				✓
Echocardiogram or MUGA scan	✓			✓ ³			✓ ³
12-lead Electrocardiogram	✓						✓
AE/Toxicity Assessment	✓ ⁴	✓ ⁴	✓ ⁴				✓ ⁴
Record Concomitant Medications	✓	✓	✓				✓
Tumor Measurement (CT, MRI, Bone scan, Photographs)	✓				✓	✓ ⁵	✓ ¹²
Serum Assay for ErbB1 & ErbB2 & Potential Proteomic Analysis	✓		✓ ⁶				✓
Hematology & Chemistry	✓ ⁷	✓ ^{7,9}	✓ ⁷				✓ ⁷
Calculate Creatinine Clearance	✓ ⁸	✓ ^{8,9}	✓ ⁸				✓ ⁸
Pharmacogenetics sample (if applicable)		✓ ¹⁰					
Dispense Randomized Therapy		✓ ¹¹	✓ ¹¹				
Ascertain Compliance of Randomized Therapy & Letrozole			✓ ¹¹				✓ ¹¹
Survival/ Post-study Follow-up Visits					✓ ¹²		

Note: Detailed description of study procedures is presented in Section 5.2 Safety and Section 5.3 Efficacy.

- Obtain archived tumor tissue within 4 weeks prior to the first dose of randomized therapy. Results will not be used to determine study eligibility. However, subjects enrolled during the extension phase of the trial must have documented amplification of ErbB2 by FISH (either locally or centrally) prior to randomization.
- Medical and surgical history to include evaluation of baseline signs and symptoms. Record in the CRF with the assigned NCI CTCAE grade on the Current Medical Conditions/Baseline Signs and Symptoms page(s)
- Echocardiograms (or MUGA scan) may be done up to 7 days prior to the actual 8-week visit to allow for flexibility in scheduling. Copies of echocardiograms (or MUGA scan) performed on subjects who experience a ≥20% relative decrease in LVEF from baseline, and cardiac ejection fraction is below the institution's LLN, will be required by GSK for review by an independent board. Echocardiograms (or MUGA scan) do not need to be repeated at withdrawal if the last cardiac assessment was <8 weeks from the date the last assessment performed.
- Subjects will be monitored at each scheduled assessment at the site, at any contact with the subject during the study, at withdrawal, and up to 30 days post-study for the occurrence of AEs/SAEs.
- Bone scans should be repeated every 6 months (±14 day window) for all subjects who had bone lesions present at baseline (e.g., soft tissue/ visceral disease with metastases to bone). Subjects with bone only disease who have repeat bone scan evaluations every 12 weeks do not need to have a bone scan performed every 6 months. However, if bone only disease is being followed by CT scan or MRI scan, then a bone scan must be obtained every 6 months.
- A serum sample for ErbB1 and ErbB2 ELISA assays and potential proteomic analysis will be drawn on Day 1 Pre-dose and every 4 weeks thereafter.
- Standard chemistry evaluation to include: sodium, potassium, calcium, glucose, BUN or urea, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin. The chemistry tests of chloride, bicarbonate, and uric acid are not routinely available in some countries and will no longer be required where there are logistical constraints. Bilirubin fractionation is recommended if total bilirubin >2 x ULN when testing is available.
- Calculated creatinine clearance if serum creatinine >1.5 mg/dL using Cockcroft and Gault Method. Calculated creatinine clearance must be ≥40 mL/min to be eligible for study enrollment.
- Review screening laboratory results. Any result outside the normal range will be repeated (prior to the first dose) at the discretion of the Investigator. Before the first dose of randomized therapy (GW572016 or placebo), all laboratory results must be within the values outlined in Section 4.2.1
- For subjects who consent to participate in pharmacogenetics (PGx) research, a 10 mL blood sample will be drawn. This sample can be drawn at any time during the study, however it is preferred that it be drawn at the first visit.
- 180 tablets of randomized therapy (GW572016 or placebo) is to be dispensed to the subject with instructions for daily administration. Randomized therapy is to be taken at approximately the same time each day either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Randomized therapy is not to be taken with grapefruit or grapefruit juice and neither, grapefruit or grapefruit juice is permitted for the duration of the study. The recommended dose of letrozole is one (1) 2.5 mg tablet administered once a day, with randomized therapy. A record of the tablets (both randomized therapy and letrozole) dispensed to and taken by each subject must be maintained.
- Subjects withdrawn from randomized therapy without PD will have radiographic and/or clinical disease assessments performed every 12 weeks until disease progression, until the subject begins a new anti-cancer therapy, or death. Copies of radiographs will be sent for independent review until the subject begins any anti-cancer therapy. Once new anti-cancer therapy begins, only response data will be collected. All subjects will be followed every 12 weeks for survival.

Source: Study EGF30008 protocol, Amendment 5, Appendix 1.

Table 9. Time and events table (week 108 until withdrawal)

Procedures	Every 12 Weeks starting at Week 108	Every 6 Months	Withdrawal/Study Conclusion
Physical Exam	✓		✓
ECOG Performance Status	✓		✓
FACT-B QOL Questionnaire	✓		✓
Vital Signs	✓		✓
Body Weight (& Height at baseline only)	✓		✓
Echocardiogram or MUGA scan	✓ ¹		✓ ¹
12-lead Electrocardiogram			✓
AE/Toxicity Assessment	✓ ²		✓ ²
Record Concomitant Medications	✓		✓
Tumor Measurement (CT, MRI, Bone scan, Photographs)	✓	✓ ³	✓ ³
Serum Assay for ErbB1 & ErbB2 & Potential Proteomic Analysis	✓ ⁴		✓
Hematology & Chemistry	✓ ⁵		✓ ⁵
Calculate Creatinine Clearance	✓ ⁶		✓ ⁶
Pharmacogenetics sample (if applicable) ⁷			
Dispense Randomized Therapy	✓ ⁸		
Ascertain Compliance of Randomized Therapy & Letrozole	✓ ⁸		✓ ⁸
Survival/ Post-study Follow-up Visits	✓ ⁹		

Note: Detailed description of study procedures is presented in Section 5.2 Safety and Section 5.3 Efficacy.

- Echocardiograms (or MUGA scan) may be done up to 7 days prior to the actual 12-week visit to allow for flexibility in scheduling. Copies of echocardiograms (or MUGA scan) performed on subjects who experience a $\geq 20\%$ relative decrease in LVEF from baseline, and cardiac ejection fraction is below the institution's LLN, will be required by GSK for review by an independent board. Echocardiograms (or MUGA scan) do not need to be repeated at withdrawal if the last cardiac assessment was < 12 weeks from the date the last assessment performed.
- Subjects will be monitored at each scheduled assessment at the site, at any contact with the subject during the study, at withdrawal, and up to 30 days post-study for the occurrence of AEs/SAEs.
- Bone scans should be repeated every 6 months (± 14 day window) for all subjects who had bone lesions present at baseline (e.g., soft tissue/ visceral disease with metastases to bone). Subjects with bone only disease who have repeat bone scan evaluations every 12 weeks do not need to have a bone scan performed every 6 months. However, if bone only disease is being followed by CT scan or MRI scan, then a bone scan must be obtained every 6 months.
- A serum sample for ErbB1 and ErbB2 ELISA assays and potential proteomic analysis will be drawn every 12 weeks starting at Week 108.
- Standard chemistry evaluation to include: sodium, potassium, calcium, glucose, BUN or urea, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin. The chemistry tests of chloride, bicarbonate, and uric acid are not routinely available in some countries and will no longer be required where there are logistical constraints. Bilirubin fractionation is recommended if total bilirubin $> 2 \times$ ULN when testing is available.
- Calculated creatinine clearance if serum creatinine > 1.5 mg/dL using Cockcroft and Gault Method. Calculated creatinine clearance must be ≥ 40 mL/min to be eligible for study enrollment.
- For subjects who consent to participate in pharmacogenetics (PGx) research, a 10 mL blood sample will be drawn. This sample can be drawn at any time during the study, however it is preferred that it be drawn at the first visit.
- 540 tablets of randomized therapy (GW572016 or placebo) is to be dispensed to the subject with instructions for daily administration. Randomized therapy is to be taken at approximately the same time each day either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Randomized therapy is not to be taken with grapefruit or grapefruit juice and neither, grapefruit or grapefruit juice is permitted for the duration of the study. The recommended dose of letrozole is one (1) 2.5 mg tablet administered once a day, with randomized therapy. A record of the tablets (both randomized therapy and letrozole) dispensed to and taken by each subject must be maintained.
- Subjects withdrawn from randomized therapy without PD will have radiographic and/or clinical disease assessments performed every 12 weeks until disease progression, until the subject begins a new anti-cancer therapy, or death. Copies of radiographs will be sent for independent review until the subject begins any anti-cancer therapy. Once new anti-cancer therapy begins, only response data will be collected. All subjects will be followed every 12 weeks for survival.

Source: Study EGF30008 protocol, Amendment 5, Appendix 1.

5.3.4 Criteria for Efficacy Assessment

Primary analysis

Efficacy was assessed by investigator-determination of the PFS in the ErbB2-positive subgroup in the primary analysis, defined as the time from randomization until the earliest date of disease progression or death due to any cause, if sooner.

Secondary analyses included PFS in the ITT population, OS, TTP, clinical benefit, time-to-response, and duration of response (response maintained at least 4 weeks in accordance with RECIST criteria). Tumor measurement by CT, MRI, bone scan or

photographs was assessed every 12 weeks during the treatment period, and after subjects stopped treatment.

After treatment was discontinued, a visit and formal assessment for tumor progression, start of new therapy, and follow up for survival were required every 12 weeks (continuing on the original schedule). Subjects withdrawn from treatment without PD had radiographic and/or clinical disease assessments performed every 12 weeks until disease progression, until subject began a new anti-cancer therapy, or death. The same method of assessment and the same technique was to be used to characterize each identified and reported lesion at baseline, and throughout the study, including during the follow-up phase and after treatment termination.

Any subject who received at least 1 dose of randomized therapy was considered eligible for response to treatment.

The following were the required baseline tumor assessments:

- Clinical disease assessments for palpable or visual lesions (for visual skin lesions, documentation of target lesions by color photography- including a ruler to estimate the size of the lesion(s) is required).
- Radiological disease assessments:
 - Chest CT (or MRI) scan which includes the entire liver, **or alternatively**, chest and abdominal CT (or MRI) scan;
 - Pelvic CT scan (or MRI scan) to be performed if clinically indicated;
 - Head CT scan (or MRI scan) to be performed if clinically indicated;
 - Bone Scan (to include evaluation of skull, total spine, clavicle, ribs, pelvis, and long bones);
 - All bone scan abnormalities at screening that could indicate metastases, must be evaluated by X-ray (e.g., plain film, CT, or MRI) to determine if they represent malignant lesions.

Tumor assessments included the following:

- Clinical disease assessments for palpable or visual lesions (for visual skin lesions, documentation of target lesions by color photography- including a ruler to estimate the size of the lesion(s) was required).
- Radiographic disease assessments were to be obtained every 12 weeks (within 7 day $\pm$ window) or sooner if clinically indicated. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.
- The same physician will evaluate the subject's tumor response/disease status at the end of each 12-week interval, when possible.
- Confirmation of disease response was necessary at four weeks after the response assessment.
- Bone scans were to be obtained to rule out the presence of new bone lesions or progression of existing bone lesions, even if the subject had no bone lesions present at baseline.

- Any new lesion(s) were to be fully recorded in the CRF. If the lesion(s) noted at screening were not evaluated at the end of the 12-week interval, this were to be noted as 'not done' (ND) in the CRF.
- For subjects with bone only disease, a bone scan, or CT scan, or MRI was required every 12 weeks (within 7 day $\pm$ window) or sooner if clinically indicated or to rule out clinical progression.
- The same diagnostic method must be used for the duration of the study (i.e., if a bone scan is performed at week 12, then a bone scan must be repeated every 12 weeks thereafter for the duration of the study).
- If a bone scan was performed and the lesion(s) were equivocal, correlative imaging (i.e., plain film, CT, or MRI) was required to demonstrate malignant characteristics of the lesion(s).

Reviewer's comment: The primary analysis was proposed by the Applicant and discussed at the pre-sNDA meeting in January 2009. Specifically, the Applicant had proposed a hierarchical closed testing procedure, whereby the effect of PFS was initially tested in the ErbB2-positive population at an alpha level of 0.05. This proposed method does not control for type I error.

Bone-only disease is difficult to assess and is considered by RECIST to be nonmeasurable disease.

Definition of Measurable and Non-measurable Disease

Measurable disease: presence of at least 1 measurable lesion.

Measurable lesion: lesions that can be accurately measured in at least 1 dimension (longest dimension) of;

- 15 mm with conventional techniques (medical photograph [skin or oral lesion], palpation, plain X-ray, CT, or MRI). In the case of CT, the minimum size of a measurable lesion must be at least double the reconstruction interval (e.g., if the reconstruction interval is 10 mm, a measurable lesion must be 20 mm).

OR

- ≥ 10 mm with spiral CT scan

Non-measurable lesion: all other lesions including lesions too small to be considered measurable (longest diameter < 15 mm with conventional techniques or < 10 mm with spiral CT scan) including bone lesions, leptomeningeal disease (note: subjects with leptomeningeal disease are not eligible for study participation), ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions, or disease documented by indirect evidence only (e.g., by lab values).

Baseline Documentation of Target and Non-target Lesions

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

The Sponsor had arranged for an independent, blinded review of all radiological scans to verify progression, or confirm or question the qualitative nature of the apparent response. For subjects with skin lesions, all photographs were sent for independent blinded review as well.

5.3.5 Criteria for Safety Assessment

CBC and serum chemistries: measured every four weeks.

Echocardiogram: performed every 8 weeks. For subjects who had received study treatment for ≥ 108 weeks, safety assessments were performed at 12-week intervals starting at Week 108.

AE and toxicity assessment: performed every four weeks.

Adverse Events (AE) and Serious Adverse Events (SAE)

Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

- a. results in death.
- b. is life-threatening.
- c. requires hospitalization or prolongation of existing hospitalization.
- d. results in disability/incapacity, or
- e. is a congenital anomaly/birth defect.

- f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

5.3.6 Statistical Analyses

Trial Specifications

Stratification factors:

- (1) site of disease (soft tissue or visceral, may also have metastases to bone versus bone only)
- (2) prior adjuvant anti-estrogen (e.g., tamoxifen or raloxifene) therapy
 - interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is ≥ 6 months, or subject never received adjuvant anti-estrogen therapy versus interval between discontinuation of adjuvant anti-estrogen therapy and initiation of randomized therapy is < 6 months.

Reviewer's comment: Study was not stratified according to HER2-status, which may lead to an imbalance in both arms.

Type of hypothesis to be tested: superiority in both ErbB2-positive and ITT populations.

Efficacy endpoints:

- Primary endpoint: investigator-evaluated PFS defined as the interval of time (in weeks) between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause.
- Secondary endpoint: investigator-assessed PFS defined as the interval of time (in weeks) between the date of randomization and the earlier of date of first documented sign of disease progression or death due to any cause.
 - Other secondary endpoints include response rate, clinical benefit, duration of response, TTP, quality of life, and OS.

Sample size consideration:

- Statistic: unstratified log-rank test
- Difference to be detected:
 - ErbB2-positive population: a hazard ratio of 0.645 or a median PFS of 15.5 months versus 10 months, for lapatinib and letrozole versus letrozole alone, respectively.

- ITT population: a hazard ratio of 0.769, or a median PFS of 13 months versus 10 months for lapatinib and letrozole versus letrozole alone, respectively.

Sample size/# of events/ α (two-sided)/power:

Population	Sample size	Number of events	α (two-sided)	Power
ErbB2-positive	218	173	0.05	80%
ITT	1280	≥ 612	0.05	$\geq 90\%$

Note: Sample size was calculated so that there were 173 events in 218 ErbB2-positive patients for the subgroup analysis. With 32 months expected for the recruitment of 218 ErbB2-positive patients at an average accrual rate of 40 patients per month, a total of 1280 patients were expected to be recruited for the study. It was anticipated that there was a minimum of 612 events in the ITT population, which will provide greater than 90% power for analysis, at the occurrence of 173 events in the ErbB2-positive subgroup.

Source: Applicant's Reporting and Analysis Plan (SAP)

Interim efficacy analyses: None.

Primary Statistical Analysis

Treatment arms were compared in PFS using log-rank test, stratified by the randomization factors. Effect of PFS was first tested in the ErbB2-positive population at the alpha level of 0.05. Testing was performed in the ITT population at the 0.05 alpha level if statistical significance is achieved in the ErbB2-positive population. Hazard ratio was calculated based on log-rank test (Pike estimator) together with 95% confidence interval for overall population and by ErbB2-status (positive or negative). The ITT population is defined as the randomized patients who received at least one dose of randomized therapy. The ErbB2-positive population subgroup comprised all patients who received at least one dose of randomized therapy and who have documented ErbB2-positivity in primary or metastatic tumor tissue.

PFS was defined as the interval of time (in weeks) between the date of randomization and the earlier date of disease progression, or date of death due to any cause based on the assessments by the investigator. The date of documented disease progression was defined as the date of radiological disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression.

The date of documented disease progression was taken from the Response Assessment page. This should have been the date of lesion evaluation in the case of radiological disease progression or the date of symptomatic progression of cancer in the case of symptomatic progression. The date of death should have been taken from that recorded on the Record of Death page. Death on study due to any cause was included.

If a subject had neither progressed nor died, then PFS was censored at the date of the

last radiological scan assessed by the investigator. For subjects who received subsequent anti-cancer therapy, the following rules applied:

- If such therapy was started **without evidence of documented disease progression**, then PFS was censored at the date of the last radiological assessment that was no later than 14 days following the date of initiation of anti-cancer therapy if the scan assessment did not document PD. If there were multiple scan dates for a given assessment then PFS was censored at the first date of the series of scan dates.

Reviewer's comment: This censoring rule is not acceptable. Patients should be censored at the last assessment before starting subsequent anti-cancer therapy.

- If initiation of anti-cancer therapy plus the 14-day window was **prior to disease progression or death** and the anti-cancer therapy start date was between the first and last date of a set of multiple scans, and the date of subsequent disease progression or death was also between the first and last date of a set of multiple scans, then PFS was censored at the first scan date of the previous assessment.
- For subjects who had a skin lesion and did not have a radiological assessment or subjects who had a node that had never been imaged, if anti-cancer therapy plus the 14-day window was started **prior to disease progression or death** then such subjects were censored at the last clinical assessment.

Reviewer's comment: This censoring rule is not acceptable. Patients should be censored at the last assessment before starting subsequent anti-cancer therapy.

- If alternative anti-cancer therapy was started on or after the date of disease progression, then PFS was unaffected.
- If the start date of the anti-cancer therapy was missing the day but has the month and year available, then the day was imputed as the 1st.
- If a subject has only a baseline visit or did not have a date of radiological scan that was no later than the date of initiation of anti-cancer therapy, PFS was censored at the date of randomization. If a subject has a skin lesion and does not have a radiological assessment or if the subject has a node that has never been imaged, then such subjects who initiate anti-cancer medication and do not have a clinical assessment later than the date of initiation of anti-cancer medication was censored at the baseline assessment.

Subjects who were withdrawn from the study and receive an alternative anti-cancer therapy were censored at the initiation of the alternative therapy if scans do not occur within 14-day window as described above.

Primary Endpoint: Progression-Free Survival in HER2+ Population (Confirmatory Independent Review)

A supportive analysis of PFS was based solely on the independently reviewed assessments. The earliest date of disease progression was based on radiological assessment of disease progression by the independent reviewer. PD as assessed by

both the independent radiologist and the oncologist was included in this analysis. In some cases where the oncologist may indicate progression prior to the radiologist, the date of the progression based on oncologist's assessment was used in the analysis. The oncologist's opinion will always be considered to override that of the radiologist. For censoring purposes, the date corresponding to the last radiological scan assessed by the independent reviewer was used. In all other aspects, the PFS analysis according to the independent reviewer will follow the same rules as for the investigator-evaluated PFS.

Sensitivity Analysis

As a sensitivity analysis, PFS was analyzed using the method of interval-censoring. Since disease progression was assessed periodically, it was not be appropriate to treat data as right-censored, as for overall survival data. The type of data for PFS was better presented in the form of interval-censored data in that if disease progression was observed in a given assessment, the actual date of occurrence could be on any day between the previous assessment and the current assessment. If disease progression was not observed by the end of the study, then the interval was from the last assessment date to an infinite date – corresponding to the right-censored data. Therefore, for the analysis of interval-censored data it was required to obtain the parameters of the interval for each subject. Treatment arms were compared using a stratified log-rank test.

Secondary Endpoint: Progression-Free Survival in ITT Population

PFS was defined as the interval of time (in weeks) between the date of randomization and the earlier of date of disease progression, or date of death due to any cause. Disease progression based on the assessments by the investigator.

The date of documented disease progression was defined as the date of radiological disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. The date of documented disease progression was taken from the Response Assessment page. This should be the date of lesion evaluation in the case of radiological disease progression or the date of symptomatic progression of cancer in the case of symptomatic progression. The date of death due should be taken from that recorded on the Record of Death page. Death on study due to any cause was included.

If a subject has neither progressed nor died, then PFS was censored at the date of the last radiological scan assessed by the investigator. For subjects who receive subsequent anti-cancer therapy, the censoring rules as stated above apply.

PFS was summarized using Kaplan-Meier curves and compared between treatment arms using a stratified log-rank test, stratifying for site of disease and prior adjuvant therapy. The Pike estimator of the treatment HR based on the log-rank test was provided, together with a 95% confidence interval (CI).

Duration of Response

For subjects who show CR or PR, duration of response was defined as time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to breast cancer, if sooner. The analysis was based on responses as evaluated by the investigator and confirmed at a repeat assessment, with the duration of response taken from the first time the response was observed, not the confirmation assessment. Disease progression was based on the radiological scans, medical photographs and also symptomatic progression assessed by the investigators. The date of documented disease progression was defined as the date of radiological disease progression as assessed by the investigator based on imaging data or symptomatic progression.

If a subject has neither progressed nor died due to breast cancer, then duration of response was censored at the date of the last radiological scan.

All deaths other than due to breast cancer were regarded as competing risks.

For subjects who receive subsequent anti-cancer therapy, the following rules will apply:

- If such therapy was started without prior evidence of documented disease progression, then duration of response was censored at the date of the last radiological assessment that was no later than the date of initiation of anti-cancer therapy. If there are multiple scan dates for a given assessment then PFS was censored at the first date of the series of scan dates.
- If anti-cancer therapy was started prior to disease progression or death due to breast cancer and the anti-cancer therapy start date was between the first and last date of a set of multiple scans, and the date of subsequent disease progression or death due to breast cancer was also between the first and last date of a set of multiple scans, then duration of response was censored at the first scan date of the previous assessment.
- If alternative anti-cancer therapy was started on or after the date of disease progression, then duration of response was unaffected.

Overall Survival

This was defined as the time from randomization until death due to any cause. For subjects who do not die, time of death was censored at the date of last contact. Cox regression analyses were performed for overall survival using the following baseline covariates:

1. Stage of disease (IIIB or IIIC vs. IV)
2. Site of disease (soft tissue/visceral disease vs. nonvisceral)
3. Hormone Receptor Status (ER+ or PR+ vs. ER- and PR- vs. ER missing or PR missing but not in the other 2 categories)

4. ECOG performance status at baseline (0 vs. ≥ 1)
5. Disease free interval (defined as time from diagnosis to metastases)
6. Number of metastatic sites (< 3 vs. ≥ 3)

Cox regression analysis examined univariate first and then all main effects plus treatment was evaluated in the model. No interaction terms were considered. No model selection was performed. A figure displaying the adjusted survival curves considering the main effect terms by Cox regression was generated. Cox regression analysis was analyzed for both the HER2+ and ITT populations.

Overall survival will also be summarized using Kaplan-Meier curves and compared treatment arms using a stratified log-rank test. The Pike estimator of the treatment HR based on the log-rank test was provided, together with a 95% CI. For each treatment group, the Kaplan-Meier estimates for the median overall survival time, the first and third quartiles were presented, along with approximate 95% CI if there are a sufficient number of deaths. Greenwood's formula was used to calculate the standard error of the estimates from the Kaplan-Meier curve.

Reviewer's comment: Study EGF30008 was not powered for OS.

Data handling conventions

Premature withdrawal and missing data

Subjects were treated until disease progression or withdrawal from study treatment due to unacceptable toxicity. Subjects may also withdraw from study treatment for other reasons prior to disease progression or unacceptable toxicity. All subjects that withdraw from the study were included in analyses up until the time of withdrawal.

Subjects who are withdrawn prematurely from IP, but who are not withdrawn from the study at the same time, were included in all analyses regardless of the duration of treatment.

As the period of treatment for any subject was dependent on the treatment's efficacy and toxicity, the duration of follow-up will vary between subjects. Consequently, there was no imputation for missing data. Wherever appropriate, available data were summarized over specified intervals (e.g., from randomization until withdrawal from the study) by using suitable summary statistics.

For PFS and TTP, subjects who do not have a documented date of disease progression or death due to the breast cancer, the date of the subject's last radiographic assessment (by the investigator) was used to right-censor the subject. For overall survival, the date of last follow-up was used to right-censor the subjects who withdraw from the study.

6 Review of Efficacy

Efficacy Summary

The efficacy of lapatinib plus letrozole in hormone receptor-positive, HER2-positive metastatic breast cancer was studied in a double-blind, randomized, placebo-controlled phase 3 comparison of lapatinib plus letrozole versus placebo plus letrozole. The single pivotal Study EGF30008 enrolled 1286 patients who had previously untreated hormone receptor-positive, metastatic breast cancer.

The primary endpoint was originally TTP in the ITT population, but this was changed to the HER2-positive subgroup in Amendment 3 (October 27, 2005), after 760 subjects were already randomized. The protocol was further amended on October 31, 2007 to revise the statistical plan for the primary endpoint, after 1286 patients had already been randomized. The primary endpoint was changed from TTP to PFS in the HER2-positive. The determination of PFS was by investigator's assessment in subjects with measurable disease, according to RECIST guidelines population.

6.1 Indication

"TYKERB®, a kinase inhibitor, is indicated in combination with [REDACTED] (b) (4)

[REDACTED] (b) (4)

6.2 Methods

The primary efficacy analysis is based on a single randomized, placebo-controlled phase 3 study, EGF30008, in 1286 patients with hormone-sensitive metastatic breast cancer at primary diagnosis or relapse after neoadjuvant or adjuvant therapy.

Enrollment commenced on December 9, 2003 and terminated on December 29, 2006. As depicted in Table 10, a total of 212 centers in 29 countries across 5 regions (North America, Latin America, Western Europe, Eastern Europe and Asia Pacific) enrolled subjects in this multicenter study. The majority of subjects were recruited into the study from Western and Eastern Europe (57%), followed by North America (28%).

Table 10. Patient enrollment by country

Country	Number of subjects, N=1286	Percent of total
Argentina	13	1
Australia	13	1
Brazil	19	1
Bulgaria	18	1
Canada	29	2
Chile	18	1
Colombia	3	<1
Croatia	5	<1
Czech Republic	20	2
Denmark	20	2
France	130	10
Germany	104	8
Hungary	28	2
Ireland	53	4
Italy	19	1
South Korea	19	1
Mexico	8	<1
Netherlands	33	3
New Zealand	2	<1
Pakistan	30	2
Peru	47	4
Poland	43	3
Russia	89	7
South Africa	16	1
Spain	77	6
Tunisia	16	1
Turkey	5	<1
United Kingdom	84	7
United States	325	25

Source: Applicant's Table 6.2, Study EGF30008 Clinical Study Report

As shown in Tables 11 and 12, 1286 patients were randomized and were included in the efficacy population, but eight patients did not received treatment, six subjects in the letrozole plus placebo group and two subjects in the letrozole plus lapatinib group. The removal of eight patients leave a balance is 1278 patients who received at least one dose of study medication. This group constitutes the safety population, as seen in Table 13. The number of patients in the letrozole plus placebo group in the safety population was 624 because there were 14 patients who were randomized to receive letrozole plus placebo but who actually received letrozole plus lapatinib and 6 patients

who were randomized to letrozole plus placebo group but did not receive any treatment (N=644). The number of patients in the letrozole plus lapatinib group in the Safety population was 654 because two patients were randomized to letrozole plus lapatinib group but did not receive any treatment, and 14 patients who were randomized to receive letrozole plus placebo actually received letrozole plus lapatinib (N=654). Nine patients who were randomized to receive letrozole plus lapatinib actually received letrozole plus placebo; however, as these patients received at least 1 dose of lapatinib they are included in the letrozole plus lapatinib group for the Safety Analysis population

Table 11. Subject Enrollment by Region

Region	Number of subjects, N=1286	Percent of total
North America ^a	362	28
South America	100	8
Eastern Europe	114	9
Western Europe	520	40
Russia	89	7
Asia	19	1
Others ^b	82	6

Source: Reviewer's table, adapted from Applicant's Table 6.2, Study EGF30008 Clinical Study Report

^a Includes Canada (29), Mexico (8), and United States (325).

^b Includes Australia, New Zealand, Pakistan, South Africa, Tunisia, and Turkey.

Table 12. Efficacy Patient Population

Population	Lapatinib + letrozole, N (%)	Placebo + letrozole, N (%)	Total, N (%)
ITT (randomized)	644 (100)	642 (100)	1286 (100)
HER2-positive	111 (17)	108 (17)	219 (17)
HER2-negative	478 (74)	474 (74)	952 (74)
HER2-missing	53 (8)	62 (10)	115 (9)
ER- or PR-positive	512 (80)	513 (80)	1025 (80)

^a Adapted from Table 7.552, Applicant's Study EGF30008 Clinical Study Report

Table 13. Safety Patient Population

Population	Lapatinib + letrozole, N (%)	Placebo + letrozole, N (%)	Total, N (%)
ITT (randomized)	642 (100)	644 (100)	1286 (100)
Not treated	2 (<1)	6 (<1)	8 (<1)
Safety population ^a	654 (100)	624 (100)	1278 (100)

^a Fourteen subjects who were randomized to receive placebo but who actually received lapatinib.

Source: Applicant's Table 11, Study EGF30008 Clinical Study Report.

The protocol violations are displayed below in Table 14:

Table 14. Protocol violations

Violation^a	Lapatinib + letrozole N= 644	Placebo + letrozole N=642
Negative or unknown hormone status	129 (20)	132 (21)
Possibly received treatment with neoadjuvant intent	19 (3)	22 (4)
Nonmetastatic disease	25 (4)	30 (5)
No study treatment	2 (<1)	6 (1)
Incorrectly diagnosed as Stage III	2 (<1)	0

Source: Reviewer's table extracted from *epstat.xpt*, *dishist.xpt*, *tmtlog.xpt*

6.3 Demographics

There were 1286 women, ages 35 to 92 years, entered into the study for the ITT population. As shown in Table 15, the population studied had moderately extensive disease. Forty-five percent in the letrozole and placebo arm and 44% in the letrozole and lapatinib arm have metastatic disease at ≥ 3 sites as determined by investigator. Visceral disease was the most commonly involved site in both arms. Bone-only disease was observed at baseline in a little more than 10% of the patients in both arms. Measurable disease was a requirement, but this was removed in the Amendment 2. HER2-status was missing in 115 (9%) patients.

Table 15. Baseline Demographics in EGF30008 in the ITT Population

Parameter	Lapatinib + Letrozole, N=642 (%)	Placebo + letrozole, N=644 (%)	Total N=1286 (%)
Gender (%)			
Female	642 (100%)	644 (100%)	1286 (100%)
Age (years)			
Median	62	63	63.0
Mean	62.8	63.3	63.1
Range	31-94	35-95	31-95
Race (%)			
White	529 (82)	557 (86)	1086 (84)
American Hispanic	57 (9)	44 (7)	101 (8)
Asian	30 (5)	30 (5)	60 (5)
Black	17 (3)	10 (2)	27 (2)
Other	9 (1)	3 (1)	12 (<1)
ECOG Performance Status, N	636	595	1231
0	373 (59)	324 (54)	697 (57)
1	263 (41)	268 (45)	531 (43)
2	0	1 (<1)	1 (<1)
3	0	1 (<1)	1 (<1)
4	0	1 (<1)	1 (<1)
Histology at diagnosis			
Infiltrating ductal	483 (75)	474 (74)	957 (74)
Lobular invasive	90 (14)	97 (15)	187 (15)
Other ^d	68 (11)	71 (11)	139 (11)
Unknown	1 (<1)	2 (<1)	3 (<1)
Stage at initial diagnosis			
I	98 (15)	82 (13)	180 (14)
II	258 (40)	265 (41)	523 (41)
III	143 (22)	135 (21)	278 (22)
IV	131 (20)	147 (23)	278 (22)
Unknown	12 (2)	15 (2)	27 (2)
Stage at screening			
IIIb or IIIc with T4 lesion	25 (4)	30 (5)	55 (4)
IV	616 (96)	613 (95)	1229 (96)
Unknown	1 (<1)	1 (<1)	2 (<1)
Hormone receptor status^e			
ER-/PR-	0	2 (<1)	2 (<1)
ER-/PR+	11 (2)	20 (3)	31 (2)
ER+/PR-	151 (23)	151 (12)	270 (21)
ER+/PR+	441 (68)	455 (71)	896 (70)
ER+/PR unavailable	40 (6)	46 (7)	86 (7)
ER/PR unknown or missing	1 (<1)	0	1 (<1)
HER2 receptor status	N=642	N=644	N=1286
HER2-positive	111 (17)	108 (17)	219 (17)
HER2-negative	478 (74)	474 (74)	952 (74)

HER2-missing	53 (8)	62 (10)	115 (9)
Sites of disease^a			
Bone only^b	85 (13)	80 (12)	165 (13)
Visceral or soft tissue^c	554(86)	561 (87)	1115 (87)
Lung	146 (23)	171 (27)	317 (25)
Liver	248 (39)	242 (38)	490 (38)
Lymph node	312 (49)	304 (47)	616 (48)
Soft tissue	212 (33)	218 (34)	430 (33)
Other	125 (19)	127 (20)	252 (20)
Number of metastatic sites			
<3	359 (56)	358 (56)	712 (55)
≥3	283 (44)	285 (44)	568 (44)
Unknown	0	1 (<1)	1 (<1)

Sources: Tables 14 and 17, Study EGF30008 Clinical Study Report and *dishist.xpt*, *epstat.xpt*, *tmt.xpt*, *progfact.xpt*, *dhisles.xpt* datasets

^a Extracted from Applicant's Study EGF30008 Clinical Study Report, Table 17, p. 93

^b Subjects with nonmeasurable or measurable disease in addition to bone disease were not to be stratified in the bone only stratum.

^c Included all other subjects who were not bone only.

^d Included medullary, mucinous, tubular, adenocystic, papillary, carcinosarcoma, and other.

For the HER2-positive subgroup, which was the population analyzed for the primary endpoint, the disease characteristics are present below. Treatment characteristics were well-balanced among the two arms, although slightly more subjects had prior chemotherapy treatment. Salient differences include the slightly higher percentage of subjects in the lapatinib plus letrozole arm that had visceral or soft tissue disease and longer interval of discontinuation of endocrine treatment.

Table 16. Disease characteristics in the HER2-positive subgroup

Parameter	Lapatinib + Letrozole, N=642 (%)	Placebo + letrozole, N=644 (%)
Sites of disease^a		
Bone only^b	13 (12)	18 (17)
Visceral or soft tissue^c	98 (88)	90 (83)
Lung	43 (39)	40 (37)
Liver	33 (30)	37 (34)
Lymph node	57 (51)	43 (40)
Soft tissue	35 (32)	31 (29)
Other	19 (17)	18 (17)
Prior endocrine interval		
Discontinuation ≥ 6 months	73 (66)	67 (62)
Discontinuation ≤ 6 months	38 (34)	41 (38)
Disease and endocrine interval		
Visceral/soft tissue ≤ 6 months	32 (29)	28 (26)

Source: Tables 18 and 19, Study EGF30008 Clinical Study Report, *dishist xpt*, *epstat xpt*, *tmt.xpt*, *progfact.xpt*, *dhisles.xpt* datasets

6.3.1 Prior Therapy

In the adjuvant setting for the ITT population, approximately half of all patients in both arms were treated with hormonal therapy, mostly with either tamoxifen or toremifene. Chemotherapy as prior anti-cancer therapy was balanced between arms, 43% in the letrozole + placebo arm and 44% in the letrozole + lapatinib arm. Only three patients had prior exposure to trastuzumab, one in the letrozole + placebo arm and two in the letrozole + lapatinib arm. Forty percent of the patients in letrozole + placebo arm and 39% in the letrozole + lapatinib arm were prior therapy naïve. In general, the prior anti-cancer systemic therapies were well-balanced between both arms. Two hundred fifty-one (39%) patients in the letrozole and lapatinib arm and 259 (40%) patients in the letrozole and placebo arm were therapy-naïve.

Table 17 Prior anti-cancer systemic therapy in ITT population

Prior treatment type	Number of patients (%)	
	Lapatinib + letrozole, N=642	Placebo + letrozole, N=644
Any hormone	313 (49)	317 (49)
Anastrozole, exemestane or letrozole only	5 (2)	3 (<1)
Tamoxifen or toremifene only	300 (96)	302 (96)
One “other” hormone only	1 (<1)	4 (1)
Any chemotherapy	281 (44)	280 (43)
Anthracyclines only	171 (61)	172 (61)
Taxanes only	0	1 (<1)
Anthracyclines and taxanes	42 (15)	41 (15)
Other	68 (24)	66 (24)
Any biologic	2 (<1)	1 (<1)
Trastuzumab	2 (100)	1 (100)
Both hormone and chemotherapy	203 (32)	212 (33)
Prior therapy naïve	251 (39)	259 (40)
Prior adjuvant chemotherapy		
Discontinuation interval ≥6 months	629 (98)	636 (99)
Discontinuation interval <6 months	13 (2)	8 (1)
Prior adjuvant endocrine therapy		
Discontinuation interval ≥6 months	500 (78)	488 (76)
Discontinuation interval <6 months	142 (22)	156 (24)

Source: Applicant’s Table 25, Study EGF30008 Clinical Study Report, p. 104

Table 18 below describes prior treatment characteristics in the neoadjuvant or adjuvant setting in HER2-positive patients. Treatment characteristics were well-balanced among the two arms, although slightly more subjects had prior chemotherapy treatment. Only one patient in each arm was exposed to trastuzumab.

Table 18. Prior neo-adjuvant or adjuvant therapy in the HER2-positive subgroup

Prior treatment type	Number of patients (%)	
	Lapatinib + letrozole, N=642	Placebo + letrozole, N=644
Hormone therapy	313 (49)	317 (49)
Aromatase inhibitor	1 (1)	1 (1)
Tamoxifen or toremifene only	59 (53)	60 (55)
Hormone therapy	60 (54)	62 (57)
Chemotherapy	61 (55)	51 (47)
Anthracyclines only	41 (37)	38 (35)
Anthracyclines and taxanes	9 (8)	9 (8)
Trastuzumab	1 (<1)	1 (<1)

Source: Table 25, Study EGF30008 Clinical Study Report

6.3.2 Subject Disposition

The target dose of lapatinib was 1500 mg taken once daily. The median dose intensity for lapatinib was 1500.0 mg mg/m² (100% of the specified dose) and the median cumulative lapatinib dose was 417,000.0 mg (range 3000 to 2,143,500 mg). The median dose intensity for letrozole in the combination arm was the same as the monotherapy arm at 2.5 mg (100% of the specified 2.5 mg dose). The median cumulative letrozole dose was slightly higher in the combination arm (705 mg) compared with the monotherapy arm (655 mg). In the letrozole monotherapy arm, the median number of weeks of treatment was 37.57 weeks (range 0.9 to 216.1). In the letrozole combination arm, the median number of weeks of treatment was 40.29 weeks (range 0.1 to 213.6). Reasons for study discontinuation are shown in Table 19.

Of the 1286 patients enrolled, 620 were randomized with letrozole + lapatinib and 614 to letrozole + placebo. Almost half of the patients in both arms permanently discontinued treatment. The largest percentage of patients discontinued treatment due to death. Almost of a ratio of 3:1 patients discontinued for adverse events in the letrozole + lapatinib arm. More deaths occurred in the letrozole + lapatinib arm. Discontinuations due to lost to follow-up and protocol violations were fairly well-balanced between both arms.

Table 19. Disposition of subjects

Study	Letrozole + Lapatinib, N=642 (%)	Letrozole + Placebo, N=644 (%)
Randomized	642	644
Permanent discontinuation from study	298 (46)	295 (46)
Ongoing	344 (54)	349 (54)
Permanent discontinuation	298 (46)	295 (46)
Death due to disease progression	238 (37)	229 (36)
Consent withdrawn	29 (5)	34 (5)
Lost to follow up	22 (3)	26 (4)
Protocol violation	5 (<1)	3 (<1)
Other	4 (<1)	3 (<1)

Source: Table 7, Study EGF30008 Clinical Study Report

6.3.3 Treatment Compliance

Compliance, determined by the number of lapatinib tablets dispensed and taken by each patient at each monthly site visit, was recorded on the CRF.

A patient was defined as being noncompliant if they either failed to take at least 80% of his or her study treatment and/or they missed more than 14 days dosing in more than three treatment periods.

Table 20. Treatment compliance

	Compliance with Lapatinib	Compliance with Letrozole	
	Letrozole 2.5 mg + Lapatinib 1500 mg (N=642)	Letrozole 2.5 mg + Placebo (N=644)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=642)
Overall			
Percent compliance^a			
n evaluable	641	627	624
Mean % (standard deviation)	95.2 (13.47)	101.6 (31.73)	104.0 (36.35)
Median % (range)	98.8 (0 to 188)	99.6 (0 to 625)	99.7 (0 to 621)
Overall compliance^b			
Yes, n (%)	500 (78)	480 (75)	442 (69)
No, n (%)	141 (22)	154 (24)	193 (30)
Unknown, n (%)	1 (<1)	10 (2)	7 (1)

Source data: Table 6.196 and Table 6.204.

- Percentage compliance was calculated as [(total number of tablets dispensed – total number of tablets returned)/(number of days in visit interval x number of tablets prescribed per day)] x100, where number of days in visit interval = (date returned – date dispensed) +1 in visit interval.
- A subject was considered to be overall compliant if they were between 80% and 105% compliant, had not missed >14 consecutive days, and had no more than 1 visit interval where compliance was unknown.

Source: Applicant's Study EGF30008 Clinical Study Report, Table 27, p. 107.

6.4 Analysis of Primary Endpoint(s)

PFS in HER2-positive population

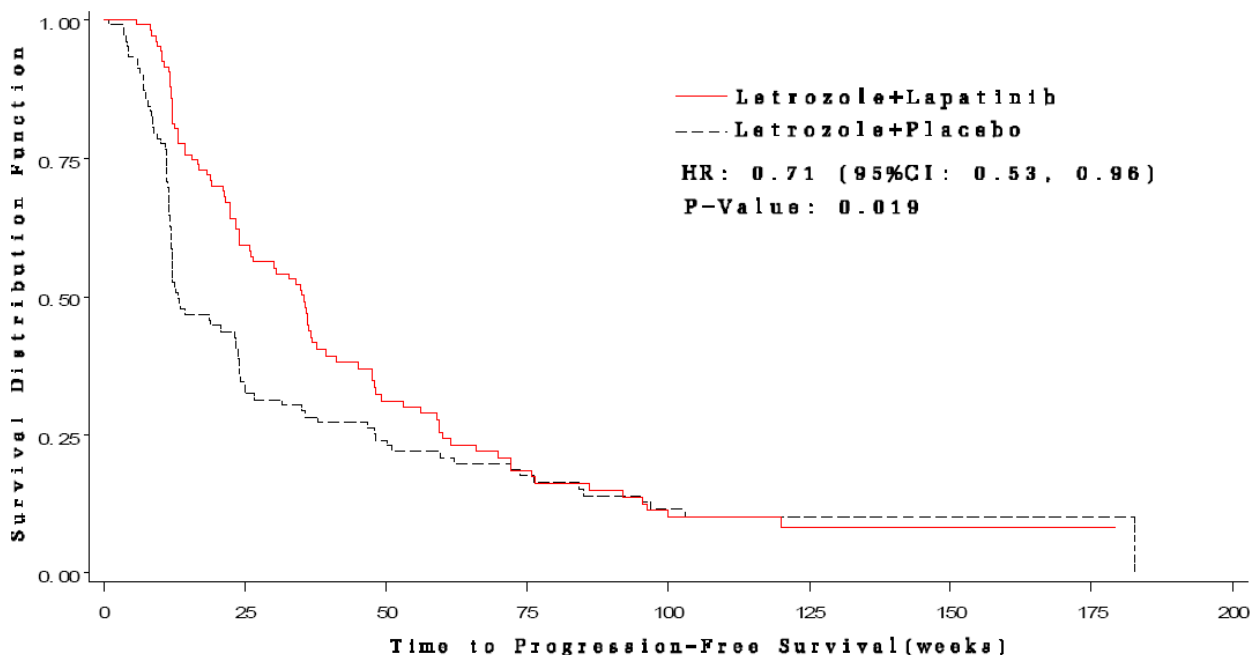
The protocol-specified primary analysis of PFS in the HER2-positive population was based upon investigator-assessed radiologic and symptomatic progressions and deaths. Median PFS was 35.4 weeks in the lapatinib plus letrozole arm and 13.0 weeks in the placebo plus letrozole arm. The hazard ratio was 0.71 and the p-value was 0.019. Table 21 depicts the PFS results based on investigator-assessed PFS. X percent of the patients had an event and 19% were censored. Figure 1 depicts the Kaplan-Meier curve of PFS.

Table 21. Investigator-assessed PFS in the HER2-positive population

	Lapatinib + Letrozole N=111 (%)	Placebo + Lapatinib N=108 (%)
PFS Events (%)	88 (79)	89 (82)
Death	3 (3)	2 (2)
PD	85 (77)	87 (81)
Censored (%)	23 (21)	19 (18)
Median PFS in weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)
p-value	0.019	
Hazard ratio (95% CI)	0.71 (0.53, 0.96)	

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 1. Kaplan-Meier Plot of Investigator Assessed PFS of the HER2-positive Population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

PFS in ITT population

The PFS in the ITT population was also based upon investigator-assessed radiologic and symptomatic progressions and deaths. Median PFS of showed of 51.7 weeks in

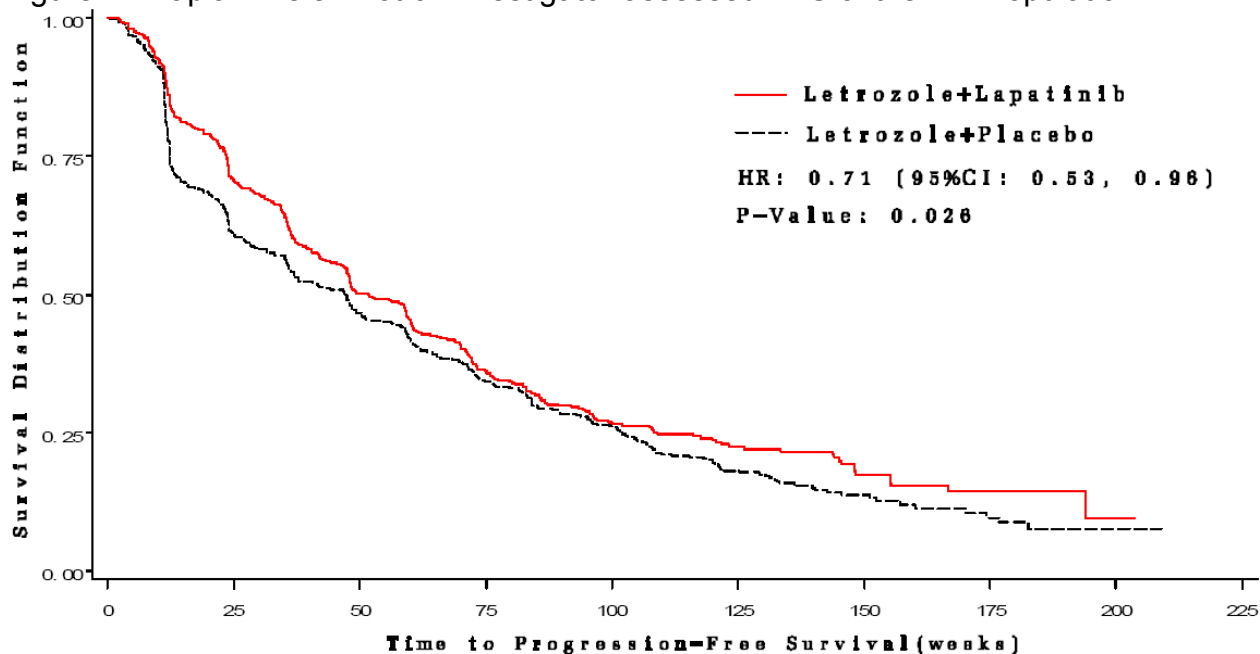
the lapatinib plus letrozole arm and 47.0 weeks in the placebo plus letrozole arm. The hazard ratio was 0.86 and the p-value was 0.026. Table 22 depicts the PFS results based on investigator-assessed PFS. X percent of the patients had an event and 19% were censored. Figure 2 depicts the Kaplan-Meier curve of PFS.

Table 22. Investigator-assessed PFS in the ITT population

	Letrozole+ Lapatinib, N=642 (%)	Placebo + Letrozole, N=644 (%)
PFS Events (%)	413 (64)	476 (74)
Death	11 (2)	18 (3)
PD	402 (63)	458 (71)
Censored (%)	229 (36)	168 (26)
Median PFS in Weeks (95% CI)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)
P-value	0.026	
Hazard Ratio (95% CI)	0.86 (0.76, 0.98)	

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 2. Kaplan-Meier Plot of Investigator-assessed PFS of the ITT Population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

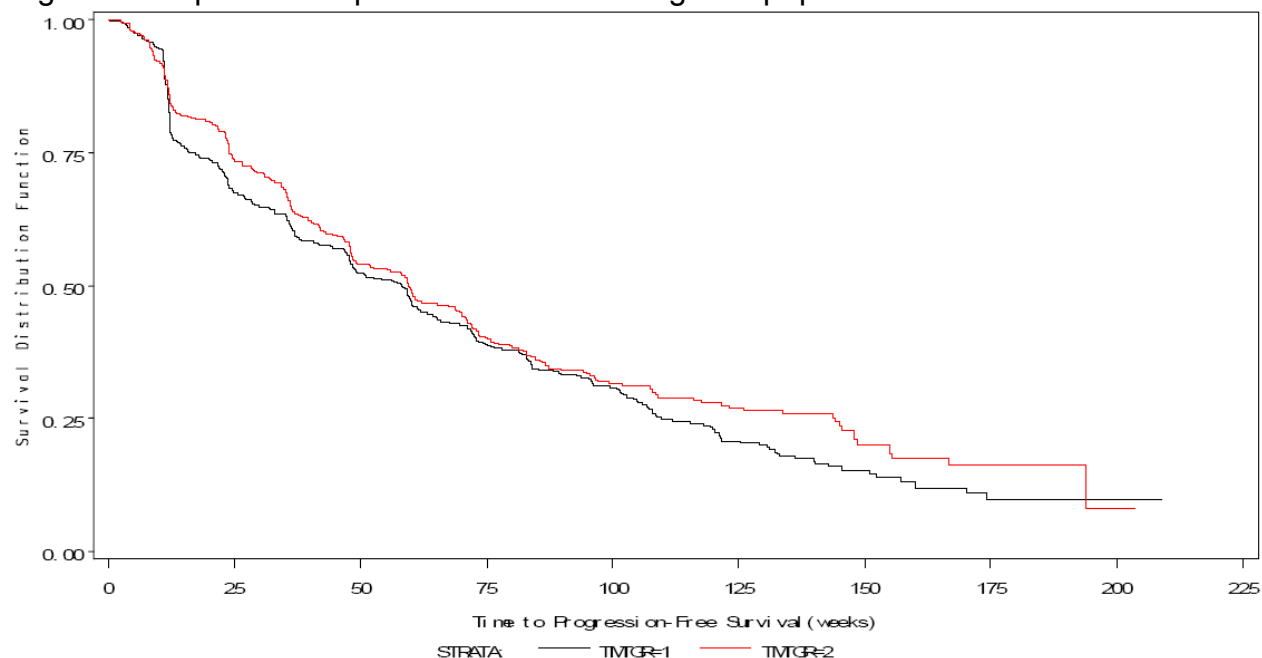
In Table 23 and Figure 3 below, the results in the HER2-positive and HER2-negative subgroups are presented. Unlike the HER2-positive subgroup, no increase in PFS was observed in the HER2-negative subgroup.

Table 23. PFS in HER2-positive and HER2-negative subgroups

	HER2-positive		HER2-negative	
	Lapatinib + Letrozole, N=111 (%)	Placebo + Letrozole, N=108 (%)	Lapatinib + Letrozole, N=478 (%)	Placebo + Letrozole, N=474 (%)
PFS events	88 (79)	89 (82)	294 (62)	342 (72)
Median PFS, weeks	35.4	13	59.7	58.3
p-value	0.019		0.188	
Hazard ratio (95% CI)	0.71 (0.53, 0.96)		0.90 (0.77, 1.05)	

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 3. Kaplan-Meier plot of PFS in HER-negative population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Reviewer's comment: Based on the results, no effect was observed in the HER2-negative subgroup with the addition of lapatinib. Therefore, the effect of lapatinib in the ITT population is derived solely from HER2-positive subgroup.

6.6 Analysis of Secondary Endpoints(s)

6.6.1 OS in the HER2-positive population

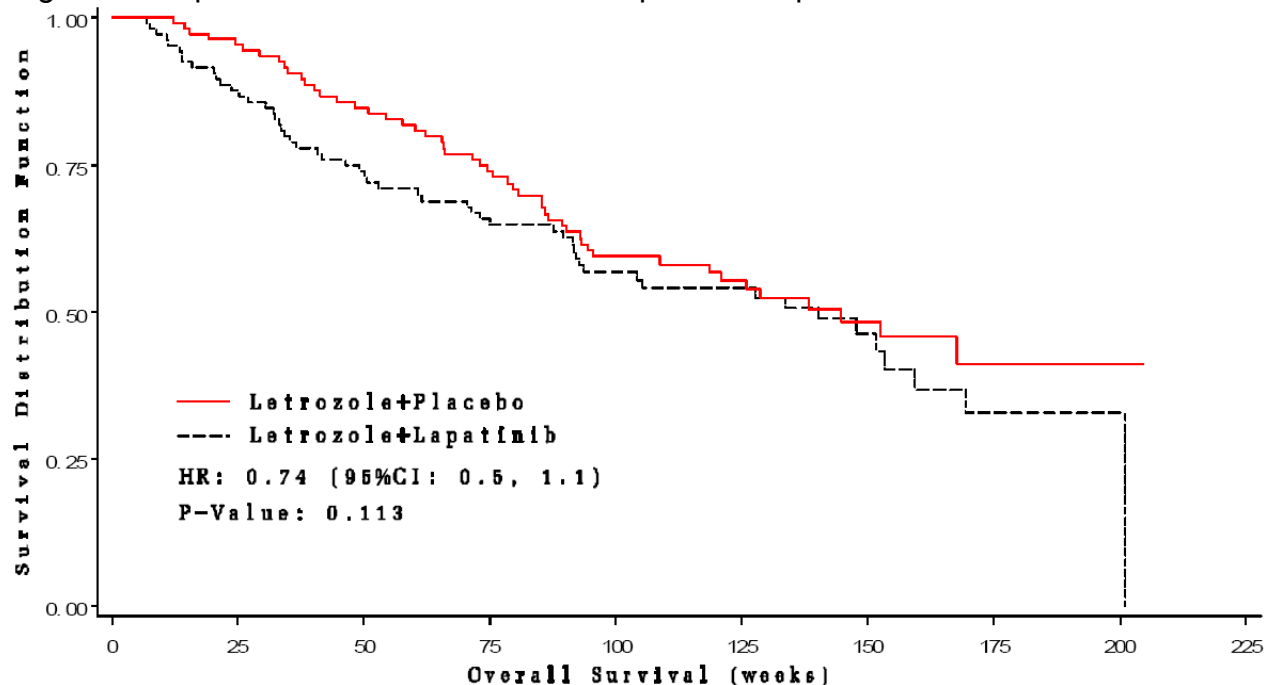
The protocol-specified secondary endpoint of OS in the HER2-positive population was based upon investigator-assessed radiologic and symptomatic progressions and deaths. Although survival data were not mature at the time of database lock, median OS was 144.7 weeks in the lapatinib plus letrozole arm and 140.3 weeks in the placebo plus letrozole arm. The hazard ratio was 0.73 and the p-value was 0.113. Table 24 depicts the OS results based on assessment by investigator. Forty-seven percent of the patients had an event and 53% were censored. Figure 4 depicts the Kaplan-Meier curve of PFS.

Table 24. OS results by assessment by investigator in HER2-positive patients

	Letrozole+ Lapatinib, N=111 (%)	Placebo + Letrozole, N=108 (%)
OS Events (%)	50 (45)	54 (50)
Censored (%)	61 (55)	54 (50)
Median OS in Weeks (95% CI)	144.7	140.3
P-value	0.113	
Hazard Ratio (95% CI)	0.73 (0.5, 1.1)	

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 4. Kaplan-Meier Plot of OS in HER2-positive Population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

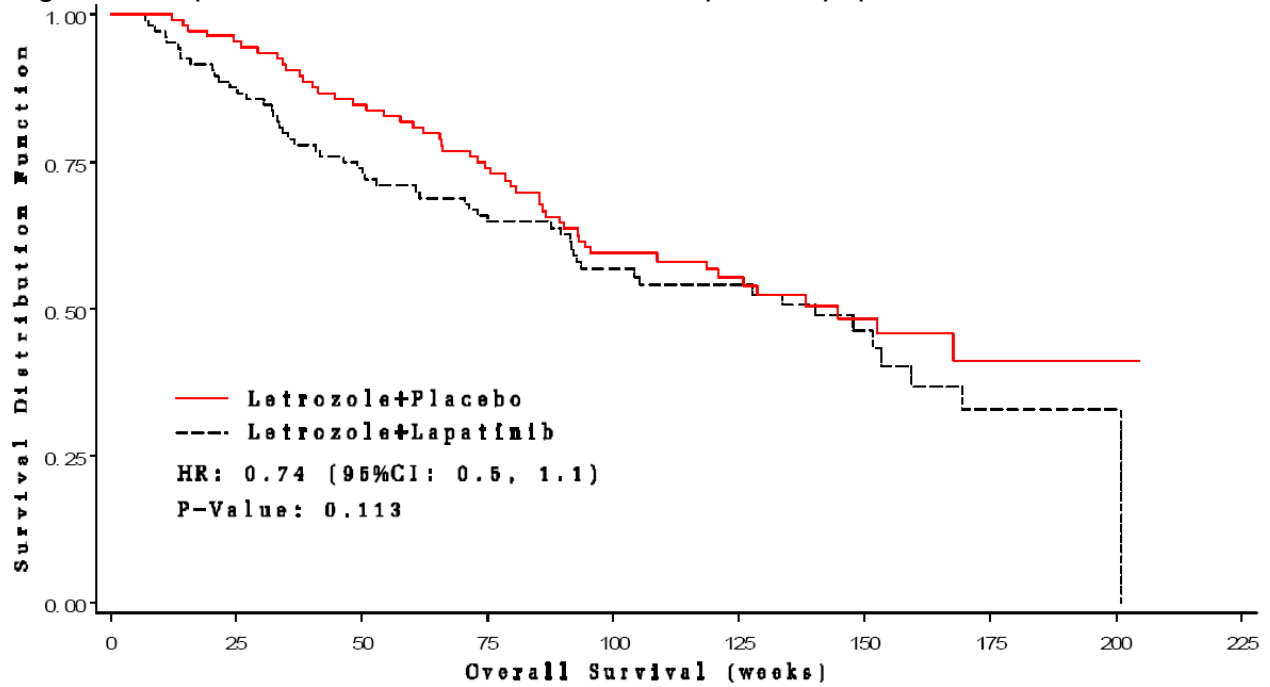
Table 25 compares the interim analysis of OS in the HER2-positive population and the ITT population. Figure 5 depicts the survival curves for OS in the HER2-positive subgroup and Figure 6 depicts the survival curves for OS in the ITT population. The difference in OS between treatment arms is very small, with a median OS difference was 4 to 6 weeks.

Table 25. OS in the HER2-positive and ITT population

	HER2-positive		HER2-negative		ITT	
	Lapatinib + letrozole, N=111	Placebo + letrozole, N=108	Lapatinib + letrozole, N=478	Placebo + letrozole, N=474	Placebo + letrozole, N=474	Lapatinib + letrozole, N=478
OS events (%)	50 (45)	54 (50)	174 (36)	153 (32)	234 (36)	240 (37)
Median OS (weeks)	144.7	140.3	174.4	179.7	176.3	170.9
p-value	0.113		0.193		0.915	
Hazard ratio (95% CI)	0.73 (0.5, 1.1)		1.15 (0.9, 1.4)		1.01 (0.8, 1.2)	

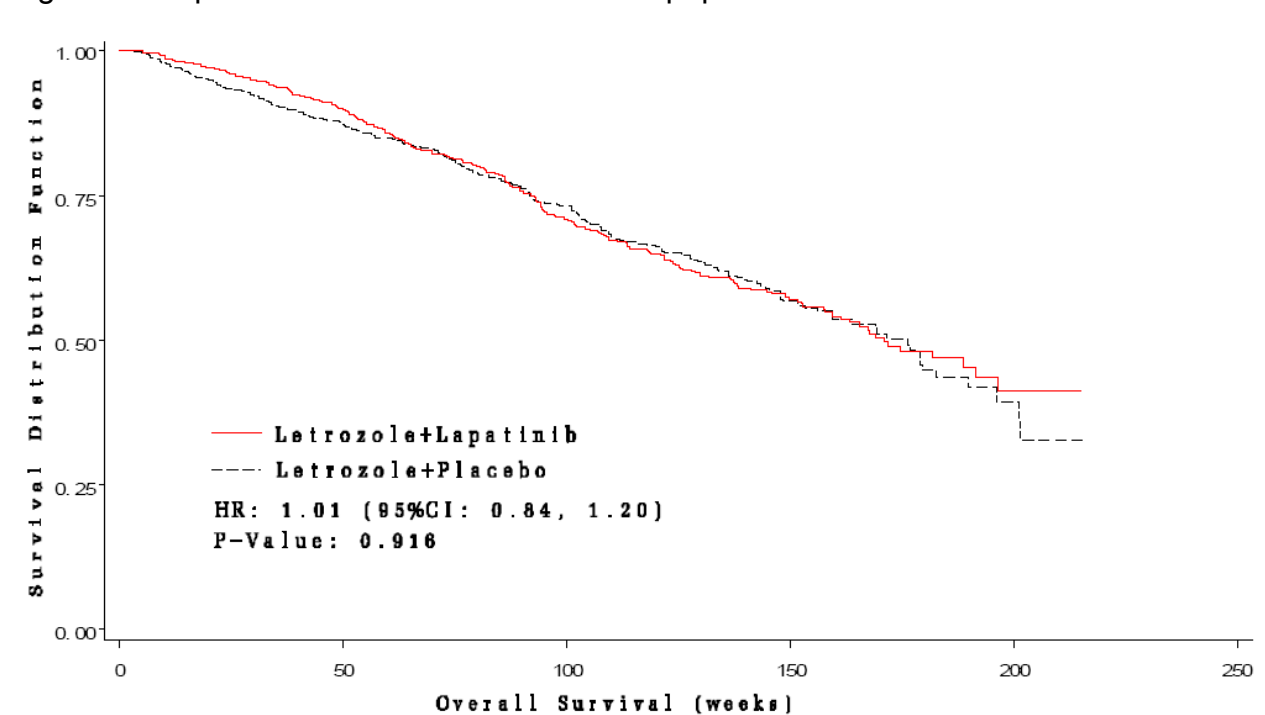
Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 5. Kaplan-Meier estimate of OS in HER2-positive population



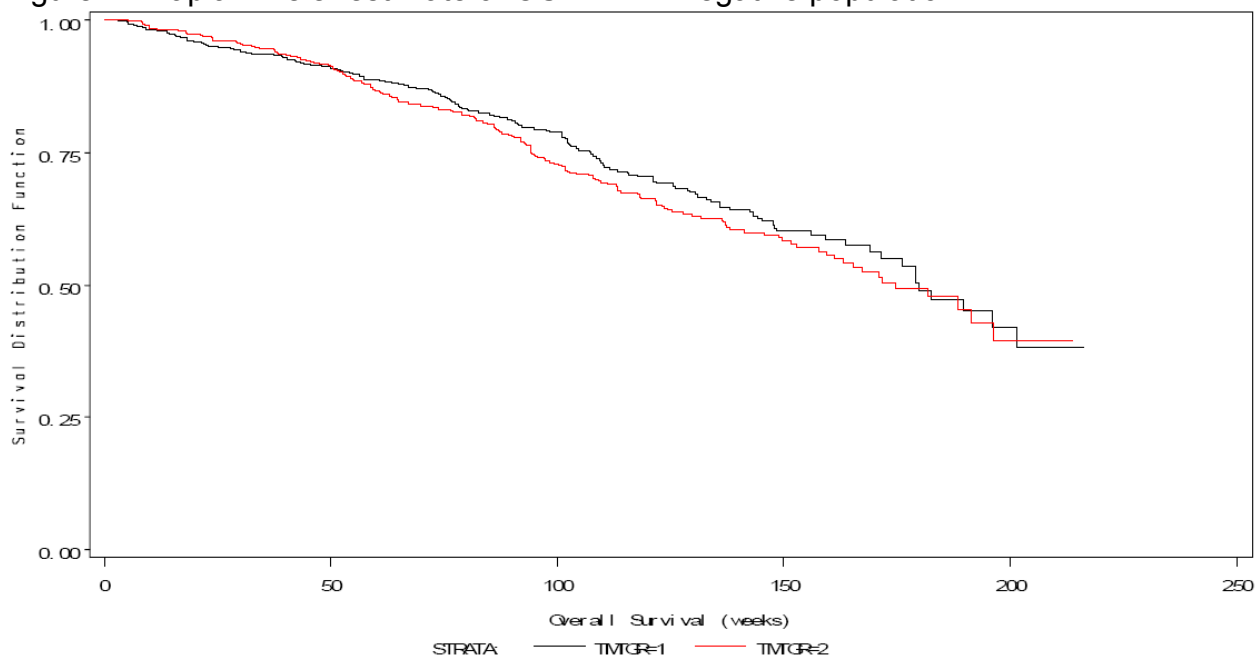
Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 6. Kaplan-Meier estimate of OS in ITT population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Figure 7. Kaplan-Meier estimate of OS in HER-negative population



Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

6.7 Other Endpoints

Best overall response

Objective tumor response (best overall response) evaluated by assessment by investigator showed that the combination of lapatinib and letrozole in patients with HER2-positive metastatic breast cancer has an increased overall response rate compared to placebo plus letrozole (27.9% versus 14.8%, $p=0.021$). The median duration of response was 84.4 weeks in the placebo plus letrozole arm compared to 47.4 weeks in the lapatinib plus letrozole arm.

Tumor response, as assessed by investigator is presented below:

Table 26. Overall Response Rate (ORR) in HER2-Positive Subgroup

	Lapatinib + letrozole, n=654 (%)	Placebo + letrozole, n=624 (%)
Best response		
Complete response	4 (4)	5 (5)
Partial response	12 (11)	26 (23)
Stable disease	35 (32)	44 (40)
Progressive disease	49 (45)	30 (27)
Unknown	8 (7)	6 (5)
ORR (95% CI)	14.8 (8.7, 22.9)	27.9 (19.8, 37.2)

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Reviewer's comment: Bone scans were required for confirmation of a CR or PR, regardless of the presence of bone disease at baseline.

Sensitivity analyses

As shown in Table 27. PFS Sensitivity Analyses, several sensitivity analyses were performed to explore the PFS effect with different assessments such as exclusion of symptomatic progressions, bone disease only at baseline excluding or combining both categories. Symptomatic progressions were excluded because these are subjective assessments, are imprecise, and subject to bias. These assessments cannot be confirmed by the FDA reviewer or the IRC and are not considered by RECIST criteria. Furthermore, The PFS results still demonstrate improvement with the combination of lapatinib plus letrozole treatment, with a difference in median PFS of 3 to 4 months.

Table 27. PFS Sensitivity Analyses

	Median PFS difference (weeks)	Hazard ratio
Exclusion of symptomatic progressions (1)	12.5	0.76
Exclusion of only bone disease at baseline (2)	21.4	0.73
Exclusion of 1 and 2	12.3	0.78

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

Reviewer's comment: Despite the exclusion of symptomatic progressions and bone only disease at baseline, the sensitivity analyses confirm the robustness of the PFS in the HER2-positive population. The Applicant stated in its protocol that response evaluations were made according to the RECIST criteria, but these evaluations are not in accordance with RECIST.

6.8 Subpopulations

PFS in the HER-negative Population

Please see Section 6.5 for this subgroup analysis.

6.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.11 Additional Efficacy Issues/Analyses

An independent review committee (IRC) was convened as supportive analysis of PFS in the HER2-positive and HER2-negative populations. Median PFS was 60 weeks in the lapatinib plus letrozole arm and 35.4 weeks in the placebo plus letrozole arm. The hazard ratio was 0.63 and the p-value was 0.023. Forty-six percent of the patients had an event and 54% were censored. In the HER2-negative population, the median PFS was 122.0 weeks in the lapatinib plus letrozole arm and 108.6 weeks in the placebo plus letrozole arm. The hazard ratio was 0.98 and the p-value was 0.866. Thirty-four percent of patients had an event and 66% were censored. Table 28 depicts the PFS results based on IRC-assessed PFS.

Table 28. IRC-Assessed PFS Results in HER2-positive and HER2-negative Populations

	ITT		HER2+		HER2-	
	Letrozole+ Placebo (N=642)	Letrozole+ Lapatinib (n=644)	Letrozole+ Placebo (N=108)	Letrozole+ Lapatinib (n=111)	Letrozole+ Placebo (N=474)	Letrozole+ Lapatinib (n=478)
PFS Events (%)	243 (38)	223 (35)	53 (49)	49 (44)	167 (35)	159 (33)
Median of PFS in Weeks (95% CI)	95.9 (75.3, 114.3)	107.6 (86.0, 131.6)	35.4 (16.0, 61.1)	60.0 (42.3, 82.6)	108.6 (91.3, 139.9)	122.0 (95.6, 148.0)
Log-rank p-value	0.198		0.023		0.866	
Hazard Ratio (95% CI)	0.89 (0.74, 1.07)		0.63 (0.43, 0.94)		0.98 (0.79, 1.22)	

Source: Qiang (Casey) Xu, Ph.D., Statistical Reviewer

7 Review of Safety

The safety analysis of lapatinib and letrozole combination regimen in metastatic breast cancer was performed by primary review of patients from study EGF30008. Study EGF30008 randomized patients to receive lapatinib + letrozole or placebo + letrozole. The safety population consisted of patients with 1278 subjects (ITT population) with hormone receptor positive (ER-positive and/or PR-positive) locally advanced or metastatic breast cancer, 624 subjects who received letrozole plus placebo and 654 subjects who received letrozole plus lapatinib. It comprised all subjects who received at least one dose of study treatment and was based on actual treatment received rather than assigned treatment.

The data submitted by the Applicant as data sets and select case report forms were reviewed and compared with applicant's analysis and conclusions. Any discrepancies that were identified were addressed below.

Safety Summary

The safety of lapatinib plus letrozole at the proposed dose and schedule was assessed by review of Study EGF30008. The safety population consisted of 1278 subjects with previously untreated hormone receptor-positive metastatic breast cancer who were randomized and received at least dose of study treatment and was based on actual treatment received rather than the assigned treatment. Thus, the safety population included 654 subjects in the lapatinib plus letrozole arm and 624 subjects in the placebo plus letrozole arm. In the lapatinib plus letrozole arm, subjects received lapatinib 1500 mg daily plus letrozole 2.5 mg daily and in the placebo plus letrozole arm, subjects received placebo and letrozole 2.5 mg daily.

The extent and duration of exposures of the lapatinib plus letrozole, for 654 subjects who received at least one dose of therapy during the study, was adequate for the assessment of safety in this subject population. However, the numbers of adverse event related treatment terminations (14 vs. 5%), dose reductions (11% for lapatinib) and dose delays (33% for lapatinib) all suggested more toxicity in the lapatinib plus letrozole arm. As a result of the toxicity profile of this combination regimen, subjects on average received only about 80% of the subjects were compliant lapatinib. Despite the higher percentage of dose reductions, treatment terminations in the combination arm, the subjects on the lapatinib plus letrozole arm however received 97% of there intended dose intensity. Letrozole exposure was equivalent in both arms.

The safety profile of lapatinib has been previously described in the Tykerb label. Using National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for grading, adverse events were observed in nearly all subjects enrolled in EGF30008. The adverse events occurring in at 10% of patients in EGF30008 trial included: diarrhea, rash, nausea and fatigue occurred in decreasing order at $\geq 20\%$ frequency in the lapatinib plus letrozole arm. Grade 3 and 4 adverse events occurred more frequently in the lapatinib plus letrozole arm with a similar percentage of patients experiencing grade 4 toxicities (5% in the letrozole plus lapatinib arm and 3% in the placebo plus letrozole arm). Diarrhea occurred in the greatest frequency of grade 3-4 severity in patients in the lapatinib plus letrozole arm. Hepatotoxicity was more frequently observed in the lapatinib plus letrozole arm (16% versus 9%). Cardiac toxicity, specifically, left ventricular ejection fraction occurred in the same percentage of patients (2%) in both arms. However, these results are inconclusive as many LVEF assessments using MUGA and echocardiograms were missing. Pertaining to liver function tests, grade 3-4 ALT and AST toxicities occurred more frequently in the lapatinib plus letrozole arm (5-6% versus <1-3%).

Review of the safety database revealed that this trial did not have additional safety signals; however, the evaluation of LVEF is inconclusive. The aforementioned adverse events are consistent with the initial approval of lapatinib.

In the 120-day safety update, analysis of adverse events did not reveal any new findings.

7.1 Methods

The safety review consisted of reviewing datasets, clinical study reports, and relevant case report forms. The following datasets were analyzed in detail: *ae.xpt*, *death.xpt*, *ecg.xpt*, *scnecho.xpt*, *scnmuga.xpt*, *trlmed.xpt*, *tmtlog.xpt*, and *vital.xpt*.

To identify any errors or discrepancies in our analysis and that of the Sponsor, case report forms were selected and reviewed.

Division of Scientific Investigations (DSI) was consulted and three sites were inspected (refer to Section 3.1, "Submission and Data Integrity"). No significant findings affecting our analysis were noted.

Overall, the methods for evaluating the safety of the subjects in study EGF30008 were adequate.

7.1.1 Clinical Trials Used to Evaluate Safety

The focus of the efficacy review will be evaluation of the pivotal phase 3 study submitted by the Applicant, Study EGF30008:

Table 29. Clinical Trial Providing Safety Data for Lapatinib in Metastatic Breast Cancer

Study/Document No.	Protocol Title	Drug Regimen/s	Number of Subjects
Pivotal Study			
EGF30008	A randomized, double-blind, placebo-controlled, multicenter, phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer	Letrozole 2.5 mg once daily + lapatinib 1500 mg once daily OR Letrozole 2.5 mg once daily + placebo	Total: 1286 Letrozole + lapatinib: 654 Letrozole + placebo: 624

In Study EGF30008, a total of 1286 subjects were enrolled into the study; 644 subjects to letrozole plus placebo treatment and 642 subjects to letrozole plus lapatinib treatment (ITT population). The safety population in Study EGF30008 comprised all subjects who received at least 1 dose of study treatment and was based on the actual treatment received rather than the assigned treatment. Thus, the safety population included 1278 subjects; 624 subjects who received letrozole plus placebo and 654 subjects who received letrozole plus lapatinib. The difference between the ITT (N=1286) and Safety (N=1278) populations as due to 8 subjects who did not receive treatment (6 subjects in the letrozole plus placebo group and 2 subjects in the letrozole plus lapatinib group). The number of subjects in the letrozole plus placebo group in the safety population was 624 because there were 14 subjects who were randomized to receive letrozole plus placebo but who actually received letrozole plus lapatinib and 6 subjects who were randomized to letrozole plus placebo group but did not receive any treatment (N=644). The number of subjects in the letrozole plus lapatinib group in the safety population was 654 because 2 subjects were randomized to letrozole plus lapatinib group but did not receive any treatment, and 14 subjects who were randomized to receive letrozole plus placebo actually received letrozole plus lapatinib (N=654). Nine subjects who were randomized to receive letrozole plus lapatinib actually received letrozole plus placebo; however, as these subjects received at least 1 dose of lapatinib they are included in the letrozole plus lapatinib group for the safety population.

7.1.2 Categorization of Adverse Events

All AEs, regardless of relationship to study treatment, were recorded from the first dose of study treatment to 30 days after the last dose of study treatment for study EGF30008, respectively. The toxicity was graded using NCI CTCAE version 3.0 and the relationship to study treatment was documented. All grade 3-4 adverse events that were considered related to study medication were followed until resolution of the event to grade 2 or less. Any AE that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, was permanently or significantly disabling or incapacitating, or was a congenital anomaly or birth defect was considered a serious adverse event (SAE). All adverse events that happened after treatment initiation were labeled as treatment emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (MedDRA) version 11.

Reviewer's comment: The toxicity grading and reporting of AEs for study EGF30008 were sufficient for evaluating the toxicity profile of lapatinib.

7.2 Adequacy of Safety Assessments

Study EGF30008 was a pivotal phase III study with an adequate number of enrolled subjects. Subjects were randomized to lapatinib and letrozole or placebo and letrozole, which is an approved treatment for breast cancer. Additionally, data from another study investigating the use of lapatinib and letrozole was provided.

A review of a representative number of case report forms to evaluate choice of MedDRA

Preferred Terms was conducted. The applicant's categorization of events with regard to choice of MedDRA preferred terms was accurate. No safety signals were related to gender or race.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The target doses were 1500 mg once daily for lapatinib and 2.5 mg once daily for letrozole in the lapatinib and letrozole combination arm. In the placebo and letrozole arm, the target dose was 2.5 mg once daily for letrozole.

The decreased dose levels due to toxicity were permitted for hematologic and nonhematologic toxicity. A subject could have a maximum of one dose reduction for lapatinib only during the study, regardless the type of toxicity. If a NCI CTCAE Grade 3 or 4 treatment-related event, other than left ventricular systolic dysfunction, interstitial pneumonitis or hepatotoxicity, occurred, the investigator discussed with the Medical Monitor whether a reduction of dose was appropriate. The reduced dose of study therapy was 5 tablets (1250 mg of lapatinib) once daily.

No dose reductions of letrozole were allowed.

Data for exposure is provided below, using the Applicant's analysis. The patient population analyzed was all subjects who received at least one dose of study drug, 654 subjects in the lapatinib and letrozole arm and 624 subjects in the placebo and letrozole arm.

Table 30. Summary of Exposure to Lapatinib and Letrozole

	Exposure to Lapatinib	Exposure to Letrozole	
	Lapatinib + Letrozole	Letrozole + Placebo	Letrozole + Lapatinib
Duration of treatment period (weeks)			
Mean (standard deviation)	55.10 (47.034)	54.53 (48.313)	55.22 (46.984)
Median (range)	40.14 (0.3 to 213.6)	37.57 (0.9 to 216.1)	40.29 (0.1 to 213.6)
Daily dose (mg)			
Mean (standard deviation)	1461.6 (102.3)	2.49 (0.031)	2.49 (0.052)
Median (range)	1500.0 (672 to 1500)	2.50 (2.1 to 2.5)	2.50 (1.8 to 2.5)
Cumulative dose (mg)			
Mean (standard deviation)	564,683.1 (482,387.55)	951.22 (842.646)	961.81 (818.262)
Median (range)	417,000.0 (3000 to 2,143,500)	655.00 (15.0 to 3780.0)	705.00 (2.5 to 3737.5)

Source: Table 56, Applicant's Study EGF30008 Clinical Study Report

Reviewer's comment: Review of *tmt.xpt* reveals that dose reductions below 1250 mg for lapatinib occurred in some subjects.

Treatment discontinuation

Ninety-five subjects (15%) in the lapatinib and letrozole arm had an adverse event that led to treatment termination compared with 35 (6%) in the placebo and letrozole arm. The most common adverse event leading to discontinuation in the lapatinib and letrozole arm was diarrhea in 24 (4%) of subjects, followed by vomiting (2%), nausea (1).

Table 31. Adverse events leading to discontinuation of investigational product of more than one subject in either treatment group

MedDRA preferred term	Number (%) of subjects [n related events]	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any AE leading to discontinuation ^{a, b}	35 (6) [19]	95 (15) [72]
Diarrhea	2 (<1) [2]	24 (4) [24]
Vomiting	2 (<1) [1]	11 (2) [10]
Nausea	0	9 (1) [9]
Rash	1 (<1) [1]	6 (<1) [5]
ALT increased	1 (<1) [1]	4 (<1) [4]
Anorexia	0	4 (<1) [3]
Ejection fraction decreased	2 (<1) [2]	4 (<1) [4]
Abdominal pain	0	3 (<1) [2]
AST increased	1 (<1) [1]	3 (<1) [3]
Asthenia	0	2 (<1) [2]
Blood alkaline phosphatase increased	0	2 (<1) [2]
Dizziness	0	2 (<1) [2]
Dyspnea	1 (<1) [1]	2 (<1) [0]
Headache	0	2 (<1) [2]
Hepatic enzyme increased	0	2 (<1) [2]
Left ventricular dysfunction	2 (<1) [2]	2 (<1) [2]
Lethargy	0	2 (<1) [2]
Pain	1 (<1) [1]	2 (<1) [2]
Paronychia	0	2 (<1) [2]
Spinal compression fracture	0	2 (<1) [0]
Hypercreatininemia	2 (<1) [0]	0

Source data: Table 8.18 and Table 8.92.

- a. The primary reason for discontinuation from treatment was not listed as AE on the case report form for some subjects.
- b. A subject could have had more than 1 event leading to discontinuation of study treatment.

Source: Applicant's Table 66, Study EGF30008 Clinical Study Report

Reviewer's comment: Of significance, no difference between both arms was observed for the cardiac and hepatic adverse events.

Dose reductions

Seventy-seven (11%) had at least one dose reduction in the 654 subjects that were randomized to lapatinib and letrozole arm. Almost all of these patients (79%) had a dose reduction due to a nonhematological toxicity. Table 32 below provides a summary of the number of subjects who had a dose reduction in the study. Per protocol, letrozole dose was not reduced in subjects, only the dose of lapatinib could be reduced.

Table 32. Dose reduction analysis for lapatinib

Number of dose reductions	Number of patients, N=654 (%)
1	71 (11)
2	3 (<1)
3	2 (<1)
4	1 (<1)
Any dose reduction	77 (12)
Reasons for dose reduction^a	
Hematological toxicity	5 (6)
Nonhematological toxicity	66 (79)
Noncompliance	6 (7)
Other	7 (8)

^a Subjects could be counted for more than one reason for dose reduction.
 Source: Applicant's Table 67, Study EGF30008 Clinical Study Report

Reviewer's comment: Reviewer's analysis of the Applicant's data revealed that the analyses were similar.

Dose delay

Data on cycle delays and dose reductions is provided by the Applicant in Section 5.4.2.6. Dose delays at some point during therapy were observed in one-third of the subjects in the lapatinib plus letrozole group. Most of these subjects had one dose delay and the primary reasons were non-hematological toxicity (43%) and "other" (39%). Sixteen percent of subjects had a dose delay of their letrozole treatment, 18% in the lapatinib plus letrozole arm, and 13% in the letrozole plus placebo arm. Letrozole dose delays were primarily due to "other" reasons (57%).

Table 33. Dose Delay

MedDRA preferred term	Number (%) of subjects		
	Dose delay for Lapatinib	Dose delay for Letrozole	
	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any delay ^a	215 (33)	82 (13)	120 (18)
Total number of dose delays	441	185	253
Number of dose delays			
0	439 (67)	542 (87)	534 (82)
1	124 (19)	52 (8)	71 (11)
2	44 (7)	14 (2)	26 (4)
3	22 (3)	6 (<1)	9 (1)
4	9 (1)	1 (<1)	7 (1)
5	4 (<1)	1 (<1)	0
6	4 (<1)	4 (<1)	0
7	3 (<1)	1 (<1)	1 (<1)
8 or more	5 (<1)	3 (<1)	6 (<1)
Reasons for delays ^b			
Hematological toxicity	26 (6)	5 (3)	6 (2)
Non-hematological toxicity	188 (43)	32 (17)	65 (26)
Subject noncompliant	55 (12)	39 (21)	40 (16)
Other	172 (39)	109 (59)	142 (56)

Source data: [Table 8.7](#) and [Table 8.9](#).

- If a subject had periodic dose delays over multiple visit periods they could still be considered compliant with treatment. A subject was considered to be overall compliant if they were between 80% and 105% compliant, had not missed >14 consecutive days, and had no more than 1 visit interval where compliance was unknown.
- Subjects were counted once for each dose delay reason recorded (could have more than 1). The number of total dose delay was used as the denominator.

Source: Table 68, Applicant's Study EGF30008 Clinical Study Report

Reviewer's comment: Reviewer's analysis of the Applicant's data revealed that the analyses were similar.

Demographics

Using *ae.xpt*, *ramos.xpt*, and *demog.xpt*, the demographics of the safety population of Study EGF30008 were analyzed. Study EGF30008 was an international, multicenter study that treated adult females (≥ 18 years) with histologically-proven invasive breast cancer with stage IV disease. This study was performed in 29 countries at 212 centers. The country with the largest number of subjects treated was the United States, with 383 (30%) subjects. Evaluating ethnicity as a variable, the following ethnicities were captured in the study, with the White characterizing the largest group: 1082 (85%) White, 98 (8%) American Hispanic, 60 (5%) Asian, 27 (2%) Black, and 11 (<1%) other. Using the *ae.xpt* dataset to evaluate safety according to age, 703 patients in Study EGF30008 were < 65 years and 575 patients were ≥ 65 years. One hundred sixty-eight (13%) patients were ≥ 75 years.

Table 34. Demographics of the safety population

	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)	Total (N=1278)
Age (years)^a			
Mean (standard deviation)	63.2 (9.95)	63.0 (9.70)	63.1 (9.82)
Median (range)	63.0 (35 to 95)	62.0 (31 to 94)	63.0 (31 to 95)
Age ranges, n (%)			
<65 years of age	344 (55)	359 (55)	703 (55)
≥65 years of age	280 (45)	295 (45)	575 (45)
≥75 years of age	88 (14)	80 (12)	168 (13)
Race, n (%)			
White	539 (86)	543 (83)	1082 (85)
American Hispanic	43 (7)	55 (8)	98 (8)
Asian	30 (5)	30 (5)	60 (5)
Black	10 (2)	17 (3)	27 (2)
Other	2 (<1)	9 (1)	11 (<1)

Source data: Study EGF30008, [Table 8.207](#).

a. Age was calculated based on the date of screening visit.

Reviewer's comment: Both arms were well-balanced demographically and a greater percentage of patients were younger than 65 years in both arms.

7.2.2 Explorations for Dose Response

Study EGF30008 was a fixed-dose study, allowing for dose reductions only for toxicity. Please refer for clinical pharmacology review for more details.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical studies submitted to NDA 22-059 were reviewed previously. Please refer to pharmacology and toxicology review for NDA 22-059 for more details.

7.2.4 Routine Clinical Testing

Subjects were evaluated by physical exams, vital signs, symptom histories for adverse events, CBCs, serum chemistries, and bilirubin fractionation if bilirubin was >2 x ULN every four weeks. An echocardiogram is to be performed every eight weeks. If the investigator feels the echocardiogram could not be performed or was not conclusive to evaluate left ventricular cardiac ejection fraction, a MUGA scan should be done. If a subject has been on study > 108 weeks, these assessments, including an echocardiogram, will be performed every 12 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolism, clearance and drug-drug interactions were reviewed previously in NDA 22-059. Please see clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Lapatinib has a “Black Box Warning” for hepatotoxicity. The applicant provided a detailed analysis of hepatobiliary events in the lapatinib clinical program, during treatment and post-treatment. Imatinib (Gleevec) has a “Warnings and Precautions” statement with regard to hepatotoxicity.

7.3 Major Safety Results

The primary analysis will be based on Study EGF30008 as it provides a direct comparison of adverse reactions expected with lapatinib plus letrozole versus letrozole alone. The analysis will rely on the Applicant’s study report, as well as independent analysis of the provided datasets as indicated. Safety evaluations included adverse events, clinical laboratory tests, vital signs, ECOG performance status, electrocardiograms, and echocardiograms or MUGA scans.

The safety population was based on actual treatment received and included all patients who received at least one dose of study medication. This included 1278 subjects, 624 who had received letrozole + placebo and 654 who had received letrozole + lapatinib. The difference between the ITT (N=1286) and safety (N=1278) populations was due to eight subjects who did not received treatment (six subjects in the letrozole + placebo and 2 subjects in the letrozole + lapatinib group). In the letrozole plus placebo group in the safety population (SP), the number of subjects was 624 because there were 14 subjects who were randomized to receive letrozole plus placebo but who actually received letrozole plus lapatinib and six subjects who were randomized to letrozole plus placebo group but did not receive any treatment (N=644). The number of subjects in the letrozole plus lapatinib group was 654 because two subjects were randomized to letrozole plus lapatinib group but did not receive any treatment, and 14 subjects who were randomized to receive letrozole plus placebo actually received letrozole plus lapatinib (N=654). Nine subjects who were randomized to receive letrozole plus lapatinib actually received letrozole plus placebo; however, as these subjects received at least 1 dose of lapatinib they are included in the letrozole plus lapatinib group for the safety analysis.

The table below categorized the types of adverse events that occurred throughout the study, in terms of severity. More adverse events occurred in the treatment arm.

Table 35. Subjects with adverse events

Category of adverse event	Letrozole + placebo, N=624	Letrozole + lapatinib, N=654
All AEs	536 (86)	628 (96)
Fatal AEs	8 (1)	8 (1)
SAEs	94 (15)	144 (22)
AEs leading to permanent discontinuation of study treatment^a	35 (6)	95 (15)
AEs of special interest^b	228 (37)	533 (81)

Source: Reviewer's table using *ae.xpt*

a. Note the numbers of subjects with AEs leading to permanent discontinuation of study treatment presented in this table are different from those presented in Table 45. This is because the primary reason for discontinuation from treatment was not listed as AE on the case report form for some subjects.

b. Included rash, diarrhea, nail changes, hepatotoxicity, LVEF decreases, and pulmonary events (AEs thought to be associated with EGFR and HER2 inhibition).

Reviewer's comment: A greater number of serious adverse events occurred in the treatment arm, although the adverse events resulting in death were similar in both arms. These will be discussed in detail in subsequent sections.

7.3.1 Deaths

Consistent with the Applicant's analysis, the *death.xpt* and *ae.xpt* files were analyzed in addition to the relevant CRFs and narratives. Using *death.xpt*, 474 subjects were identified as having died as of the database lock, 243 (37%) in the lapatinib and letrozole arm, and 231 (37%) in the placebo and letrozole arm. The majority of deaths were attributed to disease progression; however, seven (1%) of the deaths in the lapatinib and letrozole arm and six (1%) of the deaths in the placebo and letrozole arm were attributed to a serious adverse event.

7.3.2 Analysis of death cases

As shown in the table below, a total of 231 subjects in the letrozole + placebo arm and 243 in the letrozole + lapatinib arm. The majority of deaths were due to disease progression. According to cause of death, the percentages of deaths were the same in both arms. A further description of the fatal outcomes are presented following Table 36.

Table 36. Deaths During Treatment for Study EGF30008

MedDRA preferred term	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=652)
Subjects who died ^{a, b}	231 (37)	243 (37)
Primary cause of death		
Progression of cancer	217 (35)	228 (35)
Fatal AE	6 (<1)	7 (1)
Other	8 (1) ^c	8 (1) ^d

Source data: Table 8.335 and Attachment 2 (Listing 7.17).

- In the ITT population, 234 subjects and 240 subjects died in the letrozole plus placebo and letrozole plus lapatinib groups, respectively. The difference in the number of subjects is due to 3 subjects who died in the letrozole plus placebo group but who received lapatinib and have thus been presented according to the treatment they actually received.
- The total number of deaths are presented (not just subjects who were listed as withdrawing from study treatment due to death).
- This category included: 2 subjects for which the cause of death was unknown (Subject (b) (6) and Subject (b) (6)); 1 subject who had respiratory distress (Subject (b) (6)); 1 subject who moved out of the area (Subject (b) (6)); 1 subject who had aspiration pneumonia (Subject (b) (6)); 1 subject who had acute cardiac insufficiency (Subject (b) (6)); 1 subject who had a stroke (Subject (b) (6)), and 1 subject who died following a car accident (Subject (b) (6)).
- This category included: 1 subject who had a cerebral vascular accident (Subject (b) (6)); 1 subject who had pulmonary emphysema (Subject (b) (6)); 1 subject with complications secondary to MBC (Subject (b) (6)); 1 subject who had bronchopneumonia (Subject (b) (6)); 1 subject who had a cardiopulmonary arrest (Subject (b) (6)); 1 subject who had obstructive uropathy (Subject (b) (6)); 1 subject who had a cardiorespiratory arrest (Subject (b) (6)), and 1 subject who had a possible heart attack (Subject (b) (6)).

Source: Table 61, Applicant's Study EGF30008 Clinical Study Report and extracted from death.xpt.

Reviewer's comment: Analysis of the causes of the death under "other" as noted in Table 36 reveals that the causes of deaths varied and all, except for two, occurred post 30-days after study drug discontinuation. Detailed review of the CRFs yielded no pattern in the cause of death and is consistent with the Sponsor's attribution. There appears to be no causal association between treatment and causes of death. The causes of death in two cases in which the subjects were receiving study medication at the time death were car accident and emphysema. In the case of the car accident, the 71 year-old subject had been on study for more than 40 months at the time of death. Medical history included hypertension and hypothyroidism. The second subject aged 71 years had a history of dyspnea as stated on the CRF. The subject was treated with Spiriva, Atrovent, Pulmicort, Terbasmin (terbutaline), Anasma (fluticasone), prednisone. Emphysema is listed as the cause of death on the CRF, and the patient had a baseline dyspnea grade 2 at the time of study entry.

In the 120-day safety update, the incidence of death was 44% in both groups as of February 3, 2009. Eighty-seven deaths occurred from June 3, 2008 to February 3,

2009, 43 in the lapatinib plus letrozole arm and 44 in the placebo plus letrozole arm. The primary cause of death was disease progression in both arms.

Narrative summaries of deaths not due to progression are presented below and a tabulated list is presented in Table 37:

Placebo plus letrozole arm

Subject (b) (6) was a 69-year-old woman who was randomized to placebo and letrozole. Medical conditions included atrial fibrillation, disease progression, hypercalcemia, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, and pleural effusion. The subject received oral investigational product from (b) (6) to (b) (6) and oral letrozole at 2.5 mg per day from (b) (6) to (b) (6). On an unknown date in (b) (6) the patient withdrew from study after disease progression. On (b) (6) 771 days after start of study and approximately six months after the last dose, the subject developed grade 5 myocardial infarction and died. Autopsy was not performed.

Subject (b) (6) was an 83 year-old woman who was randomized to placebo and letrozole. Concomitant medications included digoxin, metoprolol, and pamidronic acid. Medical conditions at the time of the event were decreased appetite, fatigue and tension. Subject developed grade 4 cerebral vascular accident in right hemisphere 577 days after start of treatment. A brain CT showed no evidence of metastasis. Treatment with investigational product and letrozole was continued until (b) (6). After that the subject deteriorated and oral intake was no longer possible. The subject died on (b) (6) due to cerebral vascular accident. No autopsy was performed. The subject's baseline ECG (b) (6) was normal; her study withdrawal ECG (b) (6) was abnormal but not clinically significant.

Subject (b) (6) was a 62 year-old woman who was randomized to placebo and letrozole. Medical conditions at the time of the event included diabetes mellitus type 2, hypercholesterolemia, hypertension and IgA nephropathy. The subject had prior radiotherapy to her left breast and prior treatment with tamoxifen. Concomitant medications included diltiazem, zoledronic acid, HCTZ, paracetamol, lisinopril, atenolol, glibenclamide, pioglitazone, rosiglitazone maleate, amlodipine, desipramine hydrochloride, fluoxetine, clonidine, and alprazolam. The subject developed grade 5 pulmonary arrest 399 days after start of treatment. She was transported to the emergency room via ambulance. The subject was in asystole upon arrival to the hospital with no resumption of pulse. CPR was stopped at the family's request. An autopsy was not performed.

Subject (b) (6) was a 51 year-old woman randomized to receive placebo and letrozole 2.5 mg once daily from (b) (6) to (b) (6) for treatment of metastatic breast cancer. Subject had extensive lung metastases. On (b) (6)

(b) (6) 28 days after the start of investigational product and letrozole, the subject developed grade 4 acute dyspnea. No infectious cause was identified. The subject died on (b) (6) cause of death is unknown. An autopsy was not performed.

Subject (b) (6) was an 81 year-old woman randomized to receive placebo and letrozole 2.5 mg once daily from (b) (6). Concurrent medical conditions included nonsmoker, alcohol use, hypertension, hyperlipidemia, chronic stable angina, compression fracture and rheumatoid arthritis. Medical history included a four-vessel coronary artery bypass graft in 1990. Concomitant medications included Nitroglycerin patch, methotrexate, prednisone, folate, Naprosyn, atenolol, Norvasc, Vytorin, lisinopril, miacalcin nasal spray and aspirin.

On (b) (6), the subject developed a grade 3 or severe bowel obstruction seen on CT scan and then an acute myocardial infarction the following day. Laboratory results drawn on (b) (6) were as follows: white blood cell count 14,500 (normal range 4.0 to 10.0, units not reported), neutrophil count 10.93 (normal range 1.5 to 8.0, units not reported), glucose 138 (normal range 82 to 115, units not reported), troponin 0.96 (normal range 0.01 to 0.03, units not reported) and creatine kinase-MB (CK-MB) 25 (normal range 0 to 6, units not reported). On (b) (6), the subject underwent a positron emission tomography (PET) scan. During the scan, she developed a grade 5 myocardial infarction. Laboratory results drawn on (b) (6) were as follows: carbon dioxide 19 (normal range 23 to 31, units not reported), ALT 204 (normal range 10 to 35, units not reported), AST 237 (normal range 8 to 39, units not reported), troponin 5.29 (normal range 0.01 to 0.03, units not reported), CK-MB 20 (normal range 0 to 6, units not reported) and potassium 5.3 (normal range 3.6 to 5.0, units not reported). Treatment with epinephrine, atropine, sodium bicarbonate, normal saline, Lactated Ringer's was administered without success. The subject died due to the myocardial infarction and small bowel obstruction at (b) (6). No autopsy was performed.

On (b) (6), 91 days after the start of investigational product and letrozole and four days after the last dose of investigational product the subject developed lymphoma. The event was life-threatening. Follow-up scans on an unspecified date showed large lymph node. Biopsy on an unspecified date showed revealed large B-cell lymphoma. On (b) (6) pathology results showed EBV-positive large B-cell lymphoma; CD 20+, CD 30+, CD45+. Investigational product was discontinued on (b) (6). Letrozole was discontinued on an unspecified date.

Subject (b) (6) was a 72-year-old female subject started on placebo and letrozole on (b) (6). Her medical conditions included thrombosis and she was taking warfarin, clavulanic acid and ameroxol at the time of event. On (b) (6), 38 days after starting the study, the subject developed grade 3 or severe abdominal pain and was hospitalized. Treatment was interrupted on (b) (6). The investigator considered

that there was no reasonable possibility that the abdominal pain may have been caused by the treatment and the event was possibly due to other contributing factors, although no information was provided. Treatment was discontinued on [REDACTED] (b) (6) as a result of necrotic hemorrhagic pancreatitis and the subject expired on [REDACTED] (b) (6) due to hemorrhagic pancreatitis. The investigator stated that the cause of death was “necrotic hemorrhagic pancreatitis” and “multiorgan dysfunction”.

Subject [REDACTED] (b) (6) was a 64 year-old woman randomized to receive placebo and letrozole 2.5 mg once daily. Ongoing medical conditions included diabetes and renal dysfunction. Concomitant medications included glibenclamide (Daonil) and metformin hydrochloride (Glucophage retard). On [REDACTED] (b) (6), approximately four days after commencing investigational product, the subject developed fever, tooth abscess and renal insufficiency. The subject was hospitalized. Relevant test results included creatinine value 252 umol/L (normal range 40 - 150) and blood glucose level 20 mmol/L (normal range 3.5 - 6.5) confirming the subject also had developed symptom of hyperglycemia. Renal insufficiency was unresolved at the time of reporting.

On [REDACTED] (b) (6), approximately 22 days after starting treatment, the subject was admitted to hospital due to grade 3 fever and grade 3 hypertension. The following day she was found to have developed grade 2 renal function aggravated. Further information regarding investigations and test results for the reported events were unavailable at the time of reporting. Investigational product and letrozole was discontinued on [REDACTED] (b) (6) due to these events. The investigator considered there was a reasonable possibility the events fever, hypertension and renal function aggravated may have been caused by the investigational product and letrozole.

Lapatinib plus letrozole arm

Subject [REDACTED] (b) (6) was a 51 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily. Medical conditions at the time of the event included lung carcinoma, pain and arrhythmia. Concomitant medications included omeprazole (Mopral), atenolol, clodronic acid (Lytos), ketoprofen (Profenid), morphine sulfate (Skenan), codoliprane, amitriptyline hydrochloride (Laroxyl), thyroxine sodium (Levothyrox), loperamide hydrochloride (Imossel), Maalox, hydroxyzine hydrochloride (Atarax), fentanyl (Duragesic), morphine sulfate (Actiskenan) and prednisone (Cortancyl). The subject experienced an episode of grade 2 thoracic pain with acute radiating pain to the back. Treatment with investigational product was continued. The diagnosis of pulmonary embolism was ruled out. The CT scan showed element of 4.5 cm in diameter with stenosis of culmen apico-dorsal bronchus and left pulmonary artery stenosis. The CT also showed known thoracic vertebra lesions. Pain resolved spontaneously 48 hours after onset. Events resolved on [REDACTED] (b) (6) after two days.

On [REDACTED] (b) (6), 410 days after the start of letrozole, the subject was admitted to the emergency unit. Creatinine was 650 mcmol/L (normal range 80-125), acidosis

7.18 (normal range 7.35-7.45) and hyperkalemia. The subject was diagnosed with grade 3 or severe renal insufficiency and severe acidosis secondary to septic shock. The subject was hospitalized. Treatment with investigational product and letrozole was discontinued on an unspecified date. The subject was treated with perfusion of SLF B26 and Plasmion. On [REDACTED] (b) (6), the subject had pH of 7.25 and creatinine 204 mcml/L. The events were fatal. The subject died on [REDACTED] (b) (6) due to renal insufficiency. An autopsy was not performed.

Reviewer's comment: The etiology of the renal insufficiency and sepsis is not clear from the CRFs. Paucity of available data makes accurate determination difficult.

Subject [REDACTED] (b) (6) was a 56 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily. Medical history included pain, diarrhea and dyspnea. Concomitant medications included fentanyl and celecoxib.

On [REDACTED] (b) (6), 54 days after the start of investigational product and letrozole, subject developed interstitial pneumonia with dyspnea of grade 3 toxicity and was hospitalized. The investigator considered the event to be possibly associated with an infection or lymphangitis carcinomatoid or pulmonary toxicity of study medication. Relevant investigations confirmed the presence of gram positive cocci organisms. She was diagnosed with grade 4 infectious pneumopathy with associated septic shock. Treatment with study medication was discontinued due to these events on [REDACTED] (b) (6) and the subject was withdrawn from the study.

On [REDACTED] (b) (6), approximately 4 months after discontinuation of investigational product and letrozole, the subject died due to lung infection and septic shock. It was unknown whether an autopsy was performed. The investigator considered there was reasonable possibility that the infectious pneumopathy may have been caused by investigational product and letrozole.

Reviewer's comment: Interstitial pneumonia appears to be consistent with lapatinib use as it is a labeled adverse event in the "Warnings and Precautions" section of the labeling.

Subject [REDACTED] (b) (6) was an 81 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily. Medical conditions at the time of the event included anorexia, bronchitis, heart failure and hypertension arterial. Concomitant medications included digoxin, hydrochlorothiazide, furosemide and bromazepam.

Treatment with investigational product and letrozole was discontinued on [REDACTED] (b) (6) and the subject was withdrawn from the study. On [REDACTED] (b) (6) approximately 10 months (308 days) after the start of blinded trial medication and letrozole, and 4 days after last dose of investigational product and letrozole, the subject had a stroke and was then hospitalized. The investigator considered that

there was no reasonable possibility that the stroke may have been caused by blinded trial medication and letrozole and that the event was possibly due to concomitant disorder (bronchitis). The subject was hospitalized and clinical examination revealed pseudobulbar syndrome (the subject had old collateral ischemic lesions). The event was unresolved at time of reporting. The subject was reported as having died on (b) (6).

Treatment with investigational product and letrozole was discontinued on (b) (6). The subject had stopped eating and the daughter did not give her study drug since this date. The subject was then withdrawn from the study.

Reviewer's comment: The etiology of the ictal hemiplegia appears to be consistent with the subject's positive history of cardiovascular disease.

Subject (b) (6) was a 60 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily. Concomitant medications included diclofenac, sodium docusate, metoclopramide, fentanyl patches, morphine sulphate, quinine sulphate and zoledronic acid. Medical conditions included back pain, constipation, bone metastases and axillary lymphadenopathy. This subject had primary breast cancer in situ, bone metastases, and axillary lymphadenopathy.

On (b) (6), 18 days after the start of investigational product and letrozole, the subject was diagnosed with grade 4 toxicity pulmonary embolism. Treatment with investigational product and letrozole was not stopped due to these events but one day of study medication was missed on (b) (6). The subject recovered and was discharged on (b) (6) but remained on warfarin sodium treatment.

On (b) (6), 600 days after start of study, the subject developed grade 4 abdominal pain and grade 4 vomiting. Internal bleeding was suspected and the subject was admitted to a local hospital. The subject's condition deteriorated and she experienced a cardiac arrest. Subject died on (b) (6). A post-mortem was performed on (b) (6), where small bowel ischemia secondary to benign adhesions from the subject's previous hysterectomy (b) (6) for benign disease was found. The coroner is reported as saying 'the diagnosis was a small bowel ischemia secondary to benign adhesions from previous hysterectomy for benign disease'. The investigator stated that she felt 'it was unlikely to be secondary to breast cancer or the medication'.

Subject (b) (6) was a 60 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily. The subject had a history of breast cancer treated with bilateral mastectomies. She had been diagnosed as having liver metastases thought to be from her original breast cancer. Concomitant medications included hyoscine, butylebumide and amoxicillin. Medical conditions included

gallstones. The subject received oral investigational product and oral letrozole 2.5 mg daily from (b) (6)

On (b) (6) 13 days after the start of investigational product and letrozole, the subject was hospitalized with abdominal pain and vomiting. A CT scan showed bowel obstruction and confirmed presence of large metastases deposits in the liver. A large cecal tumor was also found and ileocecal resection was performed. Histopathology showed moderately differentiated invasive adenocarcinoma of the cecum which invaded through the bowel and involved local lymph nodes. On (b) (6) (b) (6) subject was admitted to the intensive care unit as she was suffering from grade 4 sepsis, possibly secondary to pneumonia. A repeat CT scan of her abdomen suggested some free gas and fluid in the abdomen, although no evidence of gross leak of intestinal contents. Intravenous antibiotics were given and she initially responded well, but later respiratory distress increased and she was intubated. She deteriorated further over (b) (6) despite 100% oxygen and full ventilatory and cardiovascular support.

The subject passed away at 10.05 on (b) (6). Sepsis was cited as the cause of the subject's multi-organ failure (grade 4). The underlying cause could either be attributed to her pneumonia or an intra-abdominal cause (most likely). No autopsy was performed as there was enough evidence to confirm the cause of death. The CT scans that were performed at the subject's admission and subsequently with the subject deterioration have confirmed quite extensive liver metastases involving both lobes of the liver. The oncologist suspected that it implied an aggressive colorectal primary as the cause of her liver metastases rather than the breast cancer. The disease has advanced quite dramatically following recent review and CT scan. This was also consistent with the findings at laparotomy confirmed multiple metastases in both lobes. Treatment with investigational product and letrozole were discontinued on (b) (6) due to event of bowel obstruction and the subject was withdrawn from the study.

The investigator considered there was no reasonable possibility that the bowel obstruction, sepsis and multi-organ failure may have been caused by investigational product. The investigator also considered the events to be possibly associated with concurrent biliary pain.

Subject (b) (6) was a 45 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily from (b) (6). Medical conditions at the time of the event included inflammation of colon. Concomitant medications included docetaxel (initiated after discontinuation of investigational product and letrozole due to progressive disease).

On (b) (6) 81 days after the start of investigational product and letrozole, and 13 days after discontinuation from investigational product and letrozole, the subject developed grade 4 inflammation of colon due to Taxotere, which was started nine days prior. On (b) (6) the subject developed grade 4 septic shock, grade 4 acute

renal failure and grade 5 rhabdomyolysis. The subject experienced abdominal pain, mild nausea and bloody diarrhea and went to the emergency room on [REDACTED] (b) (6). Body temperature was 98.3, blood pressure was 72/42 mmHg, heart rate 105, respiratory rate 18, and oxygen saturation 100 percent. The subject was alert and oriented. Relevant test results included white blood cell count of 2.2 with absolute neutrophil count of less than 500. The subject was diagnosed with possible typhilitis. She was treated with vasopressors. She developed ischemia with compartment syndrome of the right leg and underwent right leg fasciotomy. The surgery went well without complications and the subject was recovering in the intensive care unit at the time of her arrest. The subject died on [REDACTED] (b) (6) due to rhabdomyolysis leading to renal failure. The investigator considered that there was no reasonable possibility that septic shock, acute renal failure, inflammation of colon and rhabdomyolysis may have been caused by investigational product and letrozole, but were possibly due to docetaxel.

Subject [REDACTED] (b) (6) was a 59 year-old woman who was randomized to received lapatinib 1500 mg daily and letrozole 2.5 mg daily from [REDACTED] (b) (6). Medical conditions included grade 1 ALT, AST and alkaline phosphatase. Concomitant medications included loperamide, Mylanta and paracetamol.

On [REDACTED] (b) (6) 205 days after the start of investigational product and letrozole, the subject developed grade 2 or moderate hepatic dysfunction. The event was life-threatening. The subject also experienced deterioration of performance status. Laboratory test results showed increased alkaline phosphatase (1047 U/L), AST increased (216 U/L), ALT increased (108 U/L) and hyperbilirubinemia (52 umol/L). Relevant test results on [REDACTED] (b) (6) were elevated for alkaline phosphatase (1440 U/L, reference range 35-104); AST (528 U/L, reference range 9-31); ALT (253 U/L, reference range 6-30); bilirubin (8.99 mg/dL, reference range 0.1-1); direct bilirubin (5.74 mg/dL, reference range less than 3) and direct bilirubin (3.25 mg/dL, reference range 0.1-1). An MRI scan of liver revealed liver metastasis and edema. Treatment with investigational product and letrozole was discontinued on [REDACTED] (b) (6). The investigator reported that he believed the hepatic dysfunction was related to lapatinib because progression of disease had been ruled out after a computed tomography scan and liver magnetic resonance imaging showed stable liver metastases and parenchymal edema. Laboratory results on [REDACTED] (b) (6) included alkaline phosphatase of 569 IU/L (reference range 35-104), ALT of 169 U/L (reference range 6-30), AST of 530 U/L (reference range 9-31), total bilirubin of 44.4 mg/dL (reference range 0.1-1), direct bilirubin 36.9 mg/dL and indirect bilirubin of 7.2 mg/dL. The subject presented with symptoms of encephalopathy on [REDACTED] (b) (6). She experienced clinical deterioration and died on [REDACTED] (b) (6). No autopsy was performed.

Table 37. Fatal serious adverse events

Subject ID	Cause of death	Investigator's attribution	FDA's attribution
Lapatinib + Letrozole			
(b) (6)	Hepatic function abnormal	Yes	Yes
	Infectious pneumopathy	Yes	Yes
	Cerebrovascular accident	No	No
	Intestinal ischemia	No	No
	Sepsis secondary to surgery from 2nd primary	No	No
	Septic shock, ARF, rhabdomyolysis	No	No
Placebo + Letrozole			
(b) (6)	Dyspnea	Yes	Yes
	Myocardial infarction	Yes	No
	Cerebrovascular accident	No	No
	Cardiorespiratory arrest	No	No
	Lymphoma and bowel obstruction	No	No
	Hemorrhagic pancreatitis	No	No

Source: Reviewer's table

Reviewer's comment: Review of the CRFs and narratives of the fatal SAE cases revealed two cases of fatal serious adverse events in subjects (b) (6) and (b) (6) that appear to lapatinib and letrozole treatment. Furthermore, hepatotoxicity and infectious pneumopathy are both labeled adverse events for lapatinib. Lapatinib labeling contains a black box warning for hepatotoxicity. Interstitial lung disease and pneumonitis are noted in the "Warnings and Precautions" section of the labeling. Hepatotoxicity is a safety concern that will be discussed later.

The other fatal cases of serious adverse events are explained by other etiologies, either underlying diseases, concomitant medications, or co-morbid conditions.

According to the 120-day safety update, no additional fatal serious adverse events occurred during the time period between June 3, 2008 and February 3, 2009.

7.3.3 Nonfatal Serious Adverse Events

In EGF30008, more subjects in the lapatinib plus letrozole arm (n=144, 22%) than in the placebo plus letrozole arm (n=94, 15%) experienced serious adverse events. Serious adverse events were defined as any event that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, was permanently or significantly disabling or incapacitating, or was a congenital anomaly or birth defect. As shown in Table 38, ejection fraction decreased, diarrhea, and vomiting were reported in $\geq 2\%$ or more subjects in the treatment arm. No serious adverse events were reported in $\geq 2\%$ of subjects in the letrozole alone arm.

Table 38. Serious adverse events occurring in ≥ 3 patients

MedDRA preferred term	Number (%) of subjects [n related events]	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any SAE	94 (15) [27]	144 (22) [54]
Ejection fraction decreased	8 (1) [7]	17 (3) [14]
Diarrhea	2 (<1) [1]	15 (2) [10]
Vomiting	7 (1) [3]	10 (2) [4]
Dehydration	2 (<1) [1]	7 (1) [3]
Urinary tract infection	1 (<1) [1]	6 (<1) [0]
Anemia	2 (<1) [2]	5 (<1) [0]
Left ventricular dysfunction	1 (<1) [0]	5 (<1) [5]
Cellulitis	0	5 (<1) [0]
Dyspnea	4 (<1) [1]	5 (<1) [0]
Nausea	4 (<1) [1]	5 (<1) [3]
Abdominal pain	2 (<1) [0]	4 (<1) [0]
Erysipelas	2 (<1) [1]	4 (<1) [1]
Pyrexia	4 (<1) [1]	4 (<1) [0]
Asthenia	1 (<1) [0]	3 (<1) [2]
Chest pain	3 (<1) [0]	3 (<1) [0]
Femur fracture	1 (<1) [0]	3 (<1) [0]
Pulmonary embolism	3 (<1) [0]	3 (<1) [1]
Back pain	5 (<1) [0]	2 (<1) [1]
Pneumonia	3 (<1) [0]	2 (<1) [0]

a In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment arm had rash under "Infections and infestations"; none were Grade 3 or 4.

Source: Applicant's Table 63, Study EGF30008 Clinical Study Report

Table 4. Selected Laboratory Abnormalities

	Lapatinib + Letrozole			Letrozole + Placebo		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
Hepatic Parameters	%	%	%	%	%	%
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0
Total Bilirubin	22	<1	<1	11	1	<1

^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
 Source: Applicant's Table 63, Study EGF30008 Clinical Study Report

Reviewer's comments: Applicant's data in table above was verified by the reviewer. Left ventricular dysfunction/ejection fraction decreased and diarrhea are adverse events that are known to be related lapatinib; thus the higher number in the treatment arm.

The number of serious adverse events increased from June 3, 2008 to February 3, 2009, six in the lapatinib plus letrozole arm and three in the placebo plus letrozole arm. Two cases of decreased LVEF and three cases of ascites were observed in the lapatinib plus letrozole arm. Decreased LVEF is a concern and will be monitored more closely as part of Applicant's postmarketing requirements (PMRs).

7.3.4 Dropouts and/or Discontinuations

The number of patients in the ITT analysis is 1278 patients, 654 in the lapatinib plus letrozole arm and 624 in the placebo plus letrozole arm. The difference between the 1286 patients in the efficacy portion of the trial and 1278 in the safety portion was due to eight subjects who did not received treatment, 6 subjects in the letrozole plus placebo group and two subjects in the letrozole plus lapatinib group. The number of subjects in the letrozole plus placebo group in the Safety Population (SP) was 624 because there were 14 subjects who were randomized to receive letrozole plus placebo but who actually received letrozole plus lapatinib and 6 subjects who were randomized to letrozole plus placebo group but did not receive any treatment. The number of subjects in the letrozole plus lapatinib group in the SP was 654 because 2 subjects were randomized to letrozole plus lapatinib group but did not receive any treatment, and 14 subjects who were randomized to receive letrozole plus placebo actually received letrozole plus lapatinib (N=654). Nine subjects who were randomized to receive letrozole plus lapatinib actually received letrozole plus placebo; however, as these subjects received at least 1 dose of lapatinib they are included in the letrozole plus lapatinib group for the SP.

As of the data lockpoint in June 3, 2008, a total of 1088 (85%) subjects had discontinued treatment, 539 (84%) subjects in the lapatinib plus letrozole arm and 549

(85%) subjects in the placebo plus letrozole arm. For the ITT population, the primary reason for discontinuation was progression of cancer, 380 (59%) subjects in the lapatinib plus letrozole arm and 449 (69%) in the placebo plus letrozole arm. Additionally, three times more subjects (14%) withdrew due to an adverse event in the lapatinib plus letrozole arm versus the placebo and letrozole arm (5%) as shown in Table 39.

In the HER2-positive subgroup, most patients discontinued from treatment due to disease progression, 74% in the treatment arm and 79% in the letrozole alone arm. Twice (6% versus 3%) the percentage of patients withdrew from treatment due to an adverse event in the treatment arm.

Table 39. Reason for Discontinuation from Treatment

	ITT		HER2-positive	
	Lapatinib + letrozole, N=642 (%)	Letrozole + placebo, N=644 (%)	Lapatinib + letrozole, N=111 (%)	Placebo + letrozole, N=108 (%)
Discontinuation from treatment	539 (84)	549 (85)	103 (93)	98 (91)
Continuing treatment	103 (16)	95 (15)	8 (7)	10 (9)
Reason for discontinuation				
Adverse event	92 (14)	32 (5)	7 (6)	3 (3)
Consent withdrawn	33 (5)	32 (5)	9 (8)	5 (5)
Lost to follow-up	5 (<1)	2 (<1)	0	0
Protocol violation	8 (1)	9 (1)	0	3 (3)
Disease progression (radiologic/symptomatic)	380 (59)	449 (69)	82 (74)	85 (79)
Death	1 (<1)	7 (1)	0	1 (<1)
Other	20 (3)	18 (3)	5 (5)	1 (<1)

Source: Qiang Xu, Ph.D., Statistical Reviewer

7.3.5 Drug-Related Adverse Events Leading to Treatment Termination

As assessed by investigators, treatment was terminated in 548 (84%) subjects in the lapatinib plus letrozole arm and 343 (55%) subjects in the placebo plus letrozole arm due to treatment-emergent adverse events that were drug-related. Table 40 depicts the treatment-emergent adverse events that were drug-related in each arm. Diarrhea, vomiting, nausea, dry skin, and fatigue occurred 2-4 fold higher in the lapatinib plus letrozole arm, compared to the placebo plus letrozole arm.

Table 40. Adverse events leading to treatment termination

MedDRA preferred term	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any AE related to study treatment ^a	343 (55)	548 (84)
Diarrhea	79 (13)	348 (53)
Rash ^b	57 (9)	249 (38)
Nausea	69 (11)	129 (20)
Dry skin	19 (3)	69 (11)
Fatigue	46 (7)	70 (11)
Alopecia	33 (5)	64 (10)
Nail disorder	4 (<1)	66 (10)
Pruritus	35 (6)	64 (10)

Source: Applicant's Table 59, Study EGF30008 Clinical Study Report

a. Assessed by the investigator.

b. Rash reported under "Skin and subcutaneous tissue disorders" and "Infections and infestations".

Reviewer's comment: More subjects in the lapatinib plus letrozole arm had treatment discontinuations due to adverse events than in the placebo plus letrozole arm, which may unmask the treatment arm and confound the efficacy analysis. These adverse events are consistent with the reviewer's analysis using *ae.xpt*.

7.3.6 Submission Specific Primary Safety Concerns

The following adverse events associated with lapatinib are of interest:

- decreased left ventricular ejection fraction
- hepatotoxicity
- diarrhea
- interstitial lung disease
- rash and nail changes

7.3.6.1 Left Ventricular Ejection Fraction Adverse Events

Decreased left ventricular ejection fraction is a recognized adverse event with lapatinib treatment. In Study EGF30008, subjects were required to have a cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive). Subjects who have received anthracyclines in the neo-adjuvant and/or adjuvant setting, which exceeded the following doses: 360 mg/m² of doxorubicin, 720 mg/m² of epirubicin, and 72 mg/m² of mitoxantrone were also excluded. Additionally, the protocol excluded subjects with a known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure. Echocardiograms (or MUGA) had to be performed within two

weeks prior to the first dose and every eight weeks after first dose of randomized therapy. Starting at Week 108 at an every 12-week interval, an echocardiogram (or MUGA) was performed to evaluate left ventricular cardiac ejection fraction.

As analyzed by the Applicant and presented to the Agency on November 23, 2009, absolute and relative change in LVEF from baseline did not show any significant differences between the two arms as shown in Table 41:

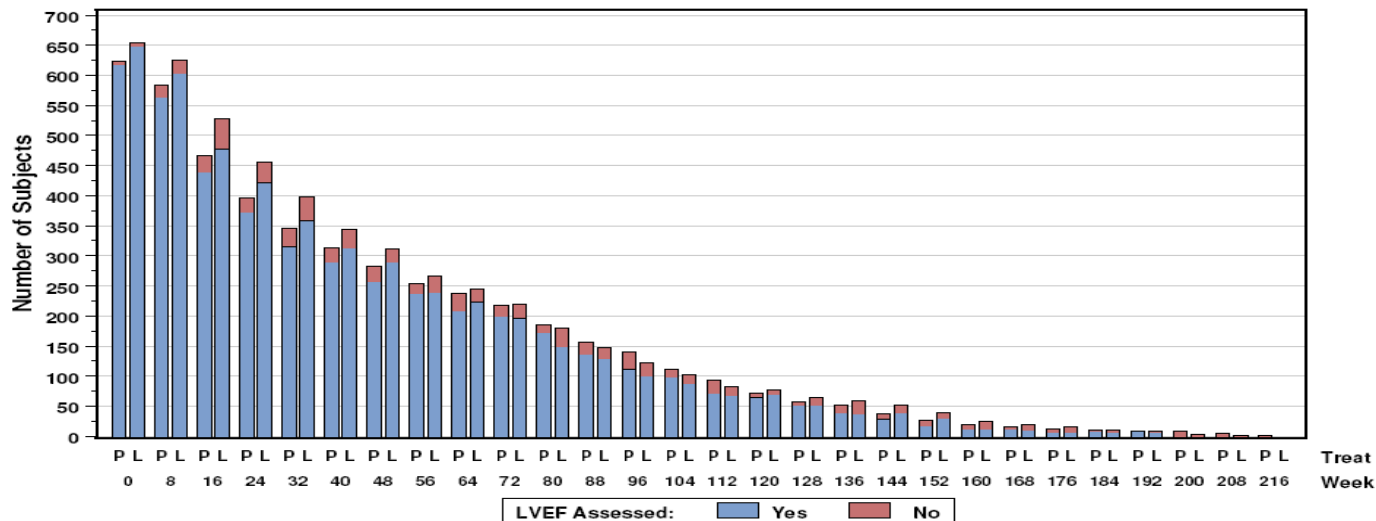
Table 41. Absolute and Relative Changes of LVEF from Baseline

	Letrozole + Placebo (N=624)	Letrozole + Lapatinib (N=654)
Number of patients*	554	601
Absolute Change from baseline		
≥20% decrease	15 (3%)	17 (3%)
≥20% decrease and below LLN	5 (1%)	8 (1%)
Relative change from baseline		
≥20% decrease	47 (8%)	66 (11%)
≥20% decrease and below LLN	10 (2%)	23 (4%)

Source: Applicant's presentation to the Agency on November 23, 2009.

The figure below represents the subjects who had LVEF at screening and post-baseline, also presented to the Agency on November 23, 2009:

Figure 8. Subjects with LVEF Monitoring at Screening and Post-baseline



Source: Applicant's presentation to the Agency on November 23, 2009.

However, the analysis of the LVEF findings, either by echocardiogram or MUGA, is inconclusive. As shown in A significant number of patients, 412 (63%) in the lapatinib plus letrozole arm, and 402 (64%) in the placebo plus letrozole arm had no follow-up or conclusive measurement of ejection fraction shown in the Table 42Table 43 below. When evaluating the absolute decreases of LVEF, the percentages of patients were similar in both arms. Conversely, the relative LVEF decrease was slightly high in the lapatinib plus placebo arm. Table 43 presents the number of patients according to the number of missing LVEF assessments. In both arms, slightly more than one-third of patients had a complete assessment of LVEF and almost 60% were missing between 1-3 LVEF assessments.

Table 42. LVEF Assessments

Event	Lapatinib + Letrozole, N=599, (%)	Placebo + Letrozole, N=581 (%)
Protocol-defined LVEF decrease (absolute) ¹	13 (2)	13 (2)
Absol. decrease >20%	7 (1)	9 (2)
LLN + absol. decrease >20%	6 (1)	4 (1)
LVEF decrease (relative) ¹	62 (10)	42 (7)
Relative decrease >20%	40 (7)	35 (6)
LLN + relative decrease >20%	22 (4)	7 (1)
No baseline EF	5 (<1)	5 (<1)
No follow-up and/or conclusive EF	412 (63)	402 (64)

Source: Qiang Xu, Ph.D., Statistical Reviewer

Table 43. Subjects with missing LVEF monitoring using ECHO or MUGA scans

Number of missing assessments	Lapatinib + letrozole, n=640 (%)	Placebo + letrozole, n=638 (%)	Total, n=1278 (%)
0	241 (38)	215 (34)	456 (36)
1-3	355 (55)	376 (59)	731 (57)
>3	44 (7)	47 (7)	91 (7)

Source: Qiang Xu, Ph.D., Statistical Reviewer

Reviewer's comment: The Applicant's analysis shows that there appears to be no safety concern with regard to lapatinib's effect on LVEF; however, this is misleading as many assessments to measure LVEF in patients were not performed, as shown in Table 42 and Table 43. Note also that the numbers were well-balanced between both arms, but as mentioned, a significant number of patients had missing pre- and post-baseline LVEF assessments.

Furthermore, the data are not conclusive at this time as there are a large number of subjects who are missing LVEF assessments and the effect of lapatinib is not truly known in patients who have previously received trastuzumab in the adjuvant setting, which is the standard of care in the United States.

Table 44 lists the cardiac events as assessed using *ae.xpt*. The number of cardiac events was two-fold higher in the treatment arm. In terms of grade 3-4 toxicity, five cases of ejection fraction decreased and one case of ventricular dysfunction occurred in the treatment arm, and one case of cardiac failure (congestive, cardiomyopathy), and one case of left ventricular failure occurred in the placebo plus letrozole arm. No death attributable to a cardiac adverse event occurred, although two cases of study withdrawal due to a cardiac event occurred in both arms.

Table 44. Analysis of cardiac adverse events

	Placebo + Letrozole, N=624		Letrozole + Lapatinib, n= 654	
Number of subjects with cardiac events	19		39	
Preferred Term	All Grades	Grade 3-4	All Grades	Grade3-4
Cardiac Failure, Congestive, Cardiomyopathy	3	1	4	0
Ejection Fraction Decreased	10	1	25	5
Ventricular Dysfunction	4	0	10	1
LV Failure	2	1	0	0
Withdrawal due to Cardiac AE	2 LV Dysfunction		2 Cardiac Failure, LV Dysfunction	
Cardiac Deaths	0		0	

Source: Qiang Xu, Ph.D., Statistical Reviewer

Reviewer's comment: More grade 3-4 cardiac adverse events occurred in the treatment arm, six in the treatment arm and three in the placebo plus letrozole arm. The cardiac adverse events presented above are consistent with lapatinib safety experience. Note that only three patients had received prior therapy with trastuzumab; hence, lapatinib's effect on LVEF is inconclusive as receipt of trastuzumab as adjuvant treatment is the standard of care in this population in the U.S.

7.3.6.2 Hepatobiliary Events

Hepatotoxicity is a known adverse event related to lapatinib treatment and is labeled as a black box warning. Hepatotoxicity observed in Study EGF30008 is consistent with what has been observed in the pre-marketing clinical trials.

Using the *ae.xpt*, the hepatic adverse events were isolated using the Hepatic SOC and Investigations SOC. Only hepatic adverse events were extracted from the Investigations SOC. As shown in Table 45, there was about a 3:1 ratio of hepatobiliary events in the lapatinib plus letrozole arm compared to the placebo plus letrozole arm. A significantly higher percentage of subjects in the lapatinib plus letrozole arm (16%) compared to letrozole plus placebo arm (9%) experienced a hepatobiliary event, and the severity of toxicity was greater in the lapatinib plus letrozole arm. One subject experienced a fatal outcome due to hepatotoxicity in the lapatinib plus letrozole arm. In the lapatinib plus letrozole arm, most hepatotoxicity events (n=107) was observed in patients 14-32 weeks into treatment.

Table 45. Characteristics of hepatotoxicity adverse events

	Lapatinib + Letrozole, N=654	Letrozole + Placebo, N=624
Number of subjects with hepatobiliary events	102 (16)	55 (9)
Number of events	384	107
Event characteristics		
Number of events	384	107
Serious	9 (2)	4 (4)
Study treatment related	268 (70)	54 (50)
Leading to discontinuation from study	14 (4)	3 (3)
Fatal	1 (<1)	0
Number of occurrences by subject		
1 or 2	53 (52)	41 (75)
3 or more	49 (48)	14 (25)
Maximum toxicity		
All grades	102	55
Grades 3-4	38 (37)	12 (22)
Grade 5	1 (<1)	0
Outcome		
Number of events	384	107
Resolved	276 (72)	72 (67)
Resolved with sequelae	18 (5)	2 (2)
Not resolved	89 (23)	33 (31)
Fatal	1 (<1)	0
Action taken		
Number of events	384	107
None	306 (80)	100 (93)
Dose adjusted	5 (1)	0
Temporarily interrupted	37 (10)	1 (<1)
Permanently discontinued	14 (4)	3 (3)
Not applicable	22 (6)	3 (3)
Time to onset, days		
Mean (standard deviation)	219 (188.13)	208 (215.49)
Median (range)	168 (1 to 926)	115 (22 to 1018)
Time to onset, weeks		
Mean (SD)	31.1 (26.88)	29.7 (30.78)
Median (range)	23.9 (0.1 to 132)	16.4 (3.1 to 145)
Time to onset		
<4 weeks	21	9
4 to <8 weeks	51	18

8 to <14 weeks	59	21
14 to <32 weeks	107	21
32 to <64 weeks	93	24
≥64 weeks	53	14

Source: Applicant's Table 71 & 72, Applicant's Study EGF30008 Clinical Study Report

Reviewer's comment: The Applicant's analysis of hepatotoxicity adverse events is similar the reviewer's evaluation. These adverse events are expected with lapatinib and the concerns regarding hepatotoxicity are reflected in the labeling.

Overall, the number of subjects with grade 1-4 hepatotoxicity as evaluated by hepatic measurements is greater in the lapatinib plus letrozole arm, as detailed in Table 46. Grade 3-4 severity of laboratory measurements of hepatic function was also greater in the lapatinib plus letrozole arm. The percentage of patients with a grade 1-4 total bilirubin was two-fold higher in the lapatinib plus letrozole arm.

Table 46. Maximum Toxicity Grade 3 or 4 Hepatic Measurements at Any Post-Baseline Visit

Hepatic laboratory parameter	Number (%) of subjects					
	Lapatinib + letrozole, N=654			Placebo + letrozole, N=624		
	Visit	Grade 3	Grade 4	Visit	Grade 3	Grade 4
Total	Screen (603)	0	0	Screen (570)	0	0
bilirubin	Any post (642)	6 (<1)	1 (<1)	Any post (616)	8 (1)	2 (<1)
AST	Screen (599)	0	0	Screen (561)	2 (<1)	0
	Any post (638)	6 (<1)	1 (<1)	Any post (615)	13 (2)	2 (<1)
ALT	Screen (611)	1 (<1)	0	Screen (576)	0	0
	Any post (643)	33 (5)	0	Any post (617)	9 (1)	0

Source: Applicant's Table 33, Integrated Summary of Safety

Reviewer's comment: These adverse events are expected with lapatinib and the concerns regarding hepatotoxicity are reflected in the labeling.

7.3.6.3 Drug-Induced Liver Injury

Using *ae.xpt*, Study EGF30008 was evaluated in further for hepatotoxicity, specifically drug-induced liver injury. The adverse event database was searched for cases of drug-induced hepatocellular injury using Hy's Law (*Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, October 2007*) as defined below:

1. The drug causes hepatocellular injury, generally shown by more frequent three-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.

2. Among subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

Based on these criteria, three subjects (Subjects (b) (6)) had hepatic abnormalities that met the criteria for Hy's Law. Only Subject (b) (6) is presented below, as the narrative for the other subject was not provided.

Subject (b) (6) AST 5.66 x ULN, Tbili 2.17 x ULN. No narrative available.

Subject (b) (6) was a 74 year-old woman that received lapatinib 1500 mg daily and letrozole 2.5 mg daily starting (b) (6). Subject was initially diagnosed with Stage II, ER/PgR-positive breast cancer on (b) (6) and underwent a modified radical mastectomy of the right breast. Subject was then diagnosed with Stage IV disease on (b) (6). Sites of metastatic disease were pleura, bone, lung, and lymph nodes. Patient had not received any prior anti-cancer therapy or radiation therapy. During the course of therapy, the patient experienced grade 2-3 elevations of liver function tests (ALT, AST and total bilirubin) and had a dose reduction of 1250 mg daily because of diarrhea also. Treatment in this subject was temporarily interrupted and the subject had a positive re-challenge; the subject was discontinued from the study due to progressive disease.

Reviewer's comment: Per the Applicant, there were two cases of drug-induced liver injury in two subjects (Subject (b) (6) as presented above and Subject (b) (6)). Subject (b) (6) had probably drug-induced liver injury, as adjudicated by the Applicant's panel of experts.

Subject (b) (6) was not captured in the reviewer's analysis as the subject did not meet the laboratory criteria for drug-induced liver injury. This subject permanently discontinued from lapatinib plus letrozole due to an event of grade 4 ALT increased on (b) (6), 113 days after study start. At the same time of this event, events of gamma glutamyl transferase increased and hyperbilirubinemia were also reported for this subject. Ultrasound taken on (b) (6) revealed liver parenchyma composting. Treatment was discontinued on that day and then permanently discontinued on (b) (6). This subject did not meet the Agency's definition of drug-induced liver injury. On (b) (6), ALT was 986 (normal 10-35, bilirubin 1.87 (normal < 1.10 mg/dl). As of (b) (6), the investigator stated that liver function had resolved.

In addition to subjects experiencing drug-induced liver toxicity, one subject (Subject (b) (6)) died of hepatic failure. This subject has been previously presented in Section 7.3.1, Deaths. She had a fatal SAE of abnormal hepatic function, thought to be related to disseminated liver metastases or cholestatic drug-induced liver injury.

Reviewer's comment: Drug-induced liver injury is a known toxicity associated with lapatinib and it has a prominent Black Box Warning in the labeling. These findings are consistent with the safety experience with lapatinib thus far. Additionally, hepatotoxicity has been observed with other tyrosine kinase inhibitors.

7.3.6.4 Diarrhea Events

Diarrhea is a noted adverse event related to lapatinib therapy and is labeled in the "Warnings and Precautions" section of the labeling. Consistent with the premarketing clinical trials, the majority (n=419, 64%) of subjects reported diarrhea in the lapatinib plus letrozole arm and of these subjects, approximately one-third (31%) of the subjects had three or more episodes of diarrhea. In terms of severity, 85% of the episodes were grade 1 or 2. In 2% (n=24) of subjects, diarrhea resulted in treatment discontinuation in the lapatinib plus letrozole arm and 9% (n=89) had treatment temporarily interrupted and 3% (n=29) had a dose adjustment. The remaining subjects continued with treatment.

Reviewer's comment: Review of *ae.xpt* confirms the Applicant's description of diarrhea as an adverse event in Study EGF30008. Diarrhea has been well-characterized as an adverse event in the labeling. The concern regarding this adverse event is that it may unmask treatment arm as there was a three-fold higher reporting of diarrhea in subjects receiving lapatinib plus letrozole (n=419, 64%) versus placebo and letrozole (n=124, 20%).

7.3.6.5 Events of rash

Rash is a noted adverse event related to lapatinib therapy and is labeled in the (b) (4) section of the labeling. Consistent with the premarketing clinical trials, half (n=328, 50%) of subjects reported diarrhea in the lapatinib plus letrozole arm and of these subjects compare to 15% (n=93) subjects in the placebo plus letrozole arm. Eighty percent of the subjects and 100% of subjects in the placebo plus letrozole arm had one or two episodes of rash. In terms of severity, almost (97%) all were either grade 1 or 2 in the lapatinib plus letrozole arm. In 2% (n=11) of subjects, rash resulted in treatment discontinuation in the lapatinib plus letrozole arm and 3% (n=20) had treatment temporarily interrupted and 1% (n=8) had a dose adjustment. The remaining subjects continued with treatment. Time to onset of first occurrence of rash was 8.94 weeks in the lapatinib plus placebo arm and 25.37 weeks in the placebo plus letrozole arm.

Reviewer's comment: Review of *ae.xpt* confirms the Applicant's description of rash as an adverse event in Study EGF30008. Rash has been well-characterized as an adverse event in the labeling. The concern regarding this adverse event is that it may unmask treatment arm as there was a three-fold higher reporting of rash in subjects receiving lapatinib plus letrozole (n=328, 50%) versus placebo and letrozole (n=93, 15%). In the lapatinib and capecitabine trial, the incidence of rash was 28% in the lapatinib and capecitabine arm, versus 14% in the capecitabine arm.

7.3.6.6 Pulmonary events

Pneumonitis and interstitial lung disease are known adverse events associated with lapatinib in monotherapy or in combination and are noted as such in the "Warnings and Precautions" section of the labeling. Four cases of pneumonitis have been reported in Study EGF30008, three in the lapatinib plus letrozole arm and one in the placebo plus letrozole arm. In three cases, (two in the lapatinib plus letrozole arm and one in the placebo plus letrozole arm), the time to onset was between 157 to 174 days. Severity was grade 2 in all cases, except for one, which was grade 1 and attribution by investigator was unrelated in all but one case, which was thought to be unrelated. Pneumonitis resolved in two cases and unresolved in the other two cases at the time of reporting.

Reviewer's comment: The Applicant's evaluation of pneumonitis has been confirmed by the reviewer, although the attribution to study drug differed. The Applicant stated that there were two cases of pneumonitis and the remaining two cases were suggestive of pneumonitis. In the two suggestive cases, attribution in one of the two appears to be lapatinib plus letrozole as there appears to be no other cause related to pneumonitis. In the other case, attribution is unclear as the subject had a possible bacterial infection.

7.4 Supportive Safety Results

The safety population of Study EGF30008 comprised the analyses of adverse reactions. The total number of patients in this combined safety population is 1276.

7.4.1 Common Adverse Events

Adverse events were reported in 100% of the safety population. As shown in Table 47, the most frequently reported non-hematologic adverse events ($\geq 20\%$) in the lapatinib plus letrozole arm, in decreasing frequency, were diarrhea (64%), rash (44%), nausea (31%), and fatigue (20%). No hematologic adverse events were reported to be $\geq 10\%$. These adverse events are similarly displayed in Table 48.

Grade 3 and 4 adverse events were reported more frequently in the treatment arm. For grade 4 events there were two events of diarrhea and one event of vomiting in the

treatment arm. One grade 4 event of diarrhea was reported in the letrozole plus placebo arm. For grade 3 events, diarrhea was experienced most frequently in the treatment arm, 9% versus <1% in the letrozole alone arm.

Table 47. Common adverse events occurring in 10% or more subjects, at higher incidence in treatment arm

System organ class MedDRA preferred term	Number (%) of subjects					
	Letrozole 2.5 mg + Placebo (N=624)			Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Metabolism and nutrition disorders						
Anorexia	54 (9)	2 (<1)	0	72 (11)	5 (<1)	0
Nervous system disorders						
Headache	83 (13)	3 (<1)	0	91 (14)	2 (<1)	0
Gastrointestinal disorders						
Diarrhea	124 (20)	6 (<1)	0	419 (64)	58 (9)	2 (<1)
Nausea	129 (21)	4 (<1)	0	200 (31)	6 (<1)	0
Vomiting	68 (11)	4 (<1)	1 (<1)	109 (17)	7 (1)	1 (<1)
Skin and subcutaneous tissue disorders						
Rash ^a	83 (13)	0	0	290 (44)	7 (1)	0
Pruritus	55 (9)	1 (<1)	0	80 (12)	2 (<1)	0
Alopecia	45 (7)	0	0	85 (13)	1 (<1)	0
Dry skin	27 (4)	0	0	87 (13)	1 (<1)	0
Nail disorder	6 (<1)	0	0	73 (11)	1 (<1)	0
General disorders and administrative site conditions						
Fatigue	108 (17)	3 (<1)	0	134 (20)	10 (2)	0
Asthenia	69 (11)	5 (<1)	0	80 (12)	5 (<1)	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11 (2)	1 (<1)	0	70 (11)	1 (<1)	0

Source data: [Table 8.12](#), [Table 8.13](#) and [Table 8.15](#).

- a. In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment group had a rash under "Infections and infestations"; none were Grade 3 or 4. This table includes events that coded to the preferred term of rash.

Source: Applicant's Table 58, Study EGF30008 Clinical Study Report

Table 48. Adverse reactions occurring in $\geq 10\%$ of patients

Reactions	Lapatinib + letrozole, (N = 654)			Placebo + letrozole, (N = 624)		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Anorexia	11	<1	0	9	<1	0
Skin and subcutaneous tissue disorders						
Rash ^b	44	1	0	13	0	0
Dry skin	13	<1	0	4	0	0
Alopecia	13	<1	0	7	0	0
Pruritus	12	<1	0	9	<1	0
Nail Disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0

Source: Applicant's Tykerb labeling, Section 6.1, *Adverse Reactions*

Reviewer's comment: These adverse events are consistent with the observations in the lapatinib and capecitabine trial for the Tykerb marketing approval. Given the high frequency of events such as diarrhea and rash in the treatment arm, the randomization arm may be unblinded in some patients.

No hematologic adverse events were reported to be $\geq 10\%$.

In the 120-day safety update, analysis of common adverse events did not reveal any new findings. The order of frequency and percentages of adverse events in both groups remained the same: diarrhea > rash > nausea > fatigue.

7.4.2 Less Common Adverse Events

No new adverse events were identified in the safety review for this sNDA. The adverse event profile is consistent with Section 6, *Adverse Reactions* in the current lapatinib labeling.

7.4.3 Laboratory Findings

Selected clinical laboratory evaluations based on hematologic and chemistry parameters of study EGF30008 were summarized as highest grade of AE observed per each parameter in each subject below. Laboratory AEs, regardless of relationship, are described below:

Table 49. Selected hematology parameters

Parameter	Visit	N evaluable	Number (%) of subjects	
			Grade 3	Grade 4
Letrozole 2.5 mg + Placebo (N=624)				
Hemoglobin	Screen	580	1 (<1)	0
	Any Post ^a	619	6 (<1)	1 (<1)
Platelets	Screen	580	1 (<1)	1 (<1)
	Any Post ^a	618	3 (<1)	2 (<1)
Total White Blood Cells	Screen	581	0	0
	Any Post ^a	619	0	1 (<1)
Neutrophils	Screen	562	1 (<1)	6 (1)
	Any Post ^a	612	6 (<1)	22 (4)
Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)				
Hemoglobin	Screen	615	1 (<1)	0
	Any Post ^a	643	4 (<1)	3 (<1)
Platelets	Screen	612	0	0
	Any Post ^a	642	1 (<1)	2 (<1)
Total White Blood Cells	Screen	614	0	1 (<1)
	Any Post ^a	643	2 (<1)	0
Neutrophils	Screen	594	1 (<1)	6 (1)
	Any Post ^a	639	8 (1)	14 (2)

Source data: Study EGF30008, [Table 8.73](#).

a. Maximum toxicity grade at any scheduled or unscheduled post-screening visit.

Table 50. Selected clinical chemistry parameters

Parameter	Visit	n	Number (%) of subjects	
			Grade 3	Grade 4
Letrozole 2.5 mg + Placebo (N=624)				
Creatinine	Screen	581	0	0
	Any Post ^a	619	0	0
Blood Urea Nitrogen	Screen	262	0	0
	Any Post ^a	293	3 (1)	0
Total bilirubin	Screen	570	0	0
	Any Post ^a	616	8 (1)	2 (<1)
AST	Screen	561	2 (<1)	0
	Any Post ^a	615	13 (2)	2 (<1)
ALT	Screen	576	0	0
	Any Post ^a	617	9 (1)	0
Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)				
Creatinine	Screen	616	0	0
	Any Post ^a	644	4 (<1)	0
Blood Urea Nitrogen	Screen	277	0	0
	Any Post ^a	312	2 (<1)	0
Total bilirubin	Screen	603	0	0
	Any Post ^a	642	6 (<1)	1 (<1)
AST	Screen	599	0	0
	Any Post ^a	638	36 (6)	0
ALT	Screen	611	1 (<1)	0
	Any Post ^a	643	33 (5)	1 (<1)

Source data: Study EGF30008, [Table 8.77](#).

a. Maximum toxicity grade at any scheduled or unscheduled post-screening visit.

Reviewer's comment: For the hematology profile, there is a greater percentage of grade 4 neutrophil decrease in the placebo plus letrozole group, but the significance is unknown.

Consistent with the adverse event profile, there are a greater number of laboratory abnormalities (AST, ALT, BIL) related to hepatic function.

7.4.4 Vital Signs

The subjects had their vital signs measured at each visit. These vital signs included blood pressure, heart rate, body weight, and temperature. The reviewer verified and confirmed the applicant's analysis that no clinically significant trends in the vital signs of either treatment group were observed.

7.4.5 Electrocardiograms (ECGs)

According to the “Warnings and Precautions” and “Clinical Pharmacology” sections of the lapatinib label , QT prolongation measured by automated machine-read evaluation of ECG was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients.

In Study EGF30008, ECGs were performed on patients at the start of the study, within two weeks prior, and at the end of study conclusion or withdrawal. The findings are presented below:

Table 51. Electrocardiogram Findings

Screening	Number (%) of subjects	
	Lapatinib + letrozole, N=654	Placebo + letrozole, N=624
N evaluable	616	598
Normal	471 (76)	444 (76)
Abnormal, not clinically significant	139 (23)	144 (24)
Abnormal, clinically significant	6 (1)	10 (2)
Conclusion of study		
N evaluable	295	267
Normal	216 (73)	198 (74)
Abnormal, not clinically significant	76 (26)	62 (23)
Abnormal, clinically significant	3 (1)	7 (3)

Source: Applicant’s Table 85, Study EGF30008 Clinical Study Report

Reviewer’s comment: The Applicant’s assessment of the ECGs was verified separately by the reviewer. There appeared to be no difference between the two treatment groups with regard to the percentage of subjects with clinically abnormal ECG findings, based on the limited number of patients that had an ECG performed at study conclusion.

This adverse reaction was also recognized separately from the review of this sNDA 22-059. It will be addressed in the updated “Adverse Reactions” section of the product labeling.

7.4.6 Special Safety Studies/Clinical Trials

No special studies were performed during the development program pertinent to this review.

7.4.7 Immunogenicity

Ten patients experienced symptoms of hypersensitivity reactions in Study EGF30008, eight in the lapatinib plus letrozole arm and two in the placebo plus letrozole arm. The reactions were all grade 1-2 in severity and all resolved.

Reviewer's comment: This adverse reaction was also recognized separately from the review of this sNDA 22-059. It will be addressed in the updated (b) (4) section of the product labeling.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A single fixed dose of Tykerb in combination with letrozole was evaluated in the phase 3 trial; therefore, no conclusions can be made regarding dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

Drug-Demographic Interactions

All subjects enrolled were women; thus, no analysis of drug-gender interaction could be performed. Similarly, almost all subjects enrolled in the trial were white (84%) and consequently, no analysis of drug-ethnicity interactions were undertaken.

Examining age as a demographic variable using *ae.xpt*, the most common adverse events (diarrhea, nausea, and rash) in the < 65 year and ≥ 65 year age categories were the same as reported in the safety population. The age distribution was somewhat evenly distributed, although there was a slightly higher percentage (55%) of subjects who were < 65 years of age. Within each treatment arm, the distribution of AEs of each toxicity grade was similar across the two age groups.

Evaluation by ethnic groups did not reveal any differences either. The majority of subjects were White and the distribution of adverse events in Whites was similar to the overall population. Furthermore, no conclusions can be made with other ethnic groups due to the small number of subjects.

7.5.4 Drug-Disease Interactions

None known.

7.5.5 Drug-Drug Interactions

There are no new drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.7 Additional Submissions / Safety Issues

The 120-Day Clinical Safety Update to the sNDA was submitted on July 21, 2009 as required by 21 CFR 314.50(d)(5)(vi)(b). The database lock date for this report is February 3, 2009.

As of February 3, 2009, 1139 (89%) subjects in the safety population discontinued study drug, 580 (89%) subjects in the lapatinib plus letrozole group and 559 (90%) subjects in the placebo plus letrozole arm. Therefore, 139 subjects total continued, 75 subjects in the lapatinib plus letrozole arm, and 64 subjects in the placebo plus letrozole arm, a decrease from 91 and 107 subjects, respectively as of June 3, 2008, the database lockpoint at the time of the sNDA submission. In the HER2-positive subgroup, 75 subjects continued the study, 39 in the placebo plus letrozole group and 36 subjects in the lapatinib plus letrozole group. Reason for discontinuation in the ITT population was due to death.

Overall, no significant changes or findings in the safety profile of lapatinib were identified since the submission of the sNDA. There was no change in the numbers of subjects with fatal adverse events. The number of subjects in the lapatinib plus letrozole arm who experienced adverse events of special interest remained the same.

8 Postmarket Experience

Lapatinib received FDA marketing approval in the United States in March 13, 2007. In clinical trials, a total of 18,641 subjects were enrolled in phase I, II, and III lapatinib studies, of which approximately 14,104 will have received lapatinib as of February 6, 2009. Of the 14,104 subjects receiving lapatinib, approximately 4532 were participating in adjuvant breast cancer studies, and 9057 participated in studies in the metastatic disease setting (e.g., breast, colorectal, gastric, non-small cell lung, and head and neck cancers). Approximately 5,664 patient years of lapatinib treatment have been prescribed worldwide as of December 2008. This calculation is based on available sales information volume and assuming a daily dose of 1250 mg.

Consistent with the safety experience in clinical trials, hepatotoxicity has been observed in the postmarketing experience. This safety event was highlighted as a black box warning in the lapatinib label. No other significant new safety issues have been identified in the post-marketing period to date.

Additionally, hypersensitivity reactions, including anaphylaxis, and nail disorders including paronychia were observed in the postmarketing safety experience.

9 Appendices

9.1 Literature Review/References

Literature pertinent to metastatic breast cancer and lapatinib were reviewed and cited throughout this review.

9.2 Labeling Recommendations

Submission of this supplemental NDA also includes a proposed label.

9.3 Advisory Committee Meeting

Although initially slated for discussion at the Oncologic Drugs Advisory Committee meeting, ODAC was cancelled due to the Applicant's decision to amend the indication. Therefore, no advisory committee was determined to be necessary for this application.

9.4 Existing Postmarketing Requirements

This sNDA is being considered for accelerated approval because Study EGF30008 did not evaluate the efficacy and safety of lapatinib in patients with hormone receptor-positive metastatic breast cancer that had previously received trastuzumab in the neoadjuvant or adjuvant setting. As a condition of accelerated approval, the Applicant has agreed to conduct additional trials to confirm the safety and efficacy of lapatinib in this patient population.

9.5 Supplemental Labeling Requests 003 and 006

On December 5, 2008, the Applicant submitted supplemental labeling request (SLR) 006 to change the Tykerb labeling and patient information leaflet to include nail disorders in the *Adverse Reactions* section and hypersensitivity to the *Contraindications* and *Adverse Reactions* sections.

Nail Disorders

Nail disorders has been reported in clinical trials, 1-4%.

The pathogenesis of TKI-induced paronychia remains speculative, however, a possible mechanism is increased penetration of nail fragments in the perungual tissue resulting from epidermal thinning as it is a EGFR inhibitor.

Postmarketing: 49 reports of nail disorder, 11 included information on positive dechallenge and 3 reports of positive rechallenge. Time to onset in these 14 reports ranges from 4 to 363 days with a mean of approx. 69 days or 10 weeks which is consistent with the literature. All reports occurred in females.

Hypersensitivity

There were 21 cases in overall dataset, 16 cases were found unassessable or confounded. The remaining five cases have been further reviewed. There was one positive rechallenge and 4 positive dechallenges. Two were spontaneous and three were from clinical trials.

In 24% (5/21) of the reports an association between the use of lapatinib and the HS/anaphylaxis is possible due to:

- Positive dechallenge data of event resolution within 30 days of lapatinib was reported in 4 of 5 patients.
- Positive rechallenge data was reported in one patient.

Time to onset was 5-10 days with a median of 7 days. None were fatal. Symptoms were rash, SOB, facial and tongue swelling, mouth sores, rhinitis, fever,

Based on disproportionality analysis, the EB05 values for this AE is not considered a signal, however, given the seriousness of hypersensitivity/anaphylaxis, it will be added to the label.

Labeling for other agents in this class:

- Sunitinib: under postmarketing AE section (b) (4) Hypersensitivity reactions, including angioedema, have been reported.
- Sorafenib: Under Contraindications: NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.

Reviewer's comment: The proposed labeling by the Applicant to include nail disorders in the Adverse Reactions section and hypersensitivity to the Contraindications and Adverse Reactions sections of the labeling are acceptable.

APPEARS THIS WAY ON ORIGINAL

References

- ⁱ Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jaenicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Chaudri-Ross H, Lang R, Wyld P, Bhatnagar A. Phase III Study of Letrozole Versus Tamoxifen as First-Line Therapy of Advanced Breast Cancer in Postmenopausal Women: Analysis of Survival and Update of Efficacy From the International Letrozole Breast Cancer Group. *J. Clinical Oncology*. 2003; 21(11):2101-2109.
- ⁱⁱ Nicholson RI, Gee JMW, Harper ME. EGFR & Cancer Prognosis. *Eur. J. Cancer*. 2001;37 (Suppl 4): 9-15.
- ⁱⁱⁱ Yarden RI, Wilson MA, Chrysogelos SA. Estrogen suppression of EGFR expression in breast cancer cells: A possible mechanism to modulate growth. *J Cell Biochem*. 2001; Suppl 36:232-46.
- ^{iv} Wang C, Edwards A, Lu Z, DiGiovanna MP. Antitumor Activity of Combinations of Tamoxifen and Herceptin in BT-474 Human Breast Cancer Cells; *Proceedings AACR*. 2003; (44), Abs 756.
- ^v Lipton A, Ali SM, Leitzel K, Demers L, Harvey HA, Chaudri-Ross HA, Brady C, Wyld P, Carney W. Serum HER-2/neu and Response to the Aromatase Inhibitor Letrozole Versus Tamoxifen. *J. Clin Oncology*. 2003a; 21(10): 1967-1972.
- ^{vi} Lipton A, Leitzel K, Ali SM, Demers L, Harvey HA, Chaudri-Ross HA, Lang R, Hackl W, Hamer P, Carney W. Serum HER-2/neu conversion to positive at the time of cancer progression in metastatic breast patients treated with letrozole vs. tamoxifen. *Proceedings ASCO*. 2003b; 3: abs 8.
- ^{vii} Read LD, Keith D Jr, Slamon DJ et al. Hormonal modulation of HER-2/neu proto-oncogene messenger ribonucleic acid and p185 protein expression in human breast cancer cell lines. *Cancer Res* 1990;50;3947-54.
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- ^{ix} Downsett M. Overexpression of HER-2 as a resistance mechanism to hormonal therapy in breast cancer. *Endocr Relat Cancer* 2001;8:191-5.
- ^x Kaufman B. Trastuzumab plus anastrozole prolongs progression-free survival in postmenopausal women with HER2 positive, hormone-dependent metastatic breast cancer (MBC). European Society for Medical Oncology (ESMO) Congress, Abstract no. LBA2, 2006.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-3	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-6	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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JENNIE T CHANG
01/25/2010

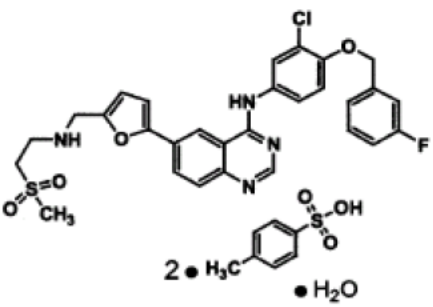
PATRICIA CORTAZAR
01/25/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

CHEMISTRY REVIEW(S)

Chemistry Review: #1	1. Division: HFD-580	2. NDA Number: 22-059
3. Name and Address of Applicant: SmithKline Beechan Corporation d/b/a GlaxoSmithKline One Franklin Plaza, 200 North 16 th Street, Philadelphia, PA 19102	4. Supplement(s): SE Number: 007 Date(s): 31-MAR-2009	
5. Name of Drug: Tykerb®	6. Nonproprietary name: lapatinib ditosylate	
7. Supplement Provides for the support of lapatinib in combination with (b) (4) (b) (4)	8. Amendment(s): N/A	
9. Pharmacological Category: Epidermal growth factor receptor (EGFR) and erbB-2 (Her2/neu) dual tyrosine kinase inhibitor	10. How Dispensed: R _x	11. Related Documents: N/A
12. Dosage Form: TAB	13. Potency: 250 mg	
14. Chemical Name and Structure: N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate		
		
16. Comments: As this is an efficacy supplement, all information related to Module 3 (Quality) is incorporated by cross-reference to the original NDA 22-059 based on the sponsor's statement. Based on the previous calculation with the current proposed indication and the sponsor's request of EA categorical exclusion, it appears to be acceptable. There is no CMC changes involved in the supplement.		
17. Conclusion: From the CMC stand point, approval is recommended based on the provided information.		
17. Name: Z. Jean Tang, Ph.D., Chemist	Signature:	Date:
18. Concurrence: Liang Zhou, Ph.D., Acting Branch Chief, Div., VIII, ONDQA	Signature:	Date:

NDA

Page X

Chemistry Review Notes: N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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ZHE J TANG
01/07/2010

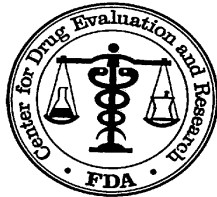
LIANG ZHOU
01/08/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: **22-059**
SERIAL NUMBER: **S-007**
DATE RECEIVED BY CENTER: **31 March 2009**
PRODUCT: **Tykerb® (lapatinib)**
INTENDED CLINICAL POPULATION: **Postmenopausal women with hormone
receptor positive metastatic breast cancer
that overexpresses the HER2 receptor; in
combination with letrozole**
APPLICANT: **GlaxoSmithKline**
DOCUMENTS REVIEWED: **Electronic Submission**
REVIEW DIVISION: **Division of Drug Oncology Products**
PHARM/TOX REVIEWER: **Kimberly A. Benson, Ph.D.**
PHARM/TOX SUPERVISOR: **Haleh Saber, Ph.D.**
DIVISION DIRECTOR: **Robert Justice, MD**
PROJECT MANAGER: **Kim Robertson**

Date of review submission to DARRTS: 29 January 2010

PHARMACOLOGY/TOXICOLOGY REVIEW**INTRODUCTION AND DRUG HISTORY**

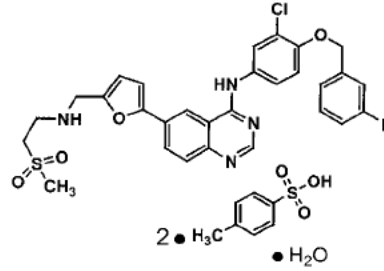
NDA number: 22-059
Review number: 3 (Labeling Review)
Sequence number/date/type of submission: S-007/31 Mar 2009/Electronic NDA
Information to Applicant: Yes () No (X)
Applicant and/or agent: GlaxoWellcome
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709-3398
Manufacturer for drug substance: Glaxo Operations UK Limited
Priory Street
Ware
Hertfordshire SG12 0DJ
United Kingdom

Reviewer name: Kimberly A. Benson, Ph.D.
Division name: Division of Drug Oncology Products
Review completion date: 28 January 2010

Drug:

Trade name: Tykerb®
Generic name: Lapatinib ditosylate
Code name: GW572016
GW572016X – free base
GW572016F – ditosylate salt
GW572016B – dichloride salt
Chemical name: *n*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-
({[2-(methylsulfonyl)ethyl]amino}methyl)-2-
furyl]quinazolin-4-amine bis(4-
methylbenzenesulfonate) monohydrate
CAS registry number: 388082-78-8
Molecular formula/molecular weight: C₂₉H₂₆ClFN₄O₄S(C₇H₈O₃S)₂H₂O/943.48

Structure:



Relevant INDs/NDAs/DMFs: IND 61,362

Pharmacologic class: kinase inhibitor

Intended clinical population: TYKERB is indicated in combination with

- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2; IHC 3+ or IHC 2+ confirmed by FISH) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Clinical formulation:

Table 1 Composition of Lapatinib Tablets, 250 mg

Component	Quantity (mg/tablet)	Function	Reference to Standard
(b) (4) Lapatinib Ditosylate ¹	405.0	Active	GSK Specification (b) (4)
Core Tablet			
Sodium Starch Glycolate			(b) (4)
Magnesium Stearate			(b) (4)
(b) (4)			
Film Coating			
(b) (4) Orange, (b) (4)			(b) (4)
(b) (4)			
Total Coated Tablet Weight	927.0	-	-

Notes:
(b) (4)

[Table excerpted from Applicant’s original submission]

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

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The following recommendations to the Applicant's proposed labeling are given. The Applicant's proposed wording is followed by the recommendation with a rationale for the recommended changes.

The Applicant proposed

5 WARNINGS AND PRECAUTIONS

(b) (4)



FDA recommends

5 WARNINGS AND PRECAUTIONS

5.7 Use in Pregnancy

TYKERB can cause fetal harm when administered to a pregnant woman. Based on findings in animals, TYKERB is expected to result in adverse reproductive effects. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth [see *Use in Specific Populations (8.1)*].

There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this

drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Rationale

- Changes recommended to conform with CFR and current practices regarding the animal data being presented in the Use in Specific Populations sections and not the Warnings and Precautions Section. Also, removed the Pregnancy Category D statement from this section. The category listed here is redundant, as placement of this information in Warnings and Precautions implies that the drug is Category D.

The Applicant proposed

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.7)].

FDA recommends

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.7)].

Based on findings in animals, TYKERB can cause fetal harm when administered to a pregnant woman. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth. When administered to pregnant animals during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits) at maternally toxic doses. There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine), 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).

Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC following 1,250 mg

dose of lapatinib plus capecitabine). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC following 1,250 mg dose of lapatinib plus capecitabine) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

Rationale

- The animal reproductive and developmental toxicity information was moved from Warnings and Precautions [5.7] based on current practices.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22059

SUPPL-7

SMITHKLINE
BEECHAM CORP
DBA
GLAXOSMITHKLIN
E

TYKERB TABLETS

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/s/

KIMBERLY A BENSON
01/29/2010

HALEH SABER
01/29/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/Serial Number: 22-059/0007

Drug Name: TYKERB™ (lapatinib)

Indication(s): Post-menopausal hormone receptor positive and HER2+ MBC

Applicant: GSK

Date(s): Submission date: 3/31/2009
PDUFA date: 1/30/2010
Review finish date: 12/18/2009

Review Priority: Standard

Biometrics Division: DBV

Primary Reviewer: Qiang (Casey) Xu

Secondary Reviewer: Shenghui Tang, Ph.D., Acting Team Leader

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Deputy Director

Medical Division: Oncology Drug Products (HFD 150)

Clinical Team: Jennie Chang, Clinical Reviewer
Patricia Cortazar, Team Leader

Project Manager: Kim Robertson

Keywords: MBC, HER2-Positive, Progression-Free Survival, Overall Survival, Kaplan-Meier product limit

This application is for the addition of a new clinical indication for the use of lapatinib in combination with letrozole (b) (4) with hormone receptor-positive HER2-positive, (b) (4) metastatic breast cancer (MBC). It is based on a Phase III, multi-center, randomized double-blind trial comparing lapatinib plus letrozole versus letrozole plus placebo as first-line therapy for MBC in post-menopausal women with endocrine sensitive breast cancer.

Five protocol amendments were made after the start of subject recruitment. In Amendment 3, the sponsor increased the ITT sample size from 760 to 1280 to ensure an adequate statistical power for analysis in HER2-positive subgroup. This change was made because further clinical and pre-clinical data indicated that lapatinib effect in breast cancer was primarily mediated through the HER2 receptor. Amendment 4 revised the study primary endpoint from time-to-progression (TTP) to progression-free-survival (PFS) in accordance with regulatory guidance endorsing PFS as the preferred endpoint and also changed the primary population of interest from ITT to HER2-positive.

The hazard ratio of investigator-evaluated PFS in the HER2-positive population was 0.71 (95% CI: 0.53, 0.96; stratified log rank p-value=0.019), favoring the lapatinib+letrozole group. The median PFS was 13.0 weeks in the letrozole plus placebo group compared with 35.4 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the ITT population was 0.86 (95% CI: 0.76, 0.98; stratified log rank p-value=0.026). The median PFS was 47.0 weeks in the letrozole plus placebo group compared with 51.7 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the HER2-negative population was 0.90 (95% CI: 0.77, 1.05; stratified log rank p-value=0.188). The median PFS was 58.3 weeks in the letrozole plus placebo group compared with 59.7 weeks in the letrozole plus lapatinib group.

The overall survival (OS) was not mature at data cut-off on 03 June 2008; only 474 (37%) of the ITT subjects had died and 54% were still being followed for survival. The OS hazard ratio estimate in HER2-positive population was 0.74 (95% CI: 0.5, 1.1; p-value=0.113), favoring the lapatinib treated group. In the ITT and HER2-negative populations, the OS hazard ratio estimates were 1.01 (95% CI: 0.8, 1.2; p-value=0.916) and 1.15 (95% CI: 0.9, 1.4; p-value=0.193), respectively, favoring the placebo group.

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Qiang (Casey) Xu) of this application. This pivotal study was not designed to test and estimate the lapatinib effect in patients who had received prior adjuvant trastuzumab, a currently widely adopted regimen in US. Therefore, the combined therapy may be considered for the patient population for whom a trastuzumab-containing chemotherapy regimen is not indicated. A randomized study is necessary to estimate the efficacy of lapatinib+letrozole in a population similar to current US patients. The inference regarding favorable benefit-risk profile for the use of lapatinib in combination with letrozole in patients with hormone receptor-positive HER2-positive MBC is deferred to the clinical review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

SHENGHUI TANG
12/31/2009

RAJESHWARI SRIDHARA
12/31/2009



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-059/0007

Drug Name: TYKERB™ (lapatinib)

Indication(s): Post-menopausal hormone receptor positive and HER2+ MBC

Applicant: GSK

Date(s): Submission date: 3/31/2009
PDUFA date: 1/30/2010
Review finish date: 12/18/2009

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Biometrics Division: DBV

Statistical Reviewer: Qiang (Casey) Xu

Concurring Reviewers: Shenghui Tang, Ph.D., Acting Team Leader
Rajeshwari Sridhara, Ph.D., Deputy Director

Medical Division: Oncology Drug Products (HFD 150)

Clinical Team: Jennie Chang, Clinical Reviewer
Patricia Cortazar, Team Leader

Project Manager: Kim Robertson

Keywords: MBC, HER2-Positive, Progression-Free Survival, Overall Survival, Kaplan-Meier product limit

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study results based on the primary endpoint progression-free survival (PFS) showed that the combined treatment of lapatinib plus letrozole had a statistically significant benefit compared to letrozole in post-menopausal women with hormone receptor positive and human epidermal growth factor receptor 2 (HER2) positive untreated advanced or metastatic breast cancer. However, a modest benefit was seen in the overall ITT subjects which mostly comprised of HER2-negative subpopulation (74%). During the review process, the sponsor modified the indicated population from ITT population to HER2-positive population.

This pivotal study was not designed to test and estimate the tested treatment effect in patients who had received prior adjuvant trastuzumab, a currently widely adopted regimen in US. Therefore, the combined therapy may potentially be considered for the patient population for whom a trastuzumab-containing chemotherapy regimen is not indicated. A randomized study is necessary to precisely estimate the efficacy of lapatinib+letrozole in a population similar to current US patients. Whether the PFS benefit observed in the HER2-positive subgroup is clinically meaningful is deferred to the clinical review team.

1.2 Brief Overview of Clinical Studies

This was a Phase III multicenter, multinational, randomized, double-blind, placebo-controlled trial to compare the combination of letrozole and lapatinib with letrozole alone in subjects with HER2-positive hormone receptor positive, untreated advanced or metastatic breast cancer.

Subjects with hormone receptor positive advanced or metastatic breast cancer (ITT population) were randomly assigned at 1:1 ratio to receive once daily oral treatment with either lapatinib (1500 mg) with letrozole (2.5 mg), or letrozole (2.5 mg) with placebo, stratified by site of disease and time since prior adjuvant endocrine therapy. The primary efficacy endpoint as amended was investigator-assessed progression free survival (PFS) in HER2-positive patients with investigator-assessed PFS in ITT population as the main secondary efficacy endpoint of interest.

A total of 1286 subjects were randomized into this study with 644 patients assigned to placebo plus letrozole group and 642 patients assigned to lapatinib plus letrozole group. Two hundred and nineteen patients (17%) were HER2-positive. Among them, 108 HER2-positive patients were in placebo plus letrozole group, and 111 were in lapatinib plus letrozole group.

1.3 Statistical Issues and Findings

The hazard ratio of investigator-evaluated PFS in the HER2-positive population was 0.71 (95% CI: 0.53, 0.96; stratified log rank p-value=0.019), favoring the lapatinib+letrozole group. The median PFS was 13.0 weeks in the letrozole plus placebo group compared with 35.4 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the ITT population was 0.86 (95% CI: 0.76, 0.98; stratified log rank p-value=0.026). The median PFS was 47.0 weeks in the letrozole plus placebo group compared with 51.7 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the HER2-negative population was 0.90 (95% CI: 0.77, 1.05; stratified log rank p-value=0.188). The median PFS was 58.3 weeks in the letrozole plus placebo group compared with 59.7 weeks in the letrozole plus lapatinib group.

The overall survival (OS) was not mature at data cut-off on 03 June 2008; only 474 (37%) of the ITT subjects had died and 54% were still being followed for survival. The OS hazard ratio estimate in HER2-positive population was 0.74 (95% CI: 0.5, 1.1; p-value=0.113), favoring the lapatinib treated group. In the ITT and HER2-negative populations, the OS hazard ratio estimates were 1.01 (95% CI: 0.8, 1.2; p-value=0.916) and 1.15 (95% CI: 0.9, 1.4; p-value=0.193), respectively, favoring the placebo group.

In summary, this reviewer has the following concerns regarding this application: (1) The primary efficacy population was changed from ITT to HER2-positive after 760 patients were randomized in this study, and sample size was increased to 1286 to have adequate HER2-positive patients; (2) Study was not stratified at randomization by HER2 status; and (3) Demonstration of OS benefit has generally been the standard for consideration of regular approval in first-line setting of breast cancer. At this time OS benefit of lapatinib treatment has not been demonstrated in the ITT or HER2-positive population.

2. INTRODUCTION

2.1 Overview

Lapatinib is an orally administered, small molecule, reversible inhibitor of the intracellular tyrosine kinase domains of EGFR and HER2. Lapatinib in combination with capecitabine was granted regulatory approval in the US (13 March 2007) for patients with locally advanced or metastatic breast cancer (MBC) whose tumors over-express HER2 and who have received prior therapy including anthracyclines, taxanes, and trastuzumab.

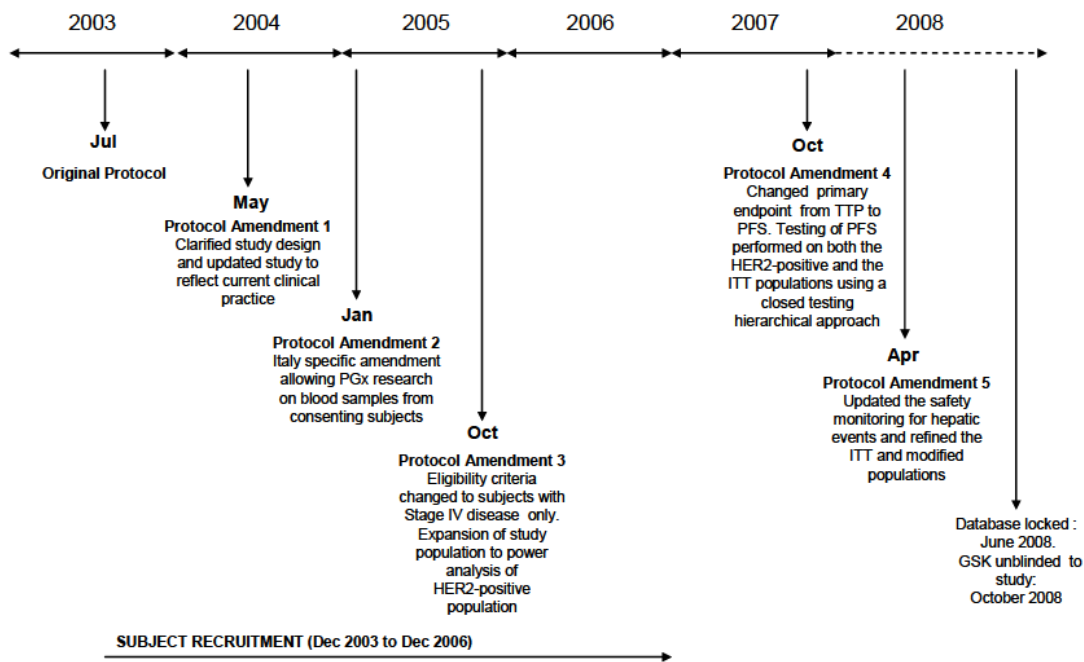
This application is for the addition of a new clinical indication for the use of lapatinib in combination with letrozole in patients with hormone receptor-positive HER2-positive MBC. This application is based on Study EGF30008, a Phase III, multi-center, randomized double-blind trial comparing lapatinib plus letrozole versus letrozole plus placebo as first-line therapy for MBC in post-menopausal women with endocrine sensitive breast cancer (ITT population).

The original EGF30008 protocol was dated 17 July 2003. Five protocol amendments were made afterwards (Figure 2.1.1), and all five were made after the start of subject recruitment. Among them, Amendments 3 and 4 were of most importance as these two amendments impacted the final efficacy analyses.

In Amendment 3 (October 2005), the sponsor increased the ITT sample size from 760 to 1280 to ensure an adequate statistical power for analysis in HER2-positive subgroup. This change was made because further clinical and pre-clinical data indicated that lapatinib effect in breast cancer was primarily mediated through the HER2 receptor.

Amendment 4 (October 2007) revised the study primary endpoint from time-to-progression (TTP) to progression-free-survival (PFS) in accordance with regulatory guidance endorsing PFS as the preferred endpoint and also changed the primary population of interest from ITT to HER2-positive. The sponsor claimed that the decision of the primary population change was not based on knowledge of the data from this trial, which remained blinded, but was made based on accumulating scientific knowledge from external data and information on the mechanism of action of lapatinib. Per sponsor, both decisions to change the primary endpoint and to change the primary population were made prospectively prior to unblinding of the database.

Figure 2.1.1 Summary of Protocol Amendments



*From the sponsor’s clinical report Figure 2

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives of Study EGF30008

The primary objective of EGF30008 was to evaluate and compare investigator-assessed PFS in subjects with ER positive and/or PgR positive, HER2-positive advanced or metastatic breast cancer treated with lapatinib and letrozole versus placebo and letrozole.

The main secondary objectives were: to evaluate and compare the two treatment groups with respect to investigator-assessed PFS in subjects with ER positive/PgRpositive advanced or metastatic breast cancer (ITT population).

3.1.2 Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, Phase III study to evaluate and compare the efficacy and tolerability of the combined treatment of lapatinib and letrozole versus the treatment of placebo and letrozole in 1286 post-menopausal women with hormone receptor positive (ER positive and/or PgR positive) advanced or metastatic breast cancer and had not received prior therapy for advanced or metastatic disease.

Patients were 1:1 randomly assigned to receive either lapatinib (1500 mg once daily orally) with letrozole (2.5 mg once daily orally), or letrozole (2.5 mg once daily orally) with placebo (which matched with lapatinib tablet) until disease progression or withdrawal from therapy. Randomization was stratified by site of disease (soft tissue/visceral or bone only disease) and time since prior adjuvant endocrine therapy (≥ 6 months versus < 6 months). Figure 3.1.2.1 shows the study design of EGF30008.

The original primary endpoint was time-to-progression (TTP) in the ITT population. In Amendment 4, the sponsor changed the primary endpoint to investigator-assessed PFS in HER2-positive population, and considered investigator-assessed PFS in ITT population as a secondary endpoint. To enable evaluation of both ITT and HER2-positive subgroup, a hierarchical testing approach was proposed. The testing was first performed in HER2-positive group and only if statistical significance was achieved at alpha level 0.05 could the ITT population be evaluated.

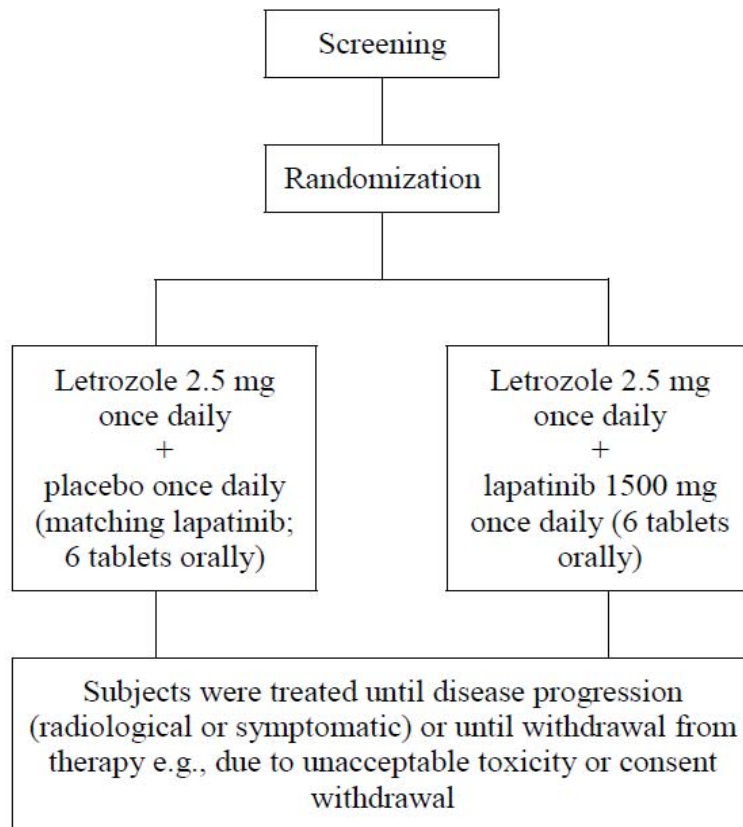
A total of 173 events (218 patients) were required in the HER2-positive population to provide 80% power to detect a hazard ratio of 0.645 corresponding to a 55% increase in median PFS in subjects who received lapatinib+letrozole (15.5 months) compared with subjects who received placebo+letrozole (10 months). A total of 612 events (1280 patients) were required in the ITT population to provide 90% power to detect a hazard

ratio of 0.769, corresponding to a 30% increase in median PFS in lapatinib+letrozole group (13 months) compared with placebo+letrozole (10 months). Treatment groups were compared using a stratified log-ranktest, stratifying for site of disease and time since prior adjuvant endocrine therapy.

Safety and efficacy assessments were performed on all subjects at 4-week and 12-week intervals, respectively, as well as at the end of treatment. For subjects who had been on study treatment for ≥ 108 weeks, safety and efficacy assessments were performed at 12-week intervals starting at Week 108. Subjects withdrawn from treatment without progression were to have radiological assessments performed every 12 weeks until disease progression, until the subject began a new anti-cancer therapy, or death. All subjects were to be followed for survival information until death.

Measurable disease and response criteria used in the protocol per RECIST guidelines and were based on radiologic assessments. Additionally, progressions could be determined by symptomatic progression or clinical disease assessments for palpable or visual lesions. Patients who neither progressed nor died were censored at the date of last tumor assessment. Patients who were lost to follow-up or started on subsequent therapy for breast cancer were censored at the date of the last tumor assessment.

Figure 3.1.2.1 Study Design



*From the sponsor's clinical report Figure 1

3.1.3 Patient Disposition

3.1.3.1 Patient Enrollment

A total of 1286 ITT patients (642 in lapatinib+letrozole group; 644 in placebo+letrozole group) with hormone-sensitive metastatic breast cancer at primary diagnosis or relapse after neo-adjuvant or adjuvant therapy were enrolled in this study. Patients were enrolled between 9 Dec 2003 and 29 Dec 2006 across 212 study sites in 29 countries across 5 regions (North America, Latin America, Western Europe, Eastern Europe and Asia Pacific).

The study enrollment was open to all subjects regardless of their HER2 status. All subjects had their HER2 status centrally tested after they were enrolled on this study. As a result, the ITT population consisted of three subpopulations: the HER2-positive, HER2-negative, and HER2-missing populations. Table 3.1.3.1 summarizes the patient population in this study.

Table 3.1.3.1 Summary of Patient Population

Population	Letrozole + Lapatinib n (%)	Letrozole + placebo n (%)	Total n (%)
ITT	642 (100)	644 (100)	1286 (100)
HER2-positive	111 (17)	108 (17)	219 (17)
HER2-negative	478 (74)	474 (74)	952 (74)
HER2-missing	53 (8)	62 (10)	115 (9)
ER or PgR-positive	513 (80)	512 (80)	1025 (80)

The HER2-missing population was defined as an exploratory population as those subjects whose HER2 status for both FISH and IHC was either missing or unevaluable. Of 115 HER2-missing subjects, 50 (43%) never had tissue submitted and 65 (57%) had tissue submitted but results could not be obtained due to insufficient or unevaluable samples.

3.1.3.2 Treatment Discontinuation and Study Termination

In the ITT population, at the clinical cut-off date (03 June 2008), the majority of subjects (693 [54%]) were still on study treatment or being followed for survival; and a total of 198 (15%) subjects were still receiving study treatment. Death due to disease progression

(467 [36%]) was the primary reason for study discontinuation. Compared with the ITT population, higher proportion of subjects (129 [59%]) in the HER2-positive population were discontinued from the study, driven by larger rate of death due to disease progression (103 [47%]), as presented in Table 3.1.3.2.

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Table 3.1.3.2 Study Discontinuation in ITT and HER2-Positive Populations

	ITT		HER2-Positive	
	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)
Discontinuation from study (%)	298 (46)	295 (46)	63 (57)	66 (61)
Ongoing (%)	344 (54)	349 (54)	48 (43)	42 (39)
Reason for Discontinuation				
Death due to PD	238 (37)	229 (36)	50 (45)	53 (49)
Consent withdrawn	29 (5)	34 (5)	10 (9)	4 (4)
Lost to follow-up	22 (3)	26 (4)	3 (3)	8 (7)
Protocol violation	5 (<1)	3 (<1)	0 (0)	1 (<1)
Other	4 (<1)	3 (<1)	0 (0)	0 (0)

The primary reasons for subjects discontinuing study treatment were disease progression and AEs. A lower percentage of subjects in the placebo+letrozole group compared with the lapatinib+letrozole group were discontinued for AEs, but a higher percentage of subjects in the placebo+letrozole group were discontinued from study treatment for cancer progression (Table 3.1.3.3).

Table 3.1.3.3 Treatment Discontinuation in ITT and HER2-Positive Populations

	ITT		HER2-Positive	
	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)
Discontinuation from treatment (%)	539 (84)	549 (85)	103 (93)	98 (91)
Continuing treatment (%)	103 (16)	95 (15)	8 (7)	10 (9)
Reason for Discontinuation				
AE	92 (14)	32 (5)	7 (6)	3 (3)
Consent withdrawn	33 (5)	32 (5)	9 (8)	5 (5)
Lost to follow-up	5 (<1)	2 (<1)	0 (0)	0 (0)
Protocol violation	8 (1)	9 (1)	0 (0)	3 (3)
Disease Progression (Radiological/Symptomatic)	380 (59)	449 (69)	82 (74)	85 (79)
Death	1 (<1)	7 (1)	0 (0)	1 (<1)
Other	20 (3)	18 (3)	5 (5)	1 (<1)

3.1.3.3 Patient Demographics and Baseline Disease Characteristics

Demographic characteristics were similar between the two treatment groups for the ITT population and HER2-positive population. All subjects were female and the majority of subjects in each treatment group were White.

The baseline disease characteristics of the ITT population were reasonably balanced between the two treatment groups in terms of site of disease, time since prior therapies, number of metastatic sites, and stage of disease. The majority of subjects (96%) had Stage IV disease at study entry. A total of 44% of subjects in each treatment group had 3 or more metastatic sites; the majority of which (86%) were visceral or soft tissue. The percentage of subjects with unknown ECOG PS was higher in the placebo+letrozole group (8%) compared with the lapatinib+letrozole group (1%) (Table 3.1.3.4).

The baseline disease characteristics of the HER2-positive population were similar between the two treatment groups. The percentage of subjects with baseline ECOG PS of 0 was slightly lower in the placebo+letrozole group (47%) compared with the lapatinib+letrozole group (53%).

Compared with ITT population, the subjects with HER2-positive tumors have a more aggressive disease as demonstrated by a slightly younger age and have recently progressed on prior adjuvant endocrine therapy.

Table 3.1.3.4 Baseline Characteristics in ITT and HER2-Positive Populations

	ITT		HER2-Positive	
	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)
Age (years)				
Mean (SD)	62.8 (9.7)	63.3 (10.0)	61.0 (9.4)	60.9 (9.2)
Median (range)	62.0 (31-94)	63.0 (35-95)	60.0 (44-85)	59.0 (45-87)
Race (%)				
White	529 (82)	557 (86)	82 (74)	91 (84)
American Hispanic	57 (9)	44 (7)	14 (13)	9 (8)
Asian	30 (5)	30 (5)	12 (11)	5 (5)
Black	17 (3)	10 (2)	2 (2)	3 (3)
Other	9 (1)	3 (<1)	1 (<1)	0 (0)
Site of Disease (%)				
Visceral/Soft tissue	554 (86)	561 (87)	98 (88)	90 (83)
Bone only	85 (13)	80 (12)	13 (12)	18 (17)
Prior adjuvant chemotherapy				
<6 months	13 (2)	8 (1)	4 (4)	2 (2)
≥6 months	629 (98)	636 (99)	107 (96)	106 (98)
Prior adjuvant endocrine therapy				
<6 months	142 (22)	156 (24)	38 (34)	41 (38)
≥6 months	500 (78)	488 (76)	73 (66)	67 (62)
ECOG performance status at baseline				
0	373 (58)	324 (50)	59 (53)	51 (47)
≥1	263 (41)	271 (42)	51 (46)	57 (53)
Number of metastatic sites				
<3	359 (56)	358 (56)	64 (58)	66 (61)
≥3	283 (44)	285 (44)	47 (42)	42 (39)
Stage of disease				
IIIB/IIIC	25 (4)	30 (5)	5 (5)	7 (6)
IV	616 (96)	613 (95)	106 (95)	101 (94)

3.1.3.4 Prior Treatment

In the ITT population, approximately 40% of the subjects had received no prior therapies. Only 3 subjects (1 subject in the placebo+letrozole group and 2 subjects in the lapatinib+letrozole group) had previously received trastuzumab (Table 3.1.3.5). The most common chemotherapy regimen contained Cyclophosphamide and fluorouracil.

Approximately 96% of subjects who received prior adjuvant endocrine therapy received tamoxifen or toremifene (Fareston). In HER2-positive population, more subjects had received prior endocrine treatment and/or chemotherapies in each treatment group compared with the ITT population.

Table 3.1.3.5 Prior Systemic Therapy

	ITT		HER2-Positive	
	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)
Hormone (%)				
Aromatase Inhibitor only	5 (1)	3 (<1)	1 (1)	1 (1)
Tamoxifen/toremifene only	300 (47)	302 (47)	59 (53)	60 (56)
Others	8 (1)	12 (2)	0 (0)	1 (1)
Chemotherapy (%)				
Anthracyclines only	171 (27)	172 (27)	41 (37)	38 (35)
Taxanes only	0 (0)	1 (<1)	0 (0)	0 (0)
Anthracyclines+taxanes	42 (7)	41 (6)	9 (8)	9 (8)
Others	68 (11)	66 (10)	11 (10)	4 (4)
Biologics (%)				
Trastuzumab	2 (<1)	1 (<1)	1 (1)	1 (1)
Both hormone and chemotherapy (%)	203 (32)	212 (33)	44 (40)	43 (40)
Prior therapy naïve (%)	251 (39)	259 (40)	34 (31)	38 (35)

3.1.4 Applicant's Efficacy Results

The primary efficacy endpoint was investigator-assessed PFS in HER2-positive population, and main secondary efficacy endpoints were investigator-assessed PFS in ITT population, overall response rate (ORR) and OS in HER2-positive and ITT populations. These endpoints were analyzed for HER2-negative population as well.

3.1.4.1 Investigator-assessed PFS

The results showed that the investigator-assessed PFS in the HER2-positive population was statistically significantly longer in the lapatinib+letrozole group compared with the placebo+letrozole group. The HR was 0.71 (95% CI: 0.53, 0.96; stratified log-rank p=0.019). Median PFS was 35.4 weeks in the lapatinib+letrozole group compared with 13.0 weeks in the placebo+letrozole group (Figure 3.1.4.1).

Based on the proposed rules of the hierarchical testing, investigator-assessed PFS was then tested in the ITT population. The HR was 0.86 (95% CI: 0.76, 0.98) with log-rank p-value of 0.026. The median PFS was 47.0 weeks in the placebo+letrozole group compared with 51.7 weeks in the lapatinib+letrozole group (Figure 3.1.4.2).

Additional analysis of the investigator-assessed PFS in the HER2-negative population was conducted as well. The HR was 0.90 (95% CI: 0.77, 1.05; stratified log-rank p=0.188). Median PFS was 59.7 weeks in the lapatinib+letrozole group compared with 58.3 weeks in the placebo+letrozole group (Figure 3.1.4.3). Table 3.1.4.1 summarizes the PFS results in HER2-positive, HER2-negative, and ITT populations.

Table 3.1.4.1 Summary of Investigator-Evaluated PFS Analyses

	HER2-Positive		HER2-Negative		ITT	
	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)	Letrozole + Lapatinib (N=478)	Letrozole + placebo (N=474)	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)
Events (%)	88 (79)	89 (82)	294 (62)	342 (72)	413 (64)	476 (74)
Median in weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)
Log-rank p-value	0.019		0.188		0.026	
Hazard Ratio (95%CI)	0.71 (0.53, 0.96)		0.90 (0.77, 1.05)		0.86 (0.76, 0.98)	

Figure 3.1.4.1 Kaplan-Meier Estimate of Investigator-Evaluated PFS in HER2-Positive Population

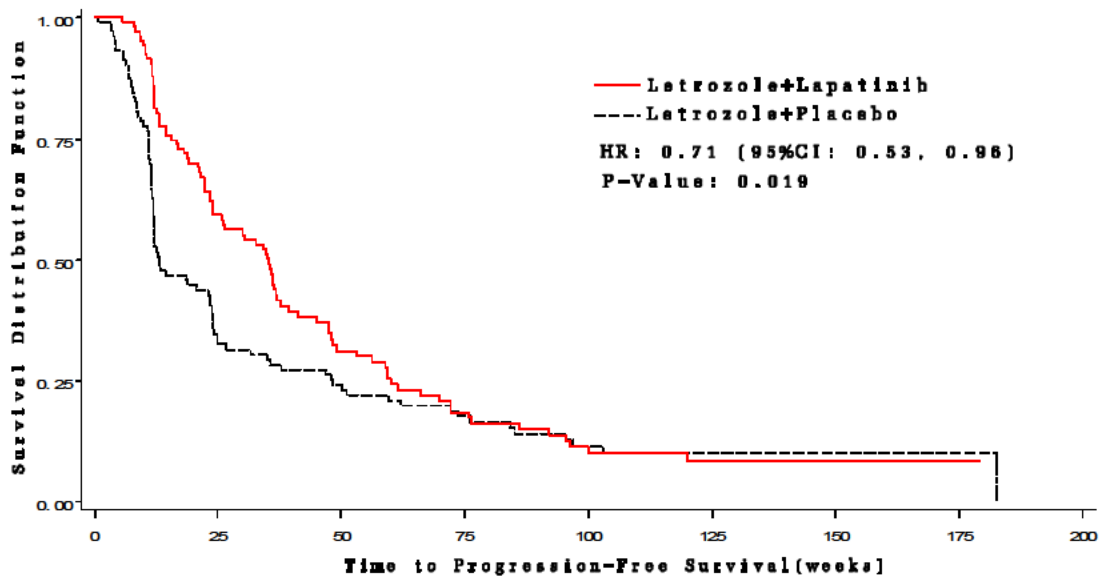


Figure 3.1.4.2 Kaplan-Meier Estimate of Investigator-Evaluated PFS in ITT Population

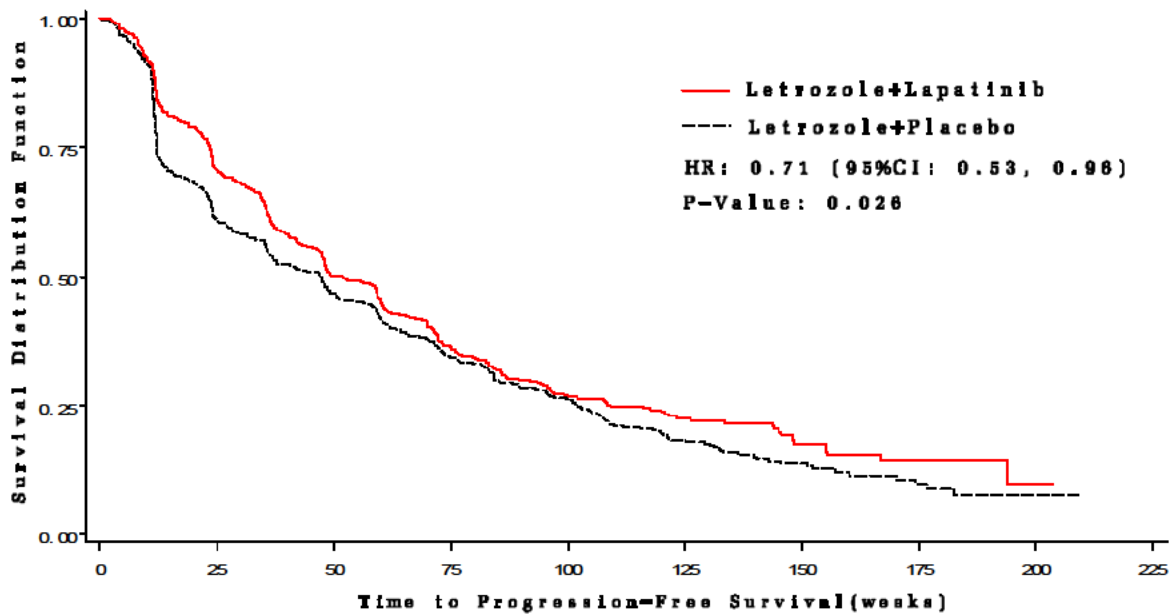
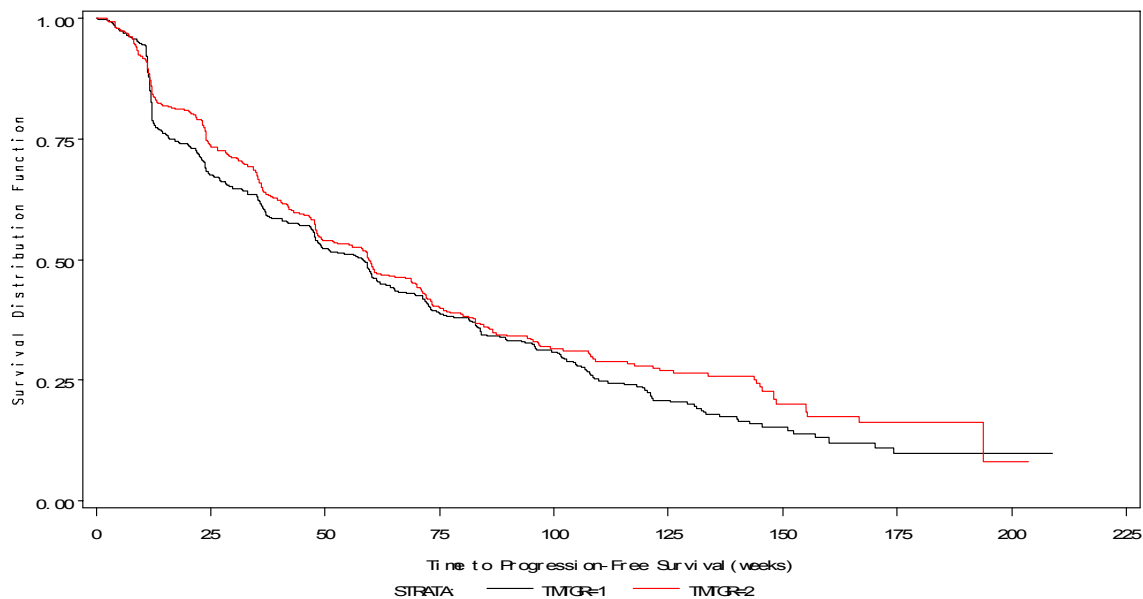


Figure 3.1.4.3 Kaplan-Meier Estimate of Investigator-Evaluated PFS in HER2-Negative Population



3.1.4.2 Overall Survival

OS data were not mature at the time of data cut-off on 03 June 2008, as only 104 (47%) of subjects had died and 41% were still being followed for survival in HER2-positive population. The HR was 0.74 (95% CI: 0.5, 1.1) with log-rank p-value of 0.113 (Table 3.1.4.2; Figure 3.1.4.4).

The HRs in ITT and HER2-negative populations were 1.01 and 1.15, respectively, with non-significant 95% CIs (Table 3.1.4.2). The survival curves of the lapatinib+letrozole group and the placebo+letrozole group mingled together in ITT population (Figure 3.1.4.5), indicating no OS benefit in lapatinib+letrozole group. HER2-negative subjects demonstrated a similar OS pattern as the ITT population, as presented in Table 3.1.4.2 and Figure 3.1.4.6.

Table 3.1.4.2 Summary of Overall Survival Analyses

	HER2-Positive		HER2-Negative		ITT	
	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)	Letrozole + Lapatinib (N=478)	Letrozole + placebo (N=474)	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)
Events (%)	50 (45)	54 (50)	174 (36)	153 (32)	240 (37)	234 (36)
Median in weeks (95% CI)	144.7 (95.6, NE)	140.3 (92.1, 159.4)	174.4 (161.1, NE)	179.7 (168.9, NE)	170.9 (157.7, 196.3)	176.3 (156.1, 189.7)
Log-rank p-value	0.113		0.193		0.916	
Hazard Ratio (95%CI)	0.74 (0.5, 1.1)		1.15 (0.9, 1.4)		1.01 (0.8, 1.2)	

Figure 3.1.4.4 Kaplan-Meier Estimate of OS in HER2-Positive Population

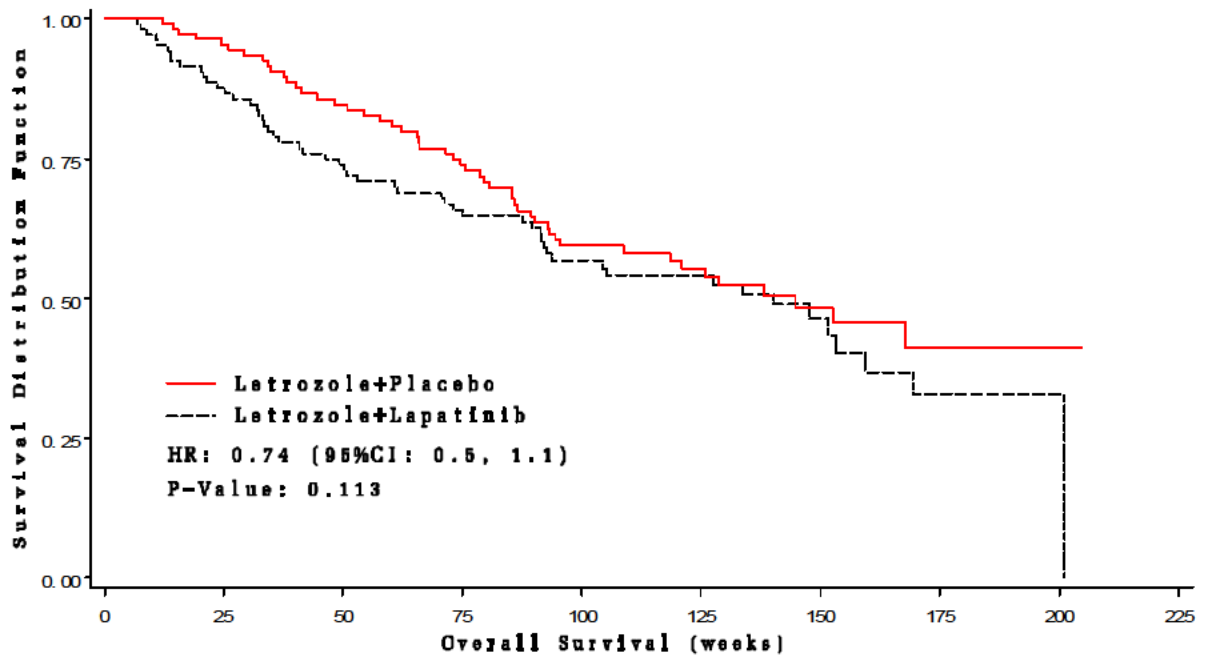


Figure 3.1.4.5 Kaplan-Meier Estimate of OS in ITT Population

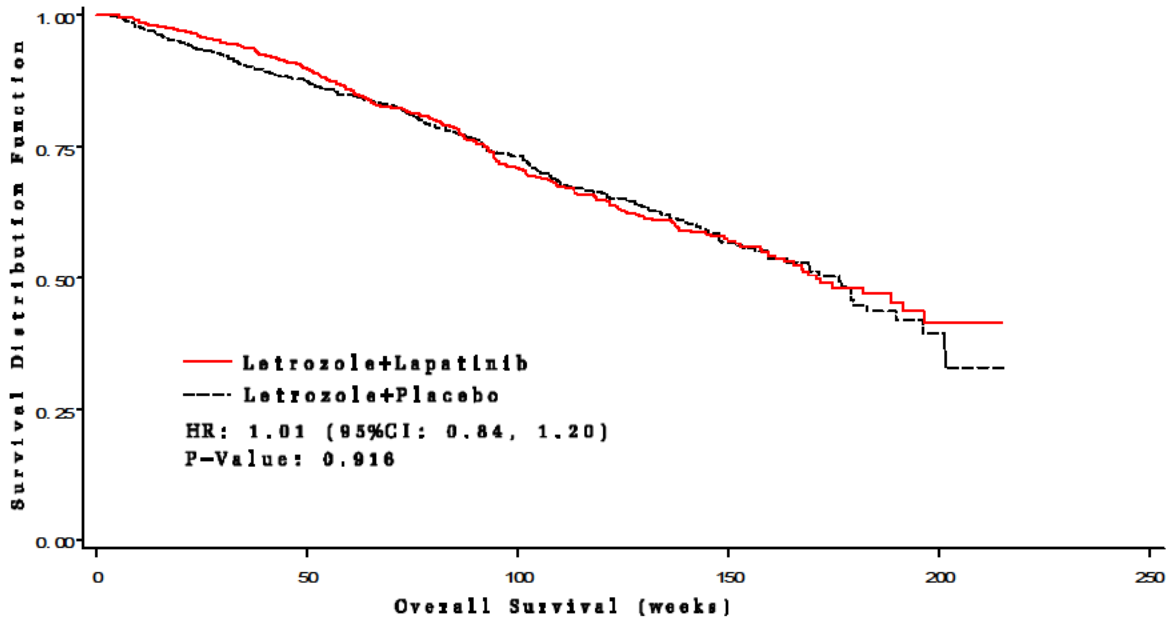
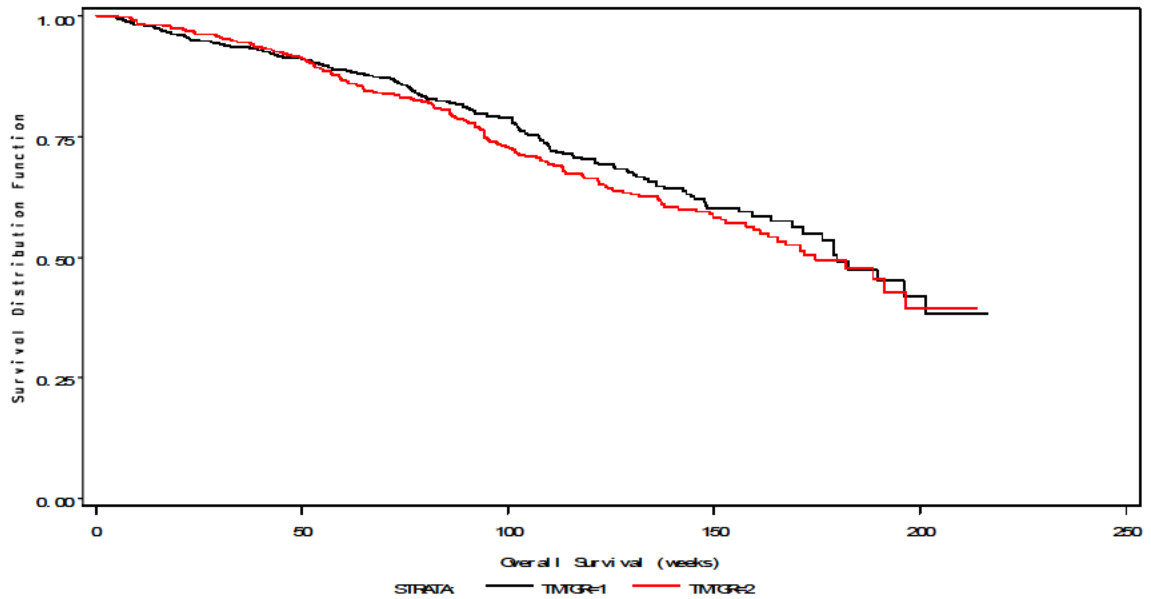


Figure 3.1.4.6 Kaplan-Meier Estimate of OS in HER2-Negative Population



3.1.4.3 Investigator-Assessed ORR

ORR was defined as the percentage of subjects achieving either a confirmed CR or PR. Response was assessed via RECIST.

In the HER2-positive population, investigator-evaluated ORR (including subjects with measurable and non-measurable disease) was 14.8 (95%CI: 8.7, 22.9) in the placebo+letrozole group and 27.9 (95%CI: 19.8, 37.2) in the lapatinib+letrozole group, with an odds ratio estimate of 0.4 (95%CI: 0.2, 0.9).

In the ITT population, ORR was 27.8% (95% CI: 24.4, 31.4) and 30.5% (95% CI: 27.0, 34.3) in the placebo+letrozole group and lapatinib+letrozole groups, respectively, with an odds ratio of 0.9 (95% CI: 0.7, 1.1). Similarly, in the HER2-negative population, ORR was 31.6% (95% CI: 27.5, 36.0) and 32.6% (95% CI: 28.4, 37.0) in the placebo+letrozole and lapatinib+letrozole groups, respectively, with an odds ratio of 0.9 (95% CI: 0.7, 1.3).

3.1.4.4 IRC-evaluated PFS

Independent review committee (IRC) reviewed PFS served as a confirmatory evidence for this study.

Results of the IRC-assessed PFS supported the findings from the PFS assessed by investigators, showing a significant improvement in PFS in HER2-positive subjects receiving lapatinib+letrozole compared with HER2-positive subjects receiving placebo+letrozole, with a HR of 0.65 (95% CI: 0.43, 0.96), although IRC-assessed PFS was noted to be longer in the analysis.

Table 3.1.4.3 Summary of IRC-Evaluated PFS Analyses

	HER2-Positive		HER2-Negative		ITT	
	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)	Letrozole + Lapatinib (N=478)	Letrozole + placebo (N=474)	Letrozole + Lapatinib (N=642)	Letrozole + placebo (N=644)
Events (%)	49 (44)	53 (49)	159 (33)	167 (35)	223 (35)	243 (38)
Median in weeks (95% CI)	60.0 (42.3, 82.6)	35.4 (16.0, 61.1)	122.0 (95.6, 148.0)	108.6 (91.3, 139.9)	107.6 (86.0, 131.6)	95.9 (75.3, 114.3)
Log-rank p-value	0.022		0.866		0.198	
Hazard Ratio (95%CI)	0.65 (0.43, 0.96)		0.98 (0.79, 1.22)		0.89 (0.74, 1.07)	

3.1.5 The Reviewer's Efficacy Analysis

This reviewer confirmed the applicant's analyses in the clinical report based on the datasets submitted by the applicant. After reviewing this application, the reviewer has the following major concerns: (1) A modest benefit in the ITT population, (2) robustness of

the efficacy of lapatinib+letrozole in terms of progression assessment method, and (3) applicability of the study results to the US population of patients with HER2-positive hormone positive metastatic breast cancer.

3.1.5.1 Treatment Efficacy in ITT population

The sponsor used a hierarchical ordered hypothesis testing procedure to control the overall type I error for tests in the primary HER2-positive population and the secondary ITT population. However, this proposed testing procedure is not truly “closed” in the sense that the rejection of the second level null in the ITT population does not necessarily lead to the rejection of the first level null in HER2-positive population, contradicting with the basic characteristic of a closed test procedure. Therefore, from the statistical aspect, the proposed method may not strictly protect overall type I error.

Moreover, as presented in Tables 3.1.4.1 and 3.1.4.2, the study results failed to demonstrate a clinically relevant benefit of the combined treatment in HER2-negative subset (74% of the ITT population) in PFS and OS endpoints. The median PFS in tested group improved only 1.4 weeks compared with the placebo+letrozole group with a hazard ratio of 0.9. The median OS in lapatinib group was approximately 5 weeks less than the placebo arm with a hazard ratio of 1.15, in favor of the placebo group. As a result, the small effect of 4.7 weeks in PFS seen in the ITT population is most likely driven by the HER2-positive population.

After communicating with the sponsor regarding a possibility of going to ODAC for this application, the sponsor decided

(b) (4)

3.1.5.2 PFS Results by Different Assessment Criteria

In this study, PFS could be determined by symptomatic progression or clinical disease assessments for palpable or visual lesions, which is subject to bias and cannot be confirmed by independent reviewers. Table 3.1.5.1 shows several sensitivity analyses performed by this reviewer to explore the lapatinib+letrozole effect in terms of PFS with different assessments such as excluding symptomatic progressions or bone disease only at baseline.

Table 3.1.5.1 Sensitivity Analyses for Different Assessment Methods

	HER2-Positive		HER2-Negative	
	Letrozole + Lapatinib (N=111)	Letrozole + placebo (N=108)	Letrozole + Lapatinib (N=478)	Letrozole + placebo (N=474)
Excluding symptomatic progressions				
Median in weeks (95% CI)	35.6 (25.7, 47.4)	23.1 (12.3, 25.0)	64.0 (59.1, 73.6)	61.3 (58.3, 72.4)
Hazard Ratio (95%CI)	0.76 (0.55, 1.04)		0.89 (0.76, 1.05)	
Excluding bone only disease at baseline				
Median in weeks (95% CI)	35.6 (25.7, 41.1)	12.6 (11.7, 23.7)	59.1 (48.0, 68.9)	58.7 (47.9, 62.0)
Hazard Ratio (95%CI)	0.69 (0.50, 0.96)		0.92 (0.78, 1.09)	
Excluding bone only disease at baseline without new lesions				
Median in weeks (95% CI)	35.0 (24.1, 39.4)	13.6 (12.1, 23.9)	58.3 (48.0, 62.3)	57.1 (47.6, 61.1)
Hazard Ratio (95%CI)	0.73 (0.53, 0.99)		0.93 (0.79, 1.09)	

The sensitivity analyses show that the tested treatment efficacy based on PFS in HER2-positive population appears robust across different assessment methods, with hazard ratio estimates from 0.69 to 0.76, in favor of lapatinib+letrozole group. There is no clinically significant benefit in HER2-negative group.

3.1.5.3 Acceptability in US Population

The population in this trial is not a representative sample of the US patients with HER2+, hormone-positive metastatic breast cancer. Only 2 of the 219 patients with HER2-positive breast cancer had prior trastuzumab, and approximately 33% of the patients were treatment naïve. Study EGF30008 was conducted mostly in foreign countries. For integrity of the analyses, the main baseline characteristics and primary PFS analyses of the US patients are presented in Tables 3.1.5.2 and 3.1.5.3, respectively.

Table 3.1.5.2 Main Baseline Characteristics in US Population

	ITT		HER2-Positive	
	Lapatinib + Letrozole N=158 (%)	Placebo + Letrozole N=167 (%)	Lapatinib + Letrozole N=20 (%)	Placebo + Letrozole N=21 (%)
Histology				
Infiltrating ductal	118 (75)	116 (69)	15 (75)	16 (76)
Lobular invasive	17 (11)	25 (15)	3 (15)	2 (10)
Other	22 (14)	24 (14)	2 (10)	3 (14)
Unknown	1 (1)	2 (1)	0 (0)	0 (0)
Stage at Screening				
IIIb/IIIc	0 (0)	5 (3)	0 (0)	1 (5)
IV	158 (100)	161 (96)	20 (100)	20 (95)
Unknown	0	1 (1)	0 (0)	0 (0)
Number of metastatic sites				
≥3	51 (32)	62 (37)	4 (20)	10 (48)
2	66 (42)	73 (44)	11 (55)	10 (48)
1	36 (23)	27 (16)	5 (25)	0 (0)
unknown	5 (2)	5 (3)	0(0)	1(5)

Table 3.1.5.3 Investigator-Assessed PFS in US Population

	ITT		HER2-Positive	
	Letrozole + Lapatinib (N=158)	Letrozole + placebo (N=167)	Letrozole + Lapatinib (N=20)	Letrozole + placebo (N=21)
Events (%)	99 (63)	134 (80)	17 (85)	20 (95)
Median in weeks (95% CI)	51.7 (42.1, 71.1)	37.9 (27.1, 51.0)	22.4 (11.6, 25.7)	11.7 (9.6, 23.7)
Log-rank p-value*	0.039		0.082	
Hazard Ratio (95%CI)	0.77 (0.59, 0.99)		0.62 (0.32, 1.18)	

* P-values were not adjusted for multiple comparisons.

As therapies for the proposed population in this study have changed over time, EGF30008 was not designed to answer the magnitude of PFS effect in patients who had received prior adjuvant trastuzumab. Therefore, the combined therapy may potentially be considered for the treatment of postmenopausal patients with hormone receptor-positive metastatic breast cancer that over-expresses the HER2 receptor and for whom a trastuzumab-containing chemotherapy regimen is not indicated. A prospective randomized study is necessary to estimate the efficacy of lapatinib+letrozole in a population similar to current US population.

3.2 Evaluation of Safety

Please refer to Clinical Review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Race and Age

Table 4.1.1 presents hazard ratios of investigator-assessed PFS by age and race, respectively, showing that the efficacy of the combined tested treatment was consistent in HER2-positive population. The hazard ratio estimates range from 0.52 to 0.75. The results in Table 4.1.1 were not controlled for multiple comparisons and thus only served for exploratory presentation.

Table 4.1.1 Hazard Ratios of Investigator-Assessed PFS by Age and Race

	HER2-Positive	HER2-Negative	ITT
Age			
≥ 65	0.63 (0.37, 1.06)	0.90 (0.71, 1.14)	0.84 (0.68, 1.03)
< 65	0.75 (0.52, 1.08)	0.88 (0.72, 1.09)	0.86 (0.73, 1.02)
Race			
White (95%CI)	0.74 (0.53, 1.04)	0.84 (0.71, 1.00)	0.82 (0.71, 0.95)
Non-White (95%CI)	0.52 (0.25, 1.08)	1.19 (0.79, 1.79)	0.97 (0.70, 1.33)

4.2 Other Special/Subgroup Populations

Please refer to Section 3.1.5.3 for PFS analyses in the US subpopulation. In the non-US population, the PFS hazard ratio was 0.72 (95%CI: 0.51, 1.00) in HER2-positive patients, 0.90 (95%CI: 0.78, 1.05) in ITT patients, and 0.96 (95%CI: 0.80, 1.15) in HER2-negative patients.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, Phase III study to evaluate and compare the efficacy and tolerability of the combined treatment of lapatinib and letrozole versus the treatment of placebo and letrozole in postmenopausal women with hormone receptor positive (ER positive and/or PgR positive) advanced or metastatic breast cancer and had not received prior therapy for advanced or metastatic disease.

Patients were 1:1 randomly assigned to receive either lapatinib (1500 mg once daily orally) with letrozole (2.5 mg once daily orally), or letrozole (2.5 mg once daily orally) with placebo (which matched with lapatinib tablet) until disease progression or withdrawal from therapy. Randomization was stratified by site of disease (soft tissue/visceral or bone only disease) and time since prior adjuvant endocrine therapy (≥ 6 months versus < 6 months).

The primary amended efficacy endpoint was investigator-assessed progression free survival (PFS) in HER2-positive patients with investigator-assessed PFS in ITT population as the main secondary efficacy endpoint of interest.

A total of 1286 subjects were randomized into this study with 644 patients assigned to placebo plus letrozole group and 642 patients assigned to lapatinib plus letrozole group. Two hundred and nineteen patients (17%) were HER2-positive. Among them, 108 HER2-positive patients were in placebo plus letrozole group, and 111 were in lapatinib plus letrozole group.

The hazard ratio of investigator-evaluated PFS in the HER2-positive population was 0.71 (95% CI: 0.53, 0.96; stratified log rank p-value=0.019), favoring the lapatinib+letrozole group. The median PFS was 13.0 weeks in the letrozole plus placebo group compared with 35.4 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the ITT population was 0.86 (95% CI: 0.76, 0.98; stratified log rank p-value=0.026). The median PFS was 47.0 weeks in the letrozole plus placebo group compared with 51.7 weeks in the letrozole plus lapatinib group. The hazard ratio of PFS in the HER2-negative population was 0.90 (95% CI: 0.77, 1.05; stratified log rank p-value=0.188). The median PFS was 58.3 weeks in the letrozole plus placebo group compared with 59.7 weeks in the letrozole plus lapatinib group.

The overall survival (OS) was not mature at data cut-off on 03 June 2008; only 474 (37%) of the ITT subjects had died and 54% were still being followed for survival. The OS hazard ratio estimate in HER2-positive population was 0.74 (95% CI: 0.5, 1.1; p-value=0.113), favoring the lapatinib treated group. In the ITT and HER2-negative populations, the OS hazard ratio estimates were 1.01 (95% CI: 0.8, 1.2; p-value=0.916) and 1.15 (95% CI: 0.9, 1.4; p-value=0.193), respectively, favoring the placebo group.

In summary, this reviewer has the following concerns regarding this application: (1) The primary efficacy population was changed from ITT to HER2-positive after 760 patients were randomized in this study, and sample size was increased to 1286 to have adequate HER2-positive patients; (2) Study was not stratified at randomization by HER2 status; and (3) Demonstration of OS benefit has generally been the standard for consideration of regular approval in first-line setting of breast cancer.

5.2 Conclusions and Recommendations

The study results based on the primary endpoint progression-free survival (PFS) showed that the combined treatment of lapatinib plus letrozole had a statistically significant benefit compared to letrozole in post-menopausal women with hormone receptor positive and human epidermal growth factor receptor 2 (HER2) positive untreated advanced or metastatic breast cancer. However, a modest benefit was seen in the overall ITT subjects which mostly comprised of HER2-negative subpopulation (74%). During the review process, the sponsor modified the indicated population from ITT population to HER2-positive population.

This pivotal study was not designed to test and estimate the tested treatment effect in patients who had received prior adjuvant trastuzumab, a currently widely adopted regimen in US. Therefore, the combined therapy may potentially be considered for the patient population for whom a trastuzumab-containing chemotherapy regimen is not indicated. A randomized study is necessary to precisely estimate the efficacy of lapatinib+letrozole in a population similar to current US patients. Whether the PFS benefit observed in the HER2-positive subgroup is clinically meaningful is deferred to the clinical review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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

/s/

QIANG XU
12/30/2009

SHENGHUI TANG
12/31/2009

RAJESHWARI SRIDHARA
12/31/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: TYKERB™

Generic name: lapatinib ditosylate

Type of dosage form and strength(s): immediate release tablet, 250 mg

Indication(s):

Previously approved: in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including trastuzumab.”

Proposed (current submission): in combination with

(b) (4)

(b) (4)

NDA number, type: NDA 22-059 SE1 007 efficacy supplement

Applicant name: GlaxoSmithKline

Submission date (letter date): 31-Mar-2009
30-Oct-2009

OCP Division name: Division of Clinical Pharmacology V

OND: Division name: Division of Drug Oncology Products

OCP Reviewer name: Gene Williams, Ph.D.

OCP Team Leader name: Qi Liu, Ph.D.

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Executive Summary

This NDA (sNDA) is an efficacy labeling supplement for TYKERB[®] (lapatinib) in combination with (b) (4) (letrozole) (b) (4)

A single pharmacokinetic study was submitted. The study results show that a single dose of Femara has little or no effect on steady-state lapatinib pharmacokinetics, and conversely, a single dose of TYKERB does not alter steady-state letrozole pharmacokinetics. As both drugs are administered continuously, the single dose design is not adequate to assess the potential for pharmacokinetic changes, and (b) (4)

1.1. Recommendations

This sNDA is acceptable from the clinical pharmacology perspective. We have recommendations for changes to the package insert (***Detailed Labeling Recommendations*** appear in section 3 of this review).

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

This sNDA contains a single clinical pharmacology related study report, Study EGF10030. In the pharmacokinetic phase of the study there were two groups. In Group 1, the effect of a single dose of letrozole on the pharmacokinetics of lapatinib was determined. In Group 2, the effect of a single dose of lapatinib on the pharmacokinetics of letrozole was determined.

Although the confidence intervals do not exclude 1.0, there appears to be a slight effect of letrozole to decrease exposure to lapatinib (lapatinib AUC decreased 16%, lapatinib C_{max} decreased 22%). A decrease in exposure could be explained by an induction of lapatinib metabolism by letrozole. However, while the package insert for Femara does not report on whether letrozole is an inducer, it is unlikely that an induction effect explains the current data, as the study design (letrozole was given as a single dose on the same day as the plasma samples for lapatinib pharmacokinetics were collected) was unlikely to result in an induction effect. Any effect occurring is more likely due to an effect of letrozole to decrease the absorption of lapatinib.

Regarding the effect of lapatinib on letrozole, the confidence intervals for AUC and C_{max} just miss meeting the usual regulatory “no effect” standard of a lower bound of 80%. However, the point estimates show little or no effect (letrozole AUC decreased 6%, letrozole C_{max} decreased 10%), and the sample size (n=8) is small. The expectation from the small sample size is

imprecision (i.e., increased width of confidence interval). The small sample size makes the results less than definitive, but the reviewer concludes that the best interpretation of the limited data is that there is no significant effect of single dose lapatinib on the pharmacokinetics of letrozole.

Because letrozole has a half-life of two days, it accumulates when given on a once-daily schedule. Similarly, lapatinib has a half-life of 14-24 hours and also accumulates when administered once daily. Because accumulation occurs, the single doses of “potential perpetrator drug” administered in each study group were not sufficient to produce the concentrations that occur with the extended dosing (continuous dosing) that occurs with treatment regimens. Thus, the conditions of the study have potential to underestimate the effect of letrozole on lapatinib that could be occurring with the continuous treatment regimen.

2. Question-Based Review

2.1. General clinical pharmacology

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

The efficacy and safety study for this efficacy supplement, study EGF30008, was a randomized, double-blind, placebo-controlled, multicenter, Phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor positive advanced or metastatic breast cancer. The doses of lapatinib was determined empirically (based on the adverse effects of the escalated lapatinib doses investigated) from the dose escalation portion of Study EGF10030. Study EGF10030 did not investigate the use of letrozole doses other than 2.5 mg QD. This dose of letrozole (2.5 mg QD) was the same in both arms of Study 30008 and the same as the package insert dose in the (b) (4) (letrozole) package insert. The lapatinib dose (1500 mg QD) is slightly higher than the current package insert dose for TYKERB (1250 mg QD).

Study EGF10030 includes a pharmacokinetic phase, the design of which will be reviewed in section 2.2.1 of this review. There are no other clinical studies in the sNDA.

- 2.1.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Biomarker analysis of tumor tissue collected during Study EGF10030 is ongoing; the applicant states that the data will be presented in a follow-up report.

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

No drug concentration data was collected in Study EGF30008. Analytical methods for Study EGF10030 are discussed in review section 2.3.

2.1.4 What are the characteristics of drug metabolism?

The following information (indented) is taken from the TYKERB package insert:

Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8.

Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly (*see Ketoconazole and Carbamazepine sections, below*). Dose adjustment of lapatinib should be considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes [*see Dosage and Administration (2.2)*].

2.2 Extrinsic Factors

2.2.1 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Yes, the efficacy supplement is for the combination of TYKERB (lapatinib) with (b) (4) (letrozole). The potential for a pharmacokinetic drug-drug interaction was assessed in the pharmacokinetic phase of Study EGF10030.

Study EGF10030 was conducted in three phases which included three cohorts of subjects. The dose escalation phase was conducted first (Cohort 1) to determine the optimally tolerated regimen (OTR). The OTR expansion phase (Cohort 2) was conducted to further evaluate the safety and tolerability of lapatinib and letrozole at the OTR dose level. The pharmacokinetic (PK) phase (Cohort 3) was subsequently conducted to determine the PK parameters of each agent when administered alone and in combination.

The OTR was defined as 1500 mg lapatinib with 2.5 mg letrozole once daily. This regimen was taken forward into the efficacy and safety study that is the primary topic of this efficacy supplement. The 1500 and 2.5 mg doses were also used in the pharmacokinetic phase of Study EGF10030.

In the pharmacokinetic phase of the study there were two groups. In Group 1, the effect of letrozole on the PK of lapatinib was determined. A schematic of the study design for Group 1 is presented as **FDA Table 1**.

FDA Table 1. Schematic of Dosing Sequences for Group 1 (applicant’s Table 2 from the study report)

Table 2 Schematic of Dosing Sequences for Pharmacokinetic Portion of the Study, Group 1

Group 1 - Effect of Letrozole on PK of GW572016						
Day	Sequence 1 (n=4)			Sequence 2 (n=4)		
1-6		GW572016			GW572016	
7		GW572016	PK ¹		GW572016	
8	Letrozole	GW572016	PK ²	Letrozole	GW572016	PK ²
9-22					GW572016	
23					GW572016	PK ¹

1. Samples for GW572016 alone were obtained on Day 7 in Sequence 1 and Day 23 in Sequence 2. Blood samples (2 mL) were drawn prior to the letrozole or GW572016 dose and at 15 and 30 minutes; 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.
2. On Day 8 when GW572016 was administered with letrozole, blood samples (4 mL) were drawn prior to the GW572016 and letrozole dose and at 15 and 30 minutes after the dose, and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours post-dose

The following information (indented) is reproduced from the (b) (4) (letrozole) package insert.

Letrozole’s terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur.

Because letrozole has a half-life of two days, it accumulates when given on a once-daily schedule. The single dose of letrozole administered on Day 8 (**FDA Table 1.**) was not sufficient to produce the letrozole concentrations that occur with the extended dosing (continuous dosing) that occurs with treatment regimens. Thus, the conditions of the study have potential to underestimate the effect of letrozole on lapatinib that could be occurring with the continuous treatment regimen. The impact of this study design on the interpretation of results will be discussed later in this review.

In Group 2, the effect of lapatinib on the PK of letrozole was determined. A schematic of the study design for Group 2 is presented as **FDA Table 2.**

FDA Table 2. Schematic of Dosing Sequences for Group 2 (applicant’s Table 3 from the study report)

Table 3 Schematic of Dosing Sequences for Pharmacokinetic Portion of the Study, Group 2

Group 2- Effect of GW572016 on PK of Letrozole						
Day	Sequence 1 (n=4)			Sequence 2 (n=4)		
1-20	Letrozole			Letrozole		
21	Letrozole		PK ¹	Letrozole	GW572016	PK ²
22-27	Letrozole			Letrozole		
28	Letrozole	GW572016	PK ²	Letrozole		PK ¹

1. Samples for letrozole alone were obtained on Day 21 in Sequence 1 and Day 28 in Sequence 2. Blood samples (2 mL) were drawn prior to the letrozole or GW572016 dose and at 15 and 30 minutes; 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.
2. On Day 28 in Sequence 1 and Day 21 in Sequence 2 when GW572016 was administered with letrozole, blood samples (4 mL) were drawn prior to the GW572016 and letrozole dose and at 15 and 30 minutes after the dose, and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours post-dose.

The following information (indented) is reproduced from the Tykerb (lapatinib) package insert.

At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

The study design for Group 2 has the same flaw as previously described for Study Group 1. Because lapatinib has a half-life of 14 hours, it accumulates when given on a once-daily schedule. The single dose of lapatinib (GW572016) administered on Days 21 and 28 (**FDA Table 2.**) was not sufficient to produce the lapatinib concentrations that occur with the extended dosing (continuous dosing) that occurs with treatment regimens. Thus, the conditions of the study have potential to underestimate the effect of lapatinib on letrozole that could be occurring with the continuous treatment regimen. The impact of this study design on the interpretation of results will be discussed later in this review section.

The pharmacokinetic results for Group 1 are summarized in **FDA Table 3.**

FDA Table 3. Effect of a single co-administered dose of letrozole on the pharmacokinetics of lapatinib (applicant’s table from page 7 of the clinical pharmacology summary)

Parameter (units)	Lapatinib alone* (n=9)	Lapatinib + Letrozole* (n=10)	Comparison** (n=9)
AUC _{tau} (h•µg/L)	31.9 (17.2-59.2)	27.0 (13.3-54.8)	0.84 (0.62-1.13)
C _{max} (µg/L)	2.47 (1.47-4.13)	1.94 (1.13-3.34)	0.78 (0.57-1.06)
C _{tau} (µg/L)	0.78 (0.37-1.66)	0.72 (0.30-1.73)	0.90 (0.63-1.28)

* Geometric mean (95% confidence interval)

** Geometric LS mean ratio (90% confidence interval)

Although the confidence intervals do not exclude 1.0, there appears to be a slight effect of letrozole to decrease exposure to lapatinib. A decrease in exposure could be explained by an induction of lapatinib metabolism by letrozole. However, while the package insert for Femara does not report on whether letrozole is an inducer, it is unlikely that an induction effect explains the current data, as the study design (letrozole was given as a single dose on the same day as the plasma samples for lapatinib pharmacokinetics were collected) was unlikely to result in an induction effect. Any effect occurring is more likely due to an effect of letrozole to decrease the absorption of lapatinib.

The pharmacokinetic results for Group 2 are summarized in **FDA Table 3**.

FDA Table 3. Effect of a single co-administered dose of lapatinib on the pharmacokinetics of letrozole (applicant’s table from page 8 of the clinical pharmacology summary)

Parameter (units)	Letrozole alone* (n=8)	Letrozole + Lapatinib* (n=8)	Comparison** (n=8)
AUCtau (h*ng/mL)	2228 (1339-3708)	2085 (1302-3339)	0.94 (0.79-1.11)
Cmax (ng/mL)	136 (82-225)	122 (78-190)	0.90 (0.79-1.02)
Ctau (ng/mL)	91 (48-172)	78 (47-130)	0.86 (0.71-1.05)

* Geometric mean (95% confidence interval)

** Geometric LS mean ratio (90% confidence interval)

The confidence intervals for AUC and Cmax just miss meeting the usual regulatory “no effect” standard of a lower bound of 80%. However, the point estimates are well-within the usual regulatory bounds of 80-125%, and the sample size (n=8) is small. The expectation from the small sample size is imprecision (i.e., increased width of confidence interval). The small sample size makes the results less than definitive, but the reviewer concludes that the best interpretation of the limited data is that there is no significant effect of single dose lapatinib on the pharmacokinetics of letrozole.

As previously noted, dosing was sub-optimal (single dosing) for each drug when it was investigated for its ability to provoke an interaction (i.e., alter the pharmacokinetics of the co-administered drug). (b) (4)

This is not a safety or efficacy issue, as the drug combination was evaluated for safety and efficacy in the clinical trial that is the basis for the current efficacy supplement. Further, neither lapatinib nor letrozole are prototypic agents for the investigation of drug interactions. (b) (4)

2.3 Analytical Section

2.3.1 Lapatinib (GW572016)

(b) (4)

(b) (4) Extracts were analysed by HPLC-MS/MS using a (b) (4)

(b) (4)

(b) (4)

samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration were to be within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria. The results from the calibration standards and quality control samples are summarized in **FDA Table 4.** and **FDA Table 5.**

FDA Table 4. Results of calibration standards for lapatinib (applicant's Table 2 from page 10 of the analytical methods report for lapatinib)

Table 2 Back - Calculated Calibration Standards and Associated Parameters from Study EGF10030

Analytical Run ID	GW572016 (Plasma) Calibration Standard Nominal Concentration (ng/mL)										Slope	Intercept	Corr. Coeff.
	5	10	25	50	100	250	500	1000	2500	5000			
EGF10030HUPL001	(b) (4)												(b) (4)
EGF10030HUPL002	(b) (4)												

Data in brackets were rejected

Summary of Statistical Parameters	Calibration Standard Concentration (ng/mL)										
	5	10	25	50	100	250	500	1000	2500	5000	
Mean	5.1	9.9	24.4	46.2	106.2	251.1	505.0	1042.3	2576.1	4731.0	
Standard Deviation	0.3	0.8	2.7	3.4	11.1	13.3	38.9	75.6	108.6	89.1	
Precision (%)	6.6	8.2	10.9	7.4	10.4	5.3	7.7	7.3	4.2	1.9	
Accuracy (%)	101.7	99.2	97.6	92.4	106.2	100.4	101.0	104.2	103.0	94.6	
n	3	4	4	4	4	4	4	4	4	4	

Statistics calculated from non-rounded data

FDA Table 5. Results of quality control samples for lapatinib (applicant’s Table 3 from page 11 of the analytical methods report for lapatinib)

Table 3 Quality Control Data Including Precision and Accuracy Statistics from Study EGF10030

Analytical Run ID	GW572016 (Plasma) ng/mL Quality Control Sample Concentration			
	20 ng/mL	Accuracy (%)	400 ng/mL	Accuracy (%)
EGF10030HUPL001	(b) (4)			
EGF10030HUPL002				
Summary of Statistical Parameters		Quality Control Sample Concentration		
		20 ng/mL	400 ng/mL	4000 ng/mL
	Overall Mean	20.0	408.5	3960.3
	Standard Deviation (within run means)	1.6	23.8	182.9
	Precision (%)	8.0	5.8	4.6
	Bias (%)	0.0	2.0	-1.2
	n	17	17	17

Statistics calculated from non-rounded data.

Across the two analytical runs, only 12 samples, all from the same patient, required re-analysis. The re-analysis was needed because the samples required dilution. The reviewer finds the performance of the analytical method for lapatinib acceptable.

2.3.2 Letrozole

Human plasma samples were analyzed for letrozole by high-performance liquid chromatography/mass spectroscopy/ mass spectroscopy (HPLC/MS/MS) after solid phase extraction using an electrospray interface with multiple reaction monitoring in positive ion mode.

The lower limit of quantitation (LLQ) for letrozole was 0.55 ng/mL; the upper limit of quantification (ULQ) was 400 ng/mL. Quality Control (QC) samples, prepared at 3 different analyte concentrations and stored with study samples, were analysed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the QC results were to deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration should be within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria. The results from the calibration standards and quality control samples are summarized in **FDA Table 6.** and **FDA Table 7.**

FDA Table 6. Results of calibration standards for letrozole (applicant’s Table 2 from page 15 of the analytical methods report for letrozole)

Table 2 Back-calculated calibration standards for Study EGF10030

Run Date	Run ID	0.500 ng/mL	1.500 ng/mL	5.000 ng/mL	15.000 ng/mL	50.000 ng/mL	200.000 ng/mL	300.000 ng/mL	400.000 ng/mL
23-Aug-2004	1	(b) (4)							
10-Sep-2004	2								
30-Nov-2004	3								
20-May-2005	4								
04-Aug-2005	7								
05-Aug-2005	6								
07-Aug-2005	8								
15-Aug-2005	10								
Mean		0.502	1.495	4.877	15.244	51.696	205.161	290.333	392.952
S.D.		0.041	0.129	0.381	1.359	3.645	11.091	20.100	18.845
%CV		8.2	8.6	7.8	8.9	7.1	5.4	6.9	4.8
%Diff		0.4	-0.3	-2.5	1.6	3.4	2.6	-3.2	-1.8
n		10	10	14	13	15	15	15	16

Reasons Deactivated

* % Diff >15%

** % Diff >20%

*** No analyte detected

FDA Table 7. Results of quality control samples for letrozole (applicant’s Table 4 from page 17 of the analytical methods report for letrozole)

Table 4 Quality control data from Study EGF10030

Run Date	Run ID	1.500 ng/mL	50.000 ng/mL	320.000 ng/mL	400.000 ng/mL
23-Aug-2004	1	(b) (4)			
10-Sep-2004	2				
30-Nov-2004	3				
20-May-2005	4				
04-Aug-2005	7				
05-Aug-2005	6				
07-Aug-2005	8				
15-Aug-2005	10				
Mean		1.538	50.872	318.414	398.636
S.D.		0.238	4.408	30.515	33.948
%CV		15.5	8.7	9.6	8.5
%Diff		2.5	1.7	-0.5	-0.3
n		16	16	16	16

> 15% Theoretical

Across the eight analytical runs, five samples were re-analyzed. **FDA Table 8.** summarizes the re-analysis results.

FDA Table 8. Samples re-assayed (derived from applicant's Tables 5 and 6 on pages 18 and 19 of the study report for letrozole)			
Sample	Reason for re-analysis	Original value	Value(s) of re-analysis
Subject (b) (6) Treatment B, Day 8, pre-dose	"client request" ¹	(b) (4)	
Subject (b) (6) Treatment B, Day 8, 1 h	"client request" ¹		
Subject (b) (6) Treatment B, Day 28, 0.5 h	internal standard not detected		
Subject (b) (6) Treatment B, Day 28, 3 h	internal standard not detected		
Subject (b) (6) Treatment B, Day 28, 4 h	internal standard not detected		

¹reviewer’s comment -- presumably “client request” occurred because value appeared anomalous to client

All of the summarized letrozole bioanalytical results (**FDA Tables 6., 7. and 8.**) are sub-optimal. However, the data are sufficient to allow a conclusion that, under the conditions studied, there is no pronounced effect of Tykerb on the pharmacokinetics of letrozole. (b) (4)

(b) (4)

3 Detailed Labeling Recommendations

The applicant's proposed package insert is reproduced. The reviewer's comments and recommendations for revisions are included as ballooned comments appearing in the right margin. To avoid confusion, the reviewer's comments and recommendations are limited to the ballooned comments; any other changes are the applicant's.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

GENE M WILLIAMS
01/25/2010

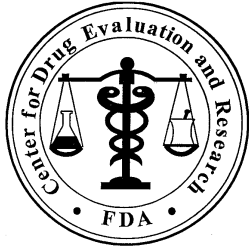
QI LIU
01/25/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 25, 2010

To: Robert Justice, MD, Division Director
Division of Drug Oncology Products (DDOP)

Through: Mary Willy, PhD, Deputy Director
Division of Risk management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk management (DRISK)

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Tykerb (lapatinib) Tablets

Application Type/Number: NDA 22-059

Submission Number: S-007

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2009-1475

1 INTRODUCTION

GlaxoSmithKline submitted a Prior Approval Efficacy Supplement to their approved New Drug Application, sNDA 22-059/007 for TYKERB (lapatinib) Tablets on March 31, 2009. TYKERB, a kinase inhibitor, is indicated in combination with:

- capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

The purpose of this supplement is to add letrozole to the indication statement as another drug that can be used in combination with TYKERB:

- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor

(b) (4)

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for TYKERB (lapatinib) Tablets. Please let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft TYKERB (lapatinib) Tablets Prescribing Information (PI) submitted March 31, 2009, revised by the Review Division throughout the current review cycle, and provided to DRISK on January 15, 2010
- Draft TYKERB (lapatinib) Tablets (PPI) March 31, 2009, revised by the Review Division throughout the current review cycle, and provided to DRISK on January 15, 2010

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

STEVE L MORIN
01/25/2010

MARY E WILLY
01/25/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum: Internal Labeling Consult

Date: January 20, 2010

To: Kim Robertson, Project Manager, DDOP

From: Keith Olin, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA # 22-059
DDMAC PI labeling comments for Tykerb (lapatinib) tablets

DDMAC has reviewed the proposed PI for Tykerb (lapatinib) tablets submitted for consult on September 25, 2009, and offers the following comments. Comments regarding the proposed PPI will be provided separately by Stephanie Victor.

The version of the draft PI used in this review was sent via email on January 13, 2010 and last modified on January 12, 2010.

(b) (4)



Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22059

SUPPL-7

SMITHKLINE
BEECHAM CORP
DBA
GLAXOSMITHKLIN
E

TYKERB TABLETS

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/s/

KEITH J OLIN
01/22/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **022059** Supplement # **007** Efficacy Supplement Type SE- 1

Proprietary Name: **TYKERB® Tablets**
Established Name: **(lapatinib)**
Strengths: **250 mg**

Applicant: **GSK**
Agent for Applicant (if applicable): **N/A**

Date of Application: **March 31, 2009**
Date of Receipt: **March 31, 2009**
Date clock started after UN: **N/A**
Date of Filing Meeting: **May 18, 2009**
Filing Date: **May 15, 2009**

Action Goal Date (optional): **January 29, 2010** User Fee Goal Date: **January 31, 2010**

Indication(s) requested: **Tykerb, in combination with letrozole is indicated for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.**

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The*

best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES NO
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments: N/A

3. This application is an eCTD NDA. YES NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 61,362
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) October 30, 2006 NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) January 5, 2008 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO

- If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
 - If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: **May 18, 2009**

NDA #: **22-059**

DRUG NAMES: **TYKERB® (lapatinib) Tablets, 250 mg**

APPLICANT: **GlaxoSmithKline**

BACKGROUND: GlaxoSmithKline has submitted an sNDA for TYKERB® (lapatinib); an orally administered, small molecule (4-anilinoquinazoline), reversible inhibitor of the intracellular tyrosine kinase domains of Epidermal Growth Factor Receptor (EGFR or ErbB1) and of Human Epidermal Receptor Type 2 (HER2 or ErbB2). Lapatinib, in combination with (b) (4)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting): See Below↓

Discipline/Organization

Reviewer

Medical:	Jennie Chang, Pharm.D.
Secondary Medical:	Patricia Cortazar, M.D.
Statistical:	Qiang (Casey) Xu, Ph.D., Shenghui Tang, Ph.D.
Pharmacology:	Kimberly Benson, Ph.D., Haleh Saber, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Zhe J. Tang, Ph.D., Liang Zhou, Ph.D
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Gene Williams, Ph.D., Brian Booth, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Anthony Orenca, M.D., FACP
OPS:	N/A
Regulatory Project Management:	Kim J. Robertson
Other Consults:	DMEPA, DDMAC, DSI, DRISK, OSE

Per reviewers, are all parts in English or English translation? YES NO
If no, explain: N/A

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO

If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments: **N/A**

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
 - The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Kim J. Robertson
Consumer Safety Officer

APPEARS THIS WAY ON ORIGINAL

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON
01/21/2010
NDA Regulatory Filing Review for Tykerb sNDA 022059

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

Date: January 20, 2010

To: Kim Robertson, Project Manager, DDOP

From: Stephanie Victor, Regulatory Review Officer, DDMAC

CC: Robert Dean, DTC Group Leader, DDMAC
Keith Olin, Regulatory Review Officer, DDMAC
Catherine Gray, Professional Group Leader, DDMAC

Subject: NDA # 22-059
DDMAC comments for Tykerb (lapatinib) tablets
PPI

DDMAC has reviewed the proposed Patient Package Information (PPI) for Tykerb (lapatinib) tablets submitted for consult on September 25, 2009, and offers the following comments. Comments regarding the proposed PI will be provided separately by Keith Olin.

The version of the draft PI and PPI used in this review is titled, "January 12 2010 GSK Proposed Latest Label.doc" sent via email on January 13, 2010. This document was last modified on January 12, 2010.

General Comment

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PPI, please contact Stephanie Victor at 301-796-3693 or Stephanie.Victor@fda.hhs.gov.

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22059

SUPPL-7

SMITHKLINE
BEECHAM CORP
DBA
GLAXOSMITHKLIN
E

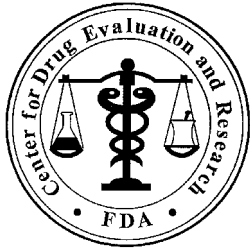
TYKERB TABLETS

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/s/

STEPHANIE L VICTOR

01/20/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: January 11, 2010

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Kellie Taylor, PharmD, MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name(s): Tykerb (Lapatinib) Tablets
250 mg

Application Type/Number: NDA 022059/S-028

Sponsor: GlaxoSmithKline

OSE RCM #: 2009-2394

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1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the proposed insert labeling submitted as part of an efficacy supplement (NDA 022059/S-028) dated March 31, 2010. The insert labeling was revised to reflect a new indication and new dosing regimen.

1.1 REGULATORY HISTORY

Tykerb (lapatinib) was approved on March 13, 2007. The labels and labeling for this product was reviewed by DMEPA prior to the drug's approval in OSE review 2006-480. DMEPA provided recommendations regarding the labels and labeling; however, we are unable to determine if these recommendations were communicated to the Applicant.

2 PRODUCT INFORMATION

The new indication and dosing regimen for Tykerb is listed below in *italics*:

Indication and Usage
Tykerb, a kinase inhibitor, is indicated in combination with: • capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. • (b) (4)
Dosage and Administration
The recommended dose of Tykerb for advanced metastatic breast cancer is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. <i>The recommended dose of Tykerb for hormone receptor positive (b) (4)</i> <i> (b) (4) When Tykerb is coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily.</i> • Tykerb should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. • Tykerb should be taken once daily. Do not divide daily doses of Tykerb. • Modify the dose for cardiac and other toxicities, severe hepatic impairment, and CYP3A4 drug interactions.

3 METHODS AND MATERIALS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Because Tykerb is a currently marketed product, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on December 22, 2009 for any medication

errors relevant to the labels or labeling of Tykerb using the following criteria: Active Ingredient “Lapat%” and Verbatim Substance “Tyk%” and the MedDRA reaction terms “Medication Errors” (HGLT) and “Product Quality Issue” (PT).

The reports were manually reviewed to determine if medication errors occurred involving factors related to either the packaging or labeling. Those cases that did not describe a medication error, and those that were determined to be irrelevant, were excluded from further analysis. Duplicate reports were grouped together into cases. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3.2 LABELING

For this product, the Applicant submitted package insert labeling which reflects the new indication and dosing regimen.

4 RESULTS

4.1 MEDICATION ERROR CASES

The AERS search retrieved a total of 52 reports involving lapatinib on December 22, 2009. There was one duplicate report, thus a total of 51 cases were retrieved.

Twenty-nine cases (n=29) pertained to adverse events that were not caused by a medication error (e.g., diarrhea, nausea, fatigue, shortness of breath). These cases were excluded from further analysis.

The remaining 22 cases were related to medication errors involving Tykerb (see Appendix A). These cases were evaluated for root cause and contributing factors to the errors and are described below (see section 5.1).

4.2 LABELING

After reviewing the insert labeling, it was determined that the labeling needs improvement in the following areas: clarification that Tykerb tablets should be administered all at once, reorganization of the Dosage and Administration section to provide more clarity, and including information in the Patient Counseling Information section about grapefruit products.

5 DISCUSSION

5.1 AERS CASES

After reviewing the 22 medication errors retrieved involving Tykerb, it was determined that the medication errors that occurred were not the result of inadequate labeling of the package insert. The cases are described below.

5.1.1 Descriptions of cases (n=22)

Twelve cases pertained to overdoses (n=12), either prescribed or accidental. The overdoses involved wrong frequency of administration (e.g., 1250 mg BID), but the package insert, patient counseling information, and the patient package insert all specify the dose is 5 tablets once daily. Six cases (n=6) pertained to the inappropriate schedule of administration of Tykerb (e.g., the dose was spread throughout the day rather than administered all at once). Three cases (n=3) pertained to crushing the Tykerb tablets (wrong technique). The insert labeling does not indicate whether or not the tablets can be crushed. One case (n=1) pertained to the maladministration of Tykerb

where the patient took the medication with food instead of taking the medication either one hour before or one hour after a meal, however, the package insert, patient counseling information, and patient package insert all specify that Tykerb should be taken at least one hour before a meal or one hour after a meal.

5.2 LABELING

Although the AERS reports did not specify that the Tykerb medication errors occurred as a result of confusing or inadequate labeling, improvement to the labeling may provide more clarity or emphasis to of the Dosage and Administration information and potentially reduce some of the aforementioned medication errors.

The wording in Section 2.1 (Recommended Dosing) of the Dosage and Administration section may be confusing as it comingles information about Tykerb and capecitabine throughout this section. This may have contributed to dosing errors as this section begins by giving dosing information for Tykerb as 5 tablets given once daily, but in the same sentence it is mentioned that capecitabine is dosed in 2 doses approximately 12 hours apart. Clarifying this section by addressing each drug separately rather than mixing the information of both drugs may help to minimize errors.

Additionally, Section 17 (Patient Counseling Information) does not instruct patients to avoid consumption of grapefruit products while taking Tykerb as it is indicated in the Patient Package Insert.

Section 17 also mentions that the Tykerb dose should not be divided. Because there are multiple tablets in one dose, the labeling could be even more specific by instructing patients to administer the medication “all at once”. This information should also be added to the Dosage and Administration section and the Patient Package Insert.

6 CONCLUSIONS AND RECOMMENDATIONS

We recommend that the Dosage and Administration section, Patient Counseling Information section, and Patient Package Insert be improved in order to provide more specific information that provides more clarity on the administration of Tykerb tablets. Therefore, we have provided recommendations below that aim at improving the aforementioned sections.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

6.1 COMMENTS TO THE DIVISION

A. Dosage and Administration- Section 2

1. HER2 positive metastatic cancer indication: Reorganize the first paragraph of Section 2.1 (Recommended Dosing) so that Tykerb and capecitabine are addressed separately in order to avoid confusion with the frequency of administration of each product. Additionally, include a statement that the Tykerb dose should be administered all at once. For example:

The recommended dose of Tykerb is 1,250 mg (b) (4) given orally once daily on Days 1-21 continuously in combination with capecitabine. Tykerb should be taken at least one hour before or one hour after a meal. The dose of Tykerb should be once daily

(administer all 5 tablets at once); dividing the daily dose is not recommended [*see Clinical Pharmacology (12.3)*].

(b) (4)
Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

2. In the second to last sentence in section 2.1 (Recommended Dosing), the phrase "If a day's dose is missed, the patient should not double the dose for the next day" does not indicate to which drug this phrase is referencing because there are two drugs referenced in this paragraph: If a day's dose (of what?) is missed, Tykerb or capecitabine? Revise this phrase to specify which drug is in question.
3. Revise the first sentence of the second paragraph of Section 2.1 for the hormone receptor positive advanced or metastatic breast cancer indication, to indicate that Tykerb should be taken all at once. For example:

The recommended dose of Tykerb is 1,500 mg (b) (4) given orally once daily continuously in combination with (b) (4)

B. Patient Counseling Information- Section 17

1. We recommend you add the statement to not eat or drink grapefruit products while taking Tykerb to this section as this statement currently appears in the Patient Package Insert and is pertinent to the proper administration of this product.
2. Include a statement in the fifth bullet of section 17.1 (Information for Patients) that the Tykerb dose should be administered all at once. For example:

The dose of Tykerb should not be divided. (b) (4)

C. Patient Package Insert

In the section "How should I take Tykerb", include a phrase in the second and third bullets that indicate the Tykerb dose should be taken all at once. For example:

For patients with advanced or metastatic breast cancer, Tykerb and capecitabine are taken in 21 day cycles. The usual dose of Tykerb is 1,250 mg (5 tablets) taken by mouth all at once, one time a day on days 1 to 21....

For patients with hormone receptor positive breast cancer, Tykerb and (b) (4) are taken daily. The usual dose is 1,500 mg (6 tablets) taken by mouth all at once, one time a day....

7 REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. OSE Review 2006-480; Consultation Response- Tykerb (Lapatinib Tablets); Pedersen, K.; October 20, 2005.

APPEARS THIS WAY ON ORIGINAL

APPENDIX

Appendix A: Tykerb medication error ISR numbers

Overdose (n=12) ISR #s
6470761-9, 6395826-X, 6395818-2, 6032539-X, 6150979-5, 6032500-5, 5805674-6, 5870570-5, 5566779-0, 5877893-4, 5380506-1, 5380055-0
Inappropriate schedule of administration (n=6) ISR #s
5380099-9, 6079145-9, 5915567-1, 5482558-7, 5380062-8, 5363575-4
Wrong technique (n=3) ISR#s
6304714-8, 6032533-9, 5588343-X
Maladministration (n=1) ISR#s
5700890-6

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

FELICIA DUFFY
01/11/2010

KELLIE A TAYLOR
01/11/2010

CAROL A HOLQUIST
01/11/2010

REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consult (DMEPA)

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/DDOP/Kim Robertson, 6-1441

DATE December 14, 2009	IND NO.	NDA NO. 22-059	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Tykerb (lapatinib) Tablets/Letrozole		PRIORITY CONSIDERATION Standard Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 14, 2010

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY	☐ PRE-NDA MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☐ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT	☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☐ OTHER (SPECIFY BELOW):

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: At this time, the DDOP is requesting that OSE please review the efficacy supplement as it pertains to sNDA 22-059. Given that the application has included a new dosing regimen, we would like this reviewed from a medication error perspective. The PDUFA Date is: January 29, 2010; Division Target Date is: January 16, 2010. The clinical reviewer is Jennie Chang.

To facilitate the review, I have attached the label and PIL to this consult. Any additional information can be found in the EDR.

EDR Location: \\CDSESUB1\EVSPROD\NDA022059

SIGNATURE OF REQUESTOR Kim Robertson, CSO	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

12/14/2009

14December09 OSE/DMEPA Consult; sNDA 022059; Tykerb/Letrozole

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 24, 2009

TO: Kim Robertson, Regulatory Project Manager
Jennie Chang, Pharm.D., Clinical Analyst
Patricia Cortazar, M.D., Medical Team Leader
Division of Drug Oncology Products, HFD-150

THROUGH: Tejashri Purohit-Sheth, MD, FAAAI
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-059/S-007

APPLICANT: GlaxoSmithKline, Inc.

DRUG: lapatinib (Tykerb)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Tykerb in combination with (b) (4)
(b) (4)

CONSULTATION REQUEST DATE: June 8, 2009 (DFS: June 26, 2009)

DIVISION ACTION GOAL DATE: December 1, 2009

PDUFA DATE: January 29, 2010

I. BACKGROUND:

Lapatinib (GW572016; TYKERB™/TYVERB™; trademarks in the U.S.A. and the European Union, respectively) is a reversible tyrosine kinase inhibitor (TKI) that potently inhibits both EGFR and HER2. Lapatinib is the only currently approved targeted therapy

(b) (4)

The sponsor submitted Protocol EGF30008 entitled “A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study Comparing Lapatinib and Letrozole versus Letrozole in Subjects with Estrogen/Progesterone Receptor-Positive Advanced or Metastatic Breast Cancer.”

EGF30008 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase III study to evaluate and compare the efficacy and tolerability of lapatinib and letrozole, compared with letrozole and placebo. This study was conducted from December 9, 2003 until June 3, 2008.

The primary objective of EGF30008 was to evaluate and compare investigator-evaluated progressive-free survival (PFS) in subjects with estrogen receptor (ER) positive and/or progesterone (PgR) positive, HER2-positive advanced or metastatic breast cancer treated with lapatinib and letrozole in comparison to letrozole and placebo. Eligible subjects were post-menopausal women with hormone receptor positive (ER positive and/or PgR positive) advanced or metastatic breast cancer, who had not received prior therapy for advanced or metastatic disease.

A total of 212 centers in 29 countries across 5 regions (North America, Latin America, Western Europe, Eastern Europe and Asia Pacific) enrolled subjects in this multicenter study sponsored by GSK. The majority of subjects were recruited into the study from Western and Eastern Europe (57%).

This study initially planned to enroll approximately 760 subjects. Protocol Amendment 03 increased enrollment by an additional 520 subjects. Subjects were randomly assigned to receive either lapatinib (1500 mg once daily orally) with letrozole (2.5 mg once daily orally), or letrozole (2.5 mg once daily orally) with placebo (which matched with lapatinib tablet). Randomization was stratified by site of disease and time since prior adjuvant endocrine therapy. There were 644 patients who were randomized in the placebo group and 642 patients who were randomized in the treatment arm. There were 229 subjects in the placebo and 238 subjects in the treatment arm, classified as “permanently discontinued treatment” due to death from disease progression.

The primary efficacy measure for EGF30008 was progressive free survival (PFS) in a HER2-positive population. All efficacy analyses were conducted on both the HER2-positive and ITT populations. PFS was defined as the interval of time (in weeks) between the date of randomization and the earlier of date of disease progression, or date of death due to any cause (Disease progression was based on the assessments by the investigator. The date of documented disease progression was defined as the date of radiological

disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. If a subject had neither progressed nor died, then PFS was censored at the date of the last radiological scan assessed by the investigator).

Three clinical sites were inspected for this study: Lima Peru (Dr. Gomez), Moscow, Russia (Dr. Lichinitser) and Besancon, France (Dr. Pivot).

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Michael (Mikhail) Lichinitser, M.D. /Site # 91399	Moscow, Russian Federation	EGF 30008	9/21-9/24, 2009	11/12/2009	VAI
Pivot Xavier, M.D. /Site #91837	Besançon, France	EGF 30008	9/14-9/18, 2009	11/21/2009	VAI
Henry Gomez, M.D. /Site #92498	Lima Peru	EGF 30008	9/14/-9/18, 2009	10/2/2009	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

PROTOCOL EGF30008

1. Prof. Michael (Mikhail) Lichinitser, M.D./Site # 91399
Russian Cancer Research Center
Dep.-Moscow-Russian Federation
24, Kashirskoye, Shosse
Moscow, Russian Federation 115478

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 21 and 24, 2009. A total of 48 subjects were screened, and 38 subjects were randomized and completed the study. The inspection evaluated the following documents of these 38 subjects: comparison of medical records to case report forms, study drug accountability logs, informed consent documents, study monitoring visits and

correspondence. Source documents were verified for consistency with data listings. A comprehensive review of 6 subjects' records was also conducted for subject randomization and treatment administration, protocol compliance, and drug accountability data.

b. Limitations of inspection:

None.

c. General observations/commentary:

A two-observation Form FDA 483 was issued at the end of the inspection: investigational drug disposition records were not adequate, and there was failure to maintain accurate case histories. Specifically,

- Subject (b) (6) source records showed a 23 mm measured lesion while the case report form was 25 mm.
- Subject (b) (6) source documentation stated that 12 tablets of the investigational drug were collected on (b) (6) but pharmacy dispensing records showed that these tablets in container 220779 were returned on (b) (6)

d. Data acceptability/reliability for consideration in the NDA review decision:

The regulatory deficiencies are considered minor and isolated, and are unlikely to significantly impact data integrity. The data in support of clinical efficacy and safety at this clinical site appear acceptable.

2. Prof. Pivot Xavier, M.D./Site #91837
CHU-Hôpital Jean Minjoz 3, Boulevard Fleming
25030 Besançon, France

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 14 to 18, 2009. A total of 48 patients were screened and completed the study. An audit of 29 subject records were randomly selected and reviewed for inclusion and exclusion criteria, adverse event reporting, efficacy and safety assessment and protocol compliance. A comprehensive audit of seven enrolled study subjects' records for efficacy and safety assessments, randomization and treatment administration, and drug accountability was also performed.

b. Limitations of inspection:

None.

c. General observations/commentary:

In general, the study appeared to have been conducted adequately. No Form FDA 483 was issued, although a few items were discussed with the clinical investigator., Per Protocol EGF30008 Section 9.90, prompt reporting of serious adverse events (SAEs) to

the sponsor (GSK) was required. The time frame required that “SAE data collection tool” was to be processed as part of the initial report within 24 hours after awareness of the event; however, the SAE reports were submitted beyond the protocol specified time frame of 24 hours. Specifically,

- Subject (b) (6) (Dossier (b) (6)) was diagnosed with adenocarcinoma of the left kidney on (b) (6) with an electronic facsimile report dated (b) (6)
- Subject (b) (6) developed Crohn’s enteritis on (b) (6) with an electronic facsimile report dated (b) (6)
- Subject (b) (6) had a cardiovascular event on (b) (6) with an electronic facsimile report dated (b) (6)
- Subject (Dossier (b) (6)) had an “ovariectomy” (oophorectomy) on (b) (6), with an electronic facsimile report dated (b) (6)

d. Data acceptability/reliability for consideration in the NDA review decision:

Although these were observed regulatory deficiencies in the context of this clinical trial, these observations do not have significant impact on data integrity, as they were reported to the sponsor, albeit late. The data in support of clinical efficacy and safety from this clinical site appear acceptable.

3. Henry Gomez, M.D. / Site #92498
Instituto Nacional de Enfermedades Neolasicas
Av. Angamos Este 2520
34 Lima, Peru

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 14-18, 2009. A total of 48 subjects were screened and 36 subjects were randomized into the study. All 9 subjects completed the study. The inspection evaluated the following documents for 6 of the randomized patients: signed informed consent forms, source documents and corresponding case report forms, primary efficacy endpoint (progression-free survival), protocol deviations, adverse events, IRB correspondence, monitoring records and test article accountability.

b. Limitations of inspection:

None.

c. General observations/commentary:

The study appeared to be conducted adequately. No Form FDA 483 was issued, and no significant regulatory violations were noted.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three foreign clinical investigator sites were inspected in support of this application for study Protocol **EGF30008**, the sponsor's "adequate and controlled clinical study," in support of lapatinib (Tykerb) approval in combination with an aromatase inhibitor, indicated for the treatment of hormone sensitive advanced or metastatic breast cancer.

Inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. No significant discrepancies were noted with the data listings provided in the NDA and source documents at the clinical sites. The data generated by these inspected sites appear reliable in support of the application.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

ANTHONY J ORENCIA
12/02/2009

TEJASHRI S PUROHIT-SHETH
12/02/2009

REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consult (DRISK)

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/DDOP/Kim Robertson, 6-1441

DATE August 18, 2009	IND NO.	NDA NO. 22-059	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Tykerb (lapatinib) Tablets/Letrozole		PRIORITY CONSIDERATION Standard Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 30, 2009

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: At this time, the DDOP is requesting that OSE please performs the following action as it pertains to sNDA 22-059: 1) Review and comment on the proposed patient package insert (PPI) for "Tykerb"; The PDUFA Date is: January 29, 2010; Division Target Date is: January 16, 2010. The clinical reviewer is Jennie Chang.

To facilitate the review, I have attached the label and PIL to this consult. Any additional information can be found in the EDR.

EDR Location: \\CDSESUB1\EVSPROD\NDA022059

SIGNATURE OF REQUESTOR Kim Robertson, CSO	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22059	----- SUPPL 7	-----	----- TYKERB TABLETS

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/s/

KIM J ROBERTSON

08/18/2009

18August09 OSE DRISK Consult; PPI; sNDA 22-059; Tykerb(lapatinib) and Letrozole; SE1 007

DSI CONSULT: Request for Clinical Inspections

Date: June 8, 2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Robert Young, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Jennie Chang, Pharm.D., Senior Clinical Analyst, DDOP
Patricia Cortazar, M.D., Medical Team Leader, DDOP

From: Kim Robertson, Consumer Safety Officer, HFD-150

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: Supplement # NDA-22,059/S-007

Applicant: GlaxoSmithKline

Applicant P.O.C.: Richard Swenson, Ph.D., Senior Director, Global Regulatory Affairs-Oncology

Tel: # [REDACTED] (b) (6)

Drug Proprietary Name: Tykerb

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): "Tykerb in combination with [REDACTED]"

(b) (4)

(b) (4)

PDUFA: January 29, 2010

Action Goal Date: January, 29, 2010

Inspection Summary Goal Date: December 1, 2009

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Study EGF30008: A randomized, double-blind, placebo-controlled, multicenter, Phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #049858 Xavier Pivot CHU-Hôpital Jean Minjoz 3, boulevard Fleming 25030 Besançon France	EGF30008	48	Lapatinib in combination with (b) (4) (b) (4)
Site #001433 Michael Lichinitser Cancer Research Center Dep.-Moscow-Russian Federation 24, Kashirskoye Shosse Moscow 115478 Russian Federation	EGF30008	38	Lapatinib in combination with (b) (4) (b) (4)
Site # Henry Gomez Instituto Nacional de Enfermedades Neoplásicas Av. Angamos Este 2520 Lima 34 Peru	EGF30008	36	Lapatinib in combination with (b) (4) (b) (4)

III. Site Selection/Rationale

Rationale for DSI Audits

The pivotal study EGF30008 was a multi center, international study. Large numbers of patients were enrolled at foreign sites which might be driving the study results. The quality of data gathered at foreign sites with large enrollments in addition to the applicability of this data to the standard of care within the United States are reasons for selecting these sites for audits.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Enrollment of large number of study subjects and has a large number of protocol violations with the proposed U.S. site.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): Enrollment of large number of study subjects and has a large number of protocol violations. Most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study. Additionally, financial interest of > \$25,000 involving (b) (4) has been reported in the financial disclosure statement.

IV. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Kim Robertson, RPM, at 301-796-1441 or Jennie Chang, Senior Clinical Analyst, at 301-796-0137.

Concurrence: (as needed)

Jennie Chang _____ Medical Reviewer
 Patricia Cortazar _____ Medical Team Leader
 Robert Justice _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

Robert Justice
6/16/2009 06:51:47 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022059Orig1s007

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022059

SUPPL # 007

HFD # 150

Trade Name Tykerb

Generic Name lapatinib

Applicant Name GlaxoSmithKline

Approval Date, If Known January 29, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study: EGF30008

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study: EGF30008

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
IND # 61,362	YES ☒	!
		! NO ☐
		! Explain:

Investigation #2		!
IND #	YES ☐	!
		! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kim J. Robertson
Title: Consumer Safety Officer
Date: January 19, 2010

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Division Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/25/2010

Exclusivity Summary for sNDA 022059/S-007; Tykerb + Letrozole

ANN T FARRELL

01/29/2010

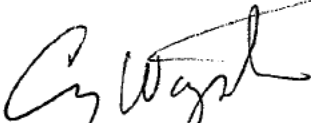
Farrell for Justice

CONFIDENTIAL

m1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 022059 Supplemental NDA for TYKERB® (lapatinib) Tablets (b) (4))



Craig Wozniak

January 2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA #	NDA Supplement # 022059 BLA STN #	If NDA, Efficacy Supplement Type: SE1-007
Proprietary Name: Tykerb Established/Proper Name: lapatinib Dosage Form: Tablet		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Kim J. Robertson		Division: Drug Oncology Products
<u>NDA</u>s: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug. <u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>January 31, 2010</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain <u>The applicant has been made aware that they will need to contact DDMAC to further discuss the submission of their promotional materials.</u>	☐ Received
❖ Application Characteristics²	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☒ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request Comments:	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) January 29, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	January 28, 2010 (sponsor proposed)
• Original applicant-proposed labeling	March 31, 2009
• Example of class labeling, if applicable	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	N/A
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☐ DMEDP ☒ DRISK January 25, 2010 ☒ DDMAC January 20 and 22, 2010 ☐ CSS ☒ Other reviews DSI; December 2, 2009; DMEPA: January 11, 2010
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	January 21, 2010
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>October 7, 2009</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Internal memoranda, telecons, etc.	December 7, 2009; January 14, 2010 (t-cons); OSE Memo, February 1, 2010
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	N/A Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None January 29, 2010 (Deputy Director)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 2
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	January 25, 2010
• Clinical review(s) (<i>indicate date for each review</i>)	January 25, 2010
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 20 of the Clinical Review.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) - REMS Memo (<i>indicate date</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☐ None requested December 2, 2009

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

Clinical Microbiology		☒ None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		☐ None
Clinical Microbiology Review(s) (indicate date for each review)		☐ None
Biostatistics		☐ None
❖ Statistical Division Director Review(s) (indicate date for each review)		☒ None
Statistical Team Leader Review(s) (indicate date for each review)		☐ None December 31, 2009
Statistical Review(s) (indicate date for each review)		☐ None December 31, 2009
Clinical Pharmacology		☐ None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		☐ None January 2?, 2010
Clinical Pharmacology review(s) (indicate date for each review)		☐ None January 2?, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)		☒ None
Nonclinical		☐ None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		☒ None
• Supervisory Review(s) (indicate date for each review)		☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		☐ None January 29 , 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		☒ No carc
❖ ECAC/CAC report/memo of meeting		☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		☒ None requested
Product Quality		☐ None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		☐ None January 8, 2010
❖ Microbiology Reviews		☒ Not needed
☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	January 8, 2010
☐ Review & FONSI (<i>indicate date of review</i>)	N/A
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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

/s/

KIM J ROBERTSON

02/01/2010

Revised Action Package Checklist NDA 022059/S-007; Tykerb + Letrozole; Breast Cancer; GSK

The population in the registration trial is not a representative sample of the US population with HER2+, hormone-positive metastatic breast cancer. The EGF30008 trial was conducted mostly in foreign countries; only 2 of the 219 patients with HER2+ breast cancer had prior trastuzumab, 50% of the patients were treatment-naïve, 36% received prior anthracyclines and none of the patients had prior taxanes. It is important to find out the magnitude of clinical benefit on patients that received prior adjuvant trastuzumab and an aromatase inhibitor.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The subpopulation to be studied in this trial is: postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and who received prior neo-adjuvant/adjuvant trastuzumab therapy.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA: 022059/S-007

Drug: Tykerb (lapatinib) Tablet; 250 mg

Sponsor: GlaxoSmithKline

Division: Division of Drug Oncology Products

Indication: (b) (4)

PMR/PMC Description:
PMR 1586-2

EGF108919 is an ongoing collaborative trial between NCIC and GSK. It is a randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>05/31/2010</u>
	Study/Clinical trial Completion Date:	<u>06/15/2011</u>
	Final Report Submission Date:	<u>04/30/2013</u>
	Final Survival Report Submission Date:	<u>07/31/2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The proposed PMR study will provide additional information to support the clinical benefit of lapatinib in the treatment of metastatic breast cancer.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab therapy.

Required

- Observational pharmacoepidemiologic study
 Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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

/s/

KIM J ROBERTSON

01/29/2010

PMRs for sNDA 022059/S-007; Tykerb + Letrozole; GlaxoSmithKline; Accelerated Approval; Met. Breast Cancer

ANN T FARRELL

01/29/2010

MEMORANDUM OF TELECON

DATE: January 14, 2010

APPLICATION NUMBER: sNDA #022059/SE1-007; Tykerb (lapatinib) tablets plus Letrozole

BETWEEN:

Name: Richard Swenson, Ph.D., Director, Global Regulatory Affairs)
Jeffrey Bloss, M.D., Vice President, Research, Development, & Medical Affairs, Oncology - N.A.
Rafael Amado, M.D., Vice President, Global Clinical Development - Oncology
Steven Stein, M.D., Vice President, Global Clinical Development - Oncology
Meg Annan, Ph.D., Project Team Leader
Allison Florance, M.S., Manager, Oncology, Biometrics, and Epidemiology
Alaknanda Preston, Ph.D., Director, Oncology, Biometrics, and Epidemiology
Michael Gress, M.S., Director, Clinical Operations - Oncology
Lisa O'Rourke, M.S.N., Lead Clinical Scientist
Roya Behbahani, PharmD., Director, Strategic Labeling - Oncology

Phone: (b) (6) Richard Swenson, Ph.D.
Representing: GlaxoSmithKline

AND

Name: Robert L. Justice, M.D., M.S., Division Director
Patricia Cortazar, M.D., Clinical Team Leader
Jennie Chang, Pharm.D., Clinical Reviewer
Shenghui Tang, Ph.D., Statistical Reviewer
Qiang (Casey) Xu, Ph.D., Statistical Reviewer
Gene Williams, Ph.D., Clinical Pharmacology Reviewer
Haleh Saber, Ph.D., Pharmacology/Toxicology Team Leader
Kimberly Benson, Ph.D., Pharmacology/Toxicology Reviewer
Kim J. Robertson, Consumer Safety Officer
Division of Drug Oncology Products, HFD-150

Phone: (301) 796-2330
Representing: Food and Drug Administration

SUBJECT: Further Discussion of GlaxoSmithKline's Proposed Ongoing/Additional Studies and the Summary of Designs of any Ongoing Studies to Fulfill PMRs for Tykerb plus Letrozole.

On January 14, 2010, the FDA discussed with GSK the trial design for the postmarketing requirements. Attachment 1 has the details for the trial design proposed by the applicant. FDA stated that the following trials could support the postmarketing requirements and asked the sponsor to submit the timelines.

1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab therapy. Patients who have extensive visceral metastasis, are rapidly progressing and are eligible for chemotherapy will not be eligible for enrollment. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

2. A randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This is an ongoing collaborative trial (Study EGF 108919; Section 4) with NCIC and the Applicant. It is a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients are stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The trial original primary endpoint is PFS. The Agency recommended that for the PMR purpose, the primary endpoint should be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane. GSK stated that since this is an ongoing study in collaboration with the NCIC, the primary endpoint of PFS will remain the same but for the regulatory purpose, GSK commits to submit an overall survival analysis.

The first trial will be submitted as a SPA with a SAP. The second trial will be submitted.

Attachment 1

NDA 22-059/S007

Lapatinib/Letrozole in 1st line Hormone Sensitive, HER2+ Metastatic Breast Cancer

GSK Response to FDA's Requirements for Postmarketing Study Commitments

1. Situation

The FDA had previously stated that sNDA 22059 of lapatinib plus letrozole (b) (4) would be considered for accelerated approval. GSK sent FDA a proposal (19 December 2009) to fulfill their request for postmarketing study commitments. In response to this proposal, the FDA stated that several postmarketing requirement (PMR) studies are necessary to confirm the efficacy and safety of lapatinib demonstrated in Study EGF30008. The FDA reviewed GSK's proposed clinical trial designs to fulfill the PMRs and determined that two new trials are going to be needed.

Specifically, GSK understands that FDA requires the following as part of the post marketing commitments for the aforementioned sNDA:

- **Study #1:** A design change to the previously proposed randomized, open-label trial of lapatinib plus trastuzumab plus and aromatase inhibitor compared to trastuzumab plus and aromatase inhibitor. These changes include: additional arm of lapatinib plus letrozole, stratification of letrozole vs AI, exclusion of locally advanced breast cancer patients, cardiac evaluation, and the FDA recommended reduction of timelines. (Section 3)
- **Study #2:** A trial design that compares lapatinib plus paclitaxel to trastuzumab plus paclitaxel as 1st line MBC therapy in patients with HER2-positive breast cancer who received prior adjuvant trastuzumab (Study EGF 108919; Section 4)
- GSK acknowledges that study EGF104535 and LPT112515 are not acceptable trials to the FDA to support the postmarketing requirements for the EGF30008 approval.

Details of GSK's proposal to fulfill the postmarketing requirements are presented in this document.

2. Postmarketing Study Commitments

In response to the requests outlined by the FDA, GSK proposes to conduct the studies outlined in Table 1, including estimated timelines. GSK notes the following as obstacles for feasibility and recruitment rate in these trials:

- Limited entry criteria (HER2-positive, hormone receptor positive, prior neo/adjuvant trastuzumab, the exclusion of patients with metastatic breast cancer at first presentation) narrows population and hence recruitment rate.
- With approval of trastuzumab and uptake by market, patients on neo/adjuvant trastuzumab do not have a high rate of disease recurrence
- Recruitment limited to only countries where trastuzumab is approved in neo/adjuvant setting
- Competition with new compounds (TDM1, pertuzumab, neratinib)
- Competition with GSK ongoing studies already including like subjects (EGF111438, EGF108919, LPT112515, etc)

GSK strongly feels that based on the above obstacles and recruitment rates of completed and ongoing studies cited (Appendix 1), there are limited number of clinical research sites with eligible patients and that the timelines proposed are still challenging milestones to achieve. Data to support feasibility projections are located in Appendix 1.

Table 1 Overview of Postmarketing Study Commitments

Study ID Enrollment ¹	Design/ Treatment	Patient Population	Endpoints	Schedule for Conduct and Reporting
Study #1 (Previously proposed new study) 0 pts enrolled 525 pts planned	Randomized, open-label lapatinib 1000 mg PO once daily + trastuzumab 4 mg/kg IV load and 2 mg/kg IV weekly + AI (at investigator's choice) trastuzumab 4 mg/kg IV load and 2 mg/kg IV weekly + AI (at investigator's choice) lapatinib 1500mg PO once daily + AI (at investigator's choice)	hormone receptor positive, HER2-positive MBC previously treated with neo-/adjuvant trastuzumab	OS PFS, ORR, CBR AEs	Protocol submitted: May 2010 Enrollment start: September 2010 end: March 2016 LSLV²: December 2017 CSR to FDA: May 2018
Study #2 (EGF108919 (NCIC CTG Trial: MA.31)) 182 pts enrolled 600 pts planned	Randomized, open label Taxane based chemotherapy plus lapatinib 1250 mg PO once daily for 24 weeks followed by single agent lapatinib 1500 mg until disease progression, or Taxane based chemotherapy plus trastuzumab IV (once weekly [loading dose 4 mg/kg, subsequent doses 2 mg/kg with paclitaxel] or every 3 weeks [loading dose 8 mg/kg, subsequent doses 6 mg/kg with docetaxel]) for 24 weeks followed by single agent trastuzumab 6 mg/kg IV every 3 weeks until disease progression.	HER2 positive MBC, no prior chemotherapy +/- HER2 targeted therapy in the metastatic setting,	PFS OS, OS in p95 subgroup, time to CNS metastases at the time of first progression; Incidence rates of CNS metastases at the time of progression; Overall ORR; time to response; and duration of response; CBR; AEs; OOL; Clinical outcomes using biomarker changes in biological samples; Health economics	Protocol submitted: March 2008 Enrollment start: 07 October 2008 end: 15 December 2010 LSLV for PFS: 12 January 2012 CSR for PFS to FDA: October 2012 LSLV for OS³: April 2015 Update to CSR for OS: January 2016
1. data as of 12 January 2010 2. defined as the projected date when 248 OS events will occur for final analysis of primary endpoint 3. defined as the projected date when 413 OS events will occur for the final analysis of OS endpoint				

3. Study #1: Changes to the Previously Proposed New Clinical Study

The following proposed study is intended to compare the safety and efficacy of lapatinib plus trastuzumab plus an AI versus trastuzumab plus an AI vs. lapatinib plus an AI as first-line therapy in patients with hormone sensitive, HER2-positive MBC who have received trastuzumab and endocrine therapy in the neo-/adjuvant setting. This study will offer data supporting the incremental survival benefit of lapatinib in patients who have had prior adjuvant trastuzumab.

3.1 Proposed Changes

This study includes the following requested changes:

- A third study arm of lapatinib plus an aromatase inhibitor is added to the trial
- The trial is stratified by aromatase inhibitor
- Patients with locally advanced breast cancer are excluded
- The trial will assess cardiac safety
- Timelines remain as originally proposed but include full recruitment of 3 arms (increased from 326 to 525 patients). GSK feels that the current timelines are reasonable based upon real recruitment experience, as outlined in Appendix 1.

3.2 Proposed New Study (Study#1) Protocol Outline

Protocol number / Draft Title: A Randomized, Open-Label, Phase III Study of lapatinib plus trastuzumab plus an AI versus trastuzumab plus an AI versus lapatinib plus an AI as first-line therapy in patients with hormone sensitive, HER2-positive MBC who have received trastuzumab and endocrine therapy in the neo-/adjuvant setting

Objectives: To demonstrate superiority of lapatinib/trastuzumab/AI combination versus trastuzumab/AI combination in the treatment of 1st line metastatic breast cancer.

Design: A three-arm, randomized, open-label, Phase III study comparing lapatinib plus trastuzumab plus an AI versus trastuzumab plus an AI versus lapatinib plus an AI in patients with hormone sensitive, HER2-positive MBC who have received trastuzumab and endocrine therapy in the neo-/adjuvant setting. Patients will be stratified by aromatase inhibitor chosen by the Investigator and time since neo/adjuvant trastuzumab (≤ 6 months/ >6 months)

Patient Population: Approximately 525 patients with histologically confirmed Stage IV invasive breast cancer. Patients must be post-menopausal female aged ≥ 18 years with tumors that are ER+ and/or PgR+ and that overexpress ErbB2 defined as either 3+ by IHC or c-erbB2 gene amplification by FISH. Patients with locally advanced (Stage IIIb/c) will be excluded. Patients with extensive symptomatic visceral disease including hepatic involvement and pulmonary lymphangitic spread of tumor, or the disease is considered by the investigator to be rapidly progressing or life threatening are not eligible

for enrollment. Patients must have had prior neo-/adjuvant trastuzumab to be eligible for enrollment. Patients may not have received prior chemotherapy, hormonal therapy, immunotherapy, biologic therapy, or anti-ErbB1/ErbB2 therapy for advanced or metastatic disease. Patients must have acceptable cardiac function at baseline (LVEF $\geq 50\%$) measured by echocardiogram or MUGA prior to randomization and an ECOG performance status of 0-1 and an electrocardiogram that within normal limits and/or not clinically significant.

Dosing Plan/treatment plan/schema: Patients will be randomized to receive lapatinib 1000mg QD plus trastuzumab (load) 2mg/kg weekly plus and AI of investigator's choice vs. trastuzumab (load) 2mg/kg weekly plus AI of investigators choice vs. lapatinib 1500mg QD plus AI of Investigator's choice

Efficacy Endpoints: Primary: Overall Survival in trastuzumab/AI versus trastuzumab/lapatinib/AI. **Secondary:** Overall Survival in trastuzumab/AI versus lapatinib/AI, Progression Free Survival (PFS), overall response rate, clinical benefit rate, safety, additional endpoints to be determined

Definition of Endpoints: Time from randomization to: **PFS** - progression of disease at any site or death from any cause as first event. **OS** - death from any cause.

Safety Monitoring: All patients will have physical exams, review of adverse events, blood chemistries and hematology.

In addition, for cardiac monitoring, patients will receive a MUGA/ECHO every 12 weeks. Patients will also receive an EKG at baseline, study withdraw and when clinically indicated. Patients will also be monitored for adverse events at each MD visit and clinically indicated.

Statistical Plan: The study would be designed as a superiority trial for OS comparing trastuzumab/AI versus trastuzumab/lapatinib/AI. The assumptions in estimation of sample size are as followed:

- 1:1:1 randomization for ITT
- Sample size based on lapatinib plus trastuzumab plus AI and the trastuzumab plus AI arm comparison as primary endpoint
 - 2-sided 0.05 alpha
 - 80% power
 - H_0 : HR=1 H_a HR= 0.71 (41% improvement over control)
 - duration 5.9 years from study start (September 2010) requiring a total of 249 OS events in 350 patients in the lapatinib plus trastuzumab plus AI and the trastuzumab plus AI arm
- estimated recruitment: 10 patients per month
- total sample size: 525 patients in 3 arms

Enrollment Start Date: September 2010

Estimated Enrollment Completion Date: March 2016

Estimated Analysis of OS Completion date: May 2018

4. Study #2: Request for new trial comparing Lapatinib + Paclitaxel vs Trastuzumab + Paclitaxel as 1st line MBC therapy in HER2+ patients who received prior trastuzumab

GSK's ongoing study (EGF108919) is a randomized, open-label, phase III study of taxane based chemotherapy with lapatinib or trastuzumab as first-line therapy for women with HER2/neu positive metastatic breast cancer. The primary objective is to compare the progression-free survival of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy, in women with HER2/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

4.1 Proposed Changes to Ongoing EGF108919

GSK proposes that this trial will address FDA's request for a study that compares lapatinib plus taxane vs. trastuzumab plus taxane with the following changes:

- Power the study based on the secondary endpoint of OS. The assumptions in estimation of the adjusted sample size are as follows:
 - 1-1 randomization for ITT
 - 2-sided 0.05 alpha
 - 80% power
 - H_0 : HR=1 H_a HR= 0.75 (33% improvement over control)
 - 12 patients per month
 - duration 6.6 years from study start (October 2008) requiring 413 events (deaths) which would occur approximately April 2015
- Primary endpoint of PFS to report after 390 PFS events (approximately 2011)
- PFS and OS in patients who have received prior adjuvant trastuzumab will be a prospectively defined subgroup analysis.

Based on the real recruitment experience outlined in Appendix 1 as well as the barriers to feasibility described in Section 2, GSK believes that further restriction of inclusion criteria to include only patients who have had prior trastuzumab will render the study nearly impossible to complete. Furthermore, as this is an NCIC study, an external partner would also have to agree to such a substantive amendment.

4.2 Current EGF108919 Protocol Outline

Protocol number / Draft Title: EGF108919 / A Randomized, Open-Label, Phase III Study Of Taxane Based Chemotherapy With Lapatinib Or Trastuzumab As First-Line Therapy For Women With Her2/Neu Positive Metastatic Breast Cancer

Primary Objective: To compare the progression-free survival of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy in women with HER2/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

Design: A two-arm, randomized, open-label, Phase III study comparing lapatinib plus a taxane weekly (paclitaxel) or every 3 weeks (docetaxel) versus trastuzumab plus paclitaxel or docetaxel in patients with HER2/neu+ MBC. Patients will be stratified by prior anti-HER2 or taxane therapy, planned taxane treatment on study, and liver metastases.

Patient Population: Approximately 600 patients, to achieve 536 centrally confirmed HER-2 positive patients (268 per treatment arm) with histologically confirmed metastatic, adenocarcinoma of the breast will be enrolled. Patients with baseline CNS metastases are excluded. Patients may have received trastuzumab or chemotherapy agents, including anthracyclines and taxanes, in the neoadjuvant or adjuvant setting provided at least 12 months has elapsed since last dose of therapy. Patients may have received endocrine therapy in the adjuvant or advanced setting provided therapy has been discontinued before randomization.

Dosing Plan/treatment plan/schema: Patients will be randomized to lapatinib orally 1250 mg once daily or trastuzumab (loading dose) followed by 2 mg/kg weekly or 6 mg/kg every 3 weeks plus one of the following: **paclitaxel** as a 3-hour intravenous infusion at 80 mg/m² weekly; or **docetaxel** as a 1-hour intravenous infusion at 75 mg/m² every 3 weeks. Patients will receive taxane based treatment for 24 weeks followed by continuation of either lapatinib 1500mg daily or trastuzumab 6 mg/kg every 3 weeks until progression.

Efficacy Endpoints: Primary: Progression-Free Survival (PFS). **Secondary:** Overall Survival (OS), Time to CNS metastases at the time of first progression, Incidence rates of CNS metastases at the time of progression, Overall objective response rate, time to response and duration of response, Clinical benefit response rate, Quality of Life (using the EORTC QLQ-C30 and a Trial Specific Checklist), Clinical outcomes using biomarker changes in biological samples, Economic Evaluation: health utilities (using the EQ-5D questionnaire) and healthcare utilization

Definition of Endpoints: Time from randomization to: **PFS** - progression of disease at any site or death from any cause as first event. **OS** - death from any cause. **Time to CNS metastases** - disease recurrence where CNS metastases is documented at the time of breast cancer progression.

Safety Monitoring: All patients will have physical exams, blood chemistries and haematology on the days of taxane administration and then every 12 weeks. In addition, MUGA or echocardiogram will be performed every 12 weeks while on treatment.

Statistical Plan: The study will evaluate whether the lapatinib plus taxane treatment regimen is non-inferior to the trastuzumab plus taxane regimen with regard to PFS. There will be an interim analysis (at 195 events) and a final analysis (at 390 events). The interim analysis will be a test for superiority. At the final analysis, if there is evidence of non-inferiority in PFS, then a test of superiority of lapatinib plus taxane compared with trastuzumab plus taxane will be performed. An IDMC will evaluate safety/efficacy at the interim analyses.

Enrollment Start Date: October 2008

Estimated Enrollment Completion Date: December 2010

Estimated CSR completion for PFS Analysis date: October 2012

Estimated Updated CSR completion for OS Analysis date: January 2016

References

Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Re´vil C, Jones A. Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2–Positive, Hormone Receptor–Positive Metastatic Breast Cancer: Results From the Randomized Phase III TAnDEM Study. *J Clin Oncol* 2009, 27: 5529-5537.

Clinical Trials.gov. Accessed on January 13, 2010 at <http://www.clinicaltrials.gov>.

APPENDIX 1

Feasibility

The following completed and ongoing studies were used to estimate feasibility of recruitment and timelines for studies being considered for Post Marketing Commitment.

EGF30008 (completed):

- Final enrollment: ITT N=1286, HER2-positive N=219
- Number of Sites: 284
- Enrollment Period: 37 months (December 03 to December 06)

HER2-positive, hormone receptor positive, no prior trastuzumab required. Enrollment rate was approximately 0.021 patients/site/month.

TAnDEM (completed study by Roche):

- Final enrollment: HER2-positive N=207
- Number of Sites: 130 (www.clinicaltrials.gov)
- Enrollment Period: 36-48 months (Kaufman 2009)

HER2-positive, hormone receptor positive, no prior trastuzumab required. Enrollment rate was approximately 0.044-0.033 pts/site/month.

EGF108919 (ongoing):

- Planned Final enrollment: HER2 positive N=600
- Current Enrollment: 182
- Planned Number of Sites: 220
- Enrollment Period: ongoing, at 16 months (began October 08)

HER2-positive, no prior trastuzumab required. Current population has a current rate of 20 patients per month or approximately 0.11-0.10 pts/site/month.

Of the 182 currently enrolled, only 14% (26/182) have had prior neo/adjuvant trastuzumab. Therefore, a HER2-positive, with prior trastuzumab required population would have a recruitment rate of approximately 0.014-0.015 pts/site/month.

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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

/s/

KIM J ROBERTSON

01/29/2010

January 14 T-con Mins. sNDA S-007; Tykerb + Letrozole; PMR Discussions

PATRICIA CORTAZAR

01/29/2010

From: Robertson, Kim
Sent: Wednesday, January 20, 2010 8:26 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: Revised PMRs??

Importance: High
Richard:

Dr. Cortazar also asked me to ensure that GSK includes the (b) (4)
(b) (4) in the PMR trials.

Regards,
Kim

From: Robertson, Kim
Sent: Wednesday, January 20, 2010 6:22 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: Revised PMRs??
Importance: High

Richard:

This is just a reiteration of the previous e-mail that was sent earlier, with some minor editorial changes.

Kim

From: Robertson, Kim
Sent: Wednesday, January 20, 2010 4:09 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: Revised PMRs??
Importance: High

Hello Richard:

Please see the following proposed indication and PMRs from the Agency:

The following is FDA's proposed wording of the Tykerb indication:

TYKERB, a kinase inhibitor, is indicated in combination with:

- letrozole for the treatment of postmenopausal women with hormone receptor positive

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Richard:

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Hello Richard:

Please see the following proposed indication and PMRs from the Agency:

The following is FDA's proposed wording of the Tykerb indication:
TYKERB, a kinase inhibitor, is indicated in combination with:

- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

The postmarketing requirements we have been discussing with you are listed below. Please complete the timelines and let us know if there are any changes.

1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab

metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

The postmarketing requirements we have been discussing with you are listed below. Please complete the timelines and let us know if there are any changes.

1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab

(b) (4) The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

The timetable you submitted states that you will conduct this trial according to the following timetable:

Final (b) (4) Protocol Submission Date: May, 2010
(b) (4) Trial Completion Date: March, 2016
(b) (4) Final Report Submission Date: May, 2018

2. A randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases.

The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

Please propose a timetable:

therapy. Patients who have extensive visceral metastasis, are rapidly progressing and are eligible for chemotherapy will not be eligible for enrollment. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

The timetable you submitted states that you will conduct this trial according to the following timetable:

Final (b) (4) Protocol Submission Date: May, 2010
(b) (4) Trial Completion Date: March, 2016
(b) (4) Final Report Submission Date: May, 2018

2. A randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

Please propose a timetable:

Final (b) (4) -Protocol Submission Date:
(b) (4) Trial Completion Date:
(b) (4) -Final Report Submission Date:

We will need GSK to respond to these items by 12Noon tomorrow.

Regards,
Kim

From: Robertson, Kim
Sent: Wednesday, January 20, 2010 4:09 PM
To: Rich.Swenson@gsk.com
Subject: RE: Revised PMRs??

Importance: High
Hello Richard:

Please see the following proposed indication and PMRs from the Agency:

The following is FDA's proposed wording of the Tykerb indication:

TYKERB, a kinase inhibitor, is indicated in combination with:

- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

The postmarketing requirements we have been discussing with you are listed below. Please complete the timelines and let us know if there are any changes.

1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

Description of the trial: This will be a Phase 3, randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and had prior neo-adjuvant/adjuvant trastuzumab

(b) (4)
(b) (4) The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor.

The timetable you submitted states that you will conduct this trial according to the following timetable:

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Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane.

Please propose a timetable:

Final ^{(b) (4)} Protocol Submission Date:
^{(b) (4)} Trial Completion Date:
^{(b) (4)} Trial Final Report Submission Date:

We will need GSK to respond to these items by 12Noon tomorrow.

Regards,
Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Wednesday, January 20, 2010 1:35 PM
To: Robertson, Kim
Subject: Re: Revised PMRs??

Hi Kim:

In our teleconference, FDA asked for the SAPs for the two studies. These were submitted last week. I did not hear a request for a revision to the PMRs, but we could do that.

Please let me know as soon as possible.

Thanks,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

20January10 Proposed Division PMRs and Indication; sNDA 022059/S-007

From: Robertson, Kim

Sent: Wednesday, January 20, 2010 3:19 PM

To: 'Rich.Swenson@gsk.com'

Subject: RE: Revised PMRs??

Richard, please stand by for this.....I believe Dr. Cortazar is working on PMR proposals.....I will let you know what my clinicians settle upon momentarily.

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Wednesday, January 20, 2010 1:35 PM

To: Robertson, Kim

Subject: Re: Revised PMRs??

Hi Kim:

In our teleconference, FDA asked for the SAPs for the two studies. These were submitted last week. I did not hear a request for a revision to the PMRs, but we could do that.

Please let me know as soon as possible.

Thanks,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

From: Robertson, Kim
Sent: Wednesday, January 20, 2010 11:00 AM
To: 'Rich.Swenson@gsk.com'
Subject: Revised PMRs??

Richard:

Would you mind terribly sending GSK's revised PMRs to me via e-mail? If I'm not mistaken, we are in receipt of the SAPs, but I don't recall us receiving the updated PMRs. Our clinicians and deputy director would like to view them.

Thanks,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Tuesday, January 19, 2010 7:41 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole Labeling

Importance: High

Attachments: January 14 2010 Label (post meeting).doc
Hello Richard:

Please find the attached Tykerb/Letrozole label. Please pay particular attention to Section 13 of the label, as the division has a very important comment for GlaxoSmithKline. Please have your team review the label and provide us with a label back no later than **Friday, January 22, 2010**.

Regards,
Kim



January 14
) Label (post r

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

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

From: Robertson, Kim
Sent: Tuesday, January 19, 2010 5:15 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: sNDA 22-059 T-con
[Thank you Richard.](#)

[Kim](#)

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Tuesday, January 19, 2010 11:04 AM
To: Robertson, Kim
Subject: Re: sNDA 22-059 T-con

Dear Kim:

Here are the names/titles of the GSK team in our t-con last week.

Jeffrey Bloss, M.D.	Vice President, Research, Development, & Medical Affairs, Oncology - N.A.
Rafael Amado, M.D.	Vice President, Global Clinical Development - Oncology
Steven Stein, M.D.	Vice President, Global Clinical Development - Oncology
Meg Annan, Ph.D.	Project Team Leader
Allison Florance, M.S.	Manager, Oncology, Biometrics, and Epidemiology
Alaknanda Preston, Ph.D.	Director, Oncology, Biometrics, and Epidemiology
Michael Gress, M.S.	Director, Clinical Operations - Oncology
Lisa O'Rourke, M.S.N.	Lead Clinical Scientist
Roya Behbahani, PharmD	Director, Strategic Labeling - Oncology
Richard Swenson, Ph.D.	Global Regulatory Affairs

Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

From: Robertson, Kim

Sent: Friday, January 15, 2010 9:31 PM

To: 'Rich.Swenson@gsk.com'

Cc: Cortazar, Patricia

Subject: RE: Tykerb Labeling Amendment - Delivery Confirmation

Thank you very much Richard for the SAPs. I will forward them to the remainder of the team.

Also, please note that I will be sending the label to you as soon as my pharmacology/toxicology discipline makes revisions to it.

Enjoy your weekend,
Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Friday, January 15, 2010 7:51 PM

To: Robertson, Kim

Cc: Cortazar, Patricia

Subject: RE: Tykerb Labeling Amendment - Delivery Confirmation

Dear Kim:

As requested in our recent teleconference, attached are our statistical analysis plans for the two proposed postmarketing requirement studies.

If you have a question regarding these plans, please call. I will submit these documents formally through the electronic gateway on Monday.

Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

From: Cortazar, Patricia
Sent: Wednesday, January 13, 2010 4:19 PM
To: 'Rich.Swenson@gsk.com'; Robertson, Kim
Subject: RE: Tykerb Labeling Amendment - Delivery Confirmation
[Yes you are correct.](#)

Patricia Cortazar, MD
Clinical Team Leader
FDA CDER DDOP

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Wednesday, January 13, 2010 3:35 PM
To: Robertson, Kim
Cc: Cortazar, Patricia
Subject: RE: Tykerb Labeling Amendment - Delivery Confirmation

Dear Kim:

We are preparing a document that addresses the FDA response related to postmarketing requirement studies. Before finalizing that document we wanted to be clear about the FDA position.

As we understand the response from 8 January 2010, FDA believes two post-marketing requirement studies (noted as "The First Trial" and "The Second New Trial") in our proposal should be put forward by GSK whereas two other studies (EGF104535 and LPT1125) that we proposed were rejected.

We want to be sure this is the FDA position; namely, that GSK should be proposing these two trials (noted as "The First Trial" and "The Second New Trial").

Can you please respond today so that we can finalize our document for discussion?

Thanks,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

As previously stated, sNDA 22059 of lapatinib plus letrozole for patients with hormone-receptor positive, HER2-positive metastatic breast cancer, will be considered for accelerated approval. Several postmarketing requirement (PMR) studies are necessary to confirm the efficacy and safety of Lapatinib demonstrated in Study EGF30008.

We reviewed your proposed clinical trial designs to fulfill the PMRs and determined that two new trials are going to be needed.

The first trial could be your proposed new trial (b) (4), a randomized, open-label trial of lapatinib plus trastuzumab plus an aromatase inhibitor compared to trastuzumab plus an aromatase inhibitor. However, for this trial to support the PMR, the following design issues should be incorporated to improve the trial design:

1. A third study arm of lapatinib plus an aromatase inhibitor is added to the trial.
2. Letrozole is the aromatase inhibitor instead of the investigator's choice.
Alternatively, the trial should stratify by aromatase inhibitor.
3. Patients with locally advanced breast cancer are excluded.
4. The trial is designed to thoroughly collect cardiac safety data.
5. The estimated dates of trial completion (March 2016) and submission of clinical study report (May 2018) are not acceptable. We suggest you increase the number of study sites and estimate new milestones for trial completion and submission of the clinical study report.

For the second new trial, we recommend the following trial design: a comparison of lapatinib plus paclitaxel to trastuzumab plus paclitaxel as 1st line MBC therapy in patients with HER2 + breast cancer who had prior trastuzumab adjuvant therapy. Overall survival should be the primary endpoint.

The designs of the other proposed studies are problematic.

1. Study EGF104535: A randomized, double-blind, placebo-controlled study of lapatinib plus paclitaxel versus paclitaxel will not support the PMRs. Paclitaxel monotherapy is not an appropriate control arm in treatment naïve HER2+ MBC.
2. Study LPT1125: A randomized, open-label study of lapatinib + trastuzumab versus trastuzumab in HER2+ MBC with CR, PR or SD following trastuzumab plus chemotherapy in first line setting could support the PMRs. However, the study primary endpoint should be OS.

From: Robertson, Kim
Sent: Friday, January 08, 2010 12:10 AM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb + Letrozole

Importance: High

Attachments: Postmarketing Requirements.pdf; GSKs Latest Proposed label with SLRs and new data Included (post).doc

Hello Richard:

Please see the attached .pdf document, as it pertains to your proposed Post Marketing Requirements. Also, please see the Tykerb + Letrozole label with our FDA inclusions/comments.

Please note that we will need GSK to review both documents and reply to us most expeditiously regarding both documents, so that we are able to stay on track and to meet our deadlines.

Regards,
Kim



Postmarketin
quirements.p



GSKs Latest
posed label w

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

January '10 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

From: Robertson, Kim
Sent: Wednesday, December 16, 2009 2:19 PM
To: Rich.Swenson@gsk.com

Importance: High

Attachments: Carci Data Format and Stat Guidance Info Sheets 07-16-09.doc
Hello Richard:

With regard to Tykerb; NDA 022059, please note that we require the following information:

- Please submit the electronic tumor datasets for the rat and mouse carcinogenicity studies, in FDA format. Please see the attached information sheet for data submission.



Carci Data
rat and Stat C

Thanks,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 07/16/2009

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2008 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can be found at the FDA website <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>. At this time, we are only requesting the tumor dataset in the format described on page 7 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf>. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4670, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2008
Electronic Submissions

Revision 2

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "Study Data Specifications"

Tumor Dataset For Statistical Analysis^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Comments
STUDYNUM	Study number	char		³
ANIMLNUM	Animal number	char		^{1,3}
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		^{3,4}
TUMORNAM	Tumor name	char		^{3,4}
ORGANCOD	Organ/tissue code	char		^{3,5}
ORGANNAM	Organ/tissue name	char		^{3,5}
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	⁴
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	⁴
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

¹ Each animal in the study should have at least one record even if it does not have a tumor.

² Additional variables, as appropriate, can be added to the bottom of this dataset.

³ ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

⁴ A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

⁵ Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

December '09 Pharmtox IR Tumor Dataset for GSK; sNDA 022059/S-007; Tykerb + Letrozole

MEMORANDUM OF TELECON

DATE: December 7, 2009

APPLICATION NUMBER: sNDA #022059/SE1-007; Tykerb (lapatinib) tablets plus Letrozole

BETWEEN:

Name: Steven Stein, M.D., Vice President Global Clinical Development
Rafael Amado, M.D., Vice President Global Clinical Development
Jeffrey Bloss, M.D., Vice President and Medicines Development Leader
Julie D. Maltzman, M.D., Director, Global Clinical Development
Meg Annan, Ph.D., Project Leader, Global Clinical Development
Erica Rappold, M.S., Lead Clinical Scientist, Global Clinical Development
Alaknanda Preston, Ph.D., Director, Statistics and Programming
Allison Florance, Ph.D., Manager, Statistics and Programming
Richard Swenson, Ph.D., Director, Global Regulatory Affairs)

Phone: (b) (6) Richard Swenson, Ph.D.

Representing: GlaxoSmithKline

AND

Name: Richard Pazdur, M.D., Office Director
Anthony Murgo, M.D., Office Associate Director
Robert L. Justice, M.D., M.S., Division Director
Patricia Cortazar, M.D., Acting Deputy Director and Clinical Team Leader
Jennie Chang, Pharm.D., Clinical Reviewer
Shenghui Tang, Ph.D., Statistical Reviewer
Qiang (Casey) Xu, Ph.D., Statistical Reviewer
Gene Williams, Ph.D., Clinical Pharmacology Reviewer
Kim J. Robertson, Consumer Safety Officer
Division of Drug Oncology Products, HFD-150

Phone: (301) 796-2330

Representing: Food and Drug Administration

SUBJECT: Discussion of GlaxoSmithKline's Proposed Ongoing/Additional Studies and the Summary of Designs of any Ongoing Studies to Fulfill PMRs for Tykerb plus Letrozole.

On December 7, 2009, the Division of Drug Oncology Products initiated a teleconference with GlaxoSmithKline to discuss the trials that GSK submitted on December 4, 2009 as a proposal to

fulfill the Postmarketing Requirement (PMR) of sNDA 022059. GSK proposed to conduct a (b) (4)

(b) (4) GSK also submitted summaries from their ongoing Phase III trials of lapatinib in breast cancer.

The Agency informed GSK that the proposed (b) (4) was unacceptable. (b) (4)

(b) (4) Another possibility for a PMR is a 3 arm trial of AI plus trastuzumab, AI plus trastuzumab plus Tykerb, and AI plus Tykerb, for patients who had received prior trastuzumab and hormonal therapy. The Agency urged GSK to submit several trial designs with realistic expectations of accrual. Dr Pazdur stated that labeling negotiations would not commence, until we have an agreement on the PMRs.

The Applicant asked the division to further clarify which type of approval for its most recent supplement (NDA 022059/SLR-007, indicated for the use of Tykerb® (b) (4) would receive, and Dr. Richard Pazdur, OODP Office Director, explicitly stated to the Applicant that if approved, the application would receive an **Accelerated** Approval.

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachments: GSK proposals

Protocol Outline (1 page for each pivotal protocol)

Protocol number / Draft Title: EGF108919 / A Randomized, Open-Label, Phase Iii Study Of Taxane Based Chemotherapy With Lapatinib Or Trastuzumab As First-Line Therapy For Women With Her2/Neu Positive Metastatic Breast Cancer

Primary Objective: To compare the progression-free survival (as assessed by independent central disease assessment review) of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy, in women with HER2/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

Design: A two-arm, randomized, open-label, Phase III study comparing lapatinib plus a taxane weekly (paclitaxel) or every 3 weeks (docetaxel) versus trastuzumab plus paclitaxel or docetaxel in patients with HER2/neu+ MBC. Patients will be stratified by prior anti-HER2 or taxane therapy, planned taxane treatment on study and liver metastases.

Patient Population: Approximately 600 patients, to achieve 536 centrally confirmed HER-2 positive patients (268 per treatment arm) with histologically confirmed metastatic, adenocarcinoma of the breast will be enrolled. Patients with baseline CNS metastases are excluded. Patients may have received trastuzumab or chemotherapy agents, including anthracyclines and taxanes, in the neoadjuvant or adjuvant setting provided at least 12 months has elapsed since last dose of therapy. Patients may have received endocrine therapy in the adjuvant or advanced setting provided therapy has been discontinued before randomization.

Dosing Plan/treatment plan/schema: Patients will be randomized to lapatinib orally 1250 mg once daily or trastuzumab (loading dose) followed by 2 mg/kg weekly or 6 mg/kg every 3 weeks plus one of the following: **paclitaxel** as a 3-hour intravenous infusion at 80 mg/m² weekly; or **docetaxel** as a 1-hour intravenous infusion at 75 mg/m² every 3 weeks. Patients will receive of taxane treatment followed by continuation of either lapatinib 1500mg daily or trastuzumab monotherapy (as defined above) until progression.

Efficacy Endpoints: Primary: Progression-Free Survival (PFS). **Secondary:** Overall Survival (OS), Overall Survival, Time to CNS metastases at the time of first progression, Incidence rates of CNS metastases at the time of progression, Overall objective response rate, time to response and duration of response, Clinical benefit response rate, Quality of Life (using the EORTC QLQ-C30 and a Trial Specific Checklist), Clinical outcomes using biomarker changes in biological samples, Economic Evaluation: health utilities (using the EQ-5D

questionnaire) and healthcare utilization

Definition of Endpoints: Time from randomization to: **PFS** - progression of disease at any site or death from any cause as first event. **OS** - death from any cause. Time to CNS metastases - disease recurrence where CNS metastases is documented at the time of breast cancer progression.

Safety Monitoring: All patients will have physical exams, blood chemistries and haematology on the days of taxane administration and then every 12 weeks. In addition, MUGA or echocardiogram will be performed every 12 weeks while on treatment.

Statistical Plan: There will be an interim analysis (at 195 events) and a final analysis (at 390 events). An IDMC will evaluate safety/efficacy at the interim analyses.

Enrollment Start Date: 7 October 2008,

Estimated Enrollment Completion Date: December 2010

Estimated Study Completion date: December 2011.

Protocol Outline (1 page for each pivotal protocol)

Protocol number / Title: EGF104535/A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Study of Lapatinib (GW572016) in Combination with Paclitaxel Versus Paclitaxel plus Placebo in Subjects with ErbB2 Amplified Metastatic Breast Cancer

Objectives: To evaluate the efficacy/safety of lapatinib added to paclitaxel in subjects with ErbB2 amplified metastatic breast cancer who have not received prior chemotherapy for their metastatic disease. This study is being conducted in countries in where access to trastuzumab is limited or not approved for use.

Design: Two-arm, randomized, double-blind, placebo-controlled Phase III study. Crossover allowed in from placebo to lapatinib is allowed.

Subject Population: Enrollment is complete with 444 subjects who have ErbB2 amplified metastatic breast cancer. Subjects may not have received any prior therapies for metastatic breast cancer; however, subjects who have received prior hormonal therapy only for hormone positive breast cancer are allowed.

Dosing Plan: Lapatinib (1500 mg QD) and paclitaxel (80 mg/m² IV weekly every 3 weeks every 4 weeks) versus paclitaxel plus placebo. Subjects will continue treatment until disease progression or unacceptable toxicity occurs. Subjects on placebo have option to receive open-label single-agent lapatinib until further disease progression. All patients are followed for survival.

Efficacy Endpoints: Overall survival (Primary). Secondary: progression-free survival, overall response rate (complete and partial responses), clinical benefit (CR/PR and SD $\geq$ 6 months), time to response, duration of response.

Definition of Endpoints: **Overall survival** - The time from randomization until death due to any cause. **Progression-free survival** – The time from randomization until disease progression or death due to any cause. **Response Rate** –Tumor response (CR/PR) by RECIST criteria. **Clinical benefit** (CR/PR or stable disease $\geq$ 6 months). **Time to Response** - The time from randomization to response. **Duration of response** – The time from initial response to disease progression or death due to breast cancer.

Safety Monitoring: Safety assessments include medical history, physical exam, laboratory analyses (CBC, chemistry) and cardiac evaluations.

Statistical Plan: Analyses of OS at least 153 deaths (for superiority and futility per IDMC) and 255 deaths. Interpolated Lan-DeMets alpha- and beta-spending stopping boundaries with one-sided 2.5% significance level will be used. The study will have 80% power to detect a hazard ratio of 0.70, corresponding to a 43% increase in median OS in patients who receive lapatinib plus paclitaxel (28.6 months) compared with patients who receive placebo plus paclitaxel (20 months).

Estimated Start and Completion Dates: Start January 2006, Complete Primary OS Analysis August 2010 (estimated target date for events achieved for primary analysis).

Protocol Outline

Protocol number / Title: EGF111438/ A Randomized, Multicentre, Open-Label, Phase III Study of Lapatinib plus Capecitabine versus Trastuzumab plus Capecitabine in Patients with Anthracycline- or Taxane-Exposed ErbB2-Positive Metastatic Breast Cancer.

Objectives: To evaluate the effect of lapatinib plus capecitabine on incidence of CNS as site of first relapse as compared with trastuzumab plus capecitabine.

Design: Two-arm, randomized, multi-centre, open-label Phase III study. Crossover to alternative treatment arm is not allowed.

Subject Population: Approximately 650 subjects with ErbB2-positive metastatic breast cancer, no history or evidence of brain metastases, and treated with prior anthracyclines or taxanes in the adjuvant or metastatic setting will be enrolled. Prior treatment with trastuzumab is not required, however prior treatment with capecitabine and ErbB2 inhibitor other than trastuzumab is not allowed.

Dosing Plan: Lapatinib 1250 mg once daily plus capecitabine 2000mg/m²/day, days 1-14, every 21 days or trastuzumab loading dose of 8mg/kg followed by 6mg/kg q3weekly infusions plus capecitabine 2500mg/m²/day, days 1-14, every 21 days). All subjects will receive study treatment until disease progression, unacceptable toxicity, or subject consent withdrawal.

Efficacy Endpoints: Primary: Incidence of CNS as site of first relapse. Secondary: progression-free survival (PFS), overall survival (OS), overall response rate (ORR), clinical benefit response rate (CBR), time to first CNS progression, duration of response, incidence of CNS progression at any time.

Definition of Endpoints: **Incidence of CNS as site of first relapse** defined as the proportion of subjects with brain metastases, regardless of whether or not progression has been documented concurrently in other sites of disease, **PFS** - time from randomization to first documented disease progression at any site or death due to any cause, **OS** - time from randomization until death due to any cause, **Time to first CNS progression** - time from randomization until documented CNS progression as a first site of relapse, **ORR** - percent of subjects experiencing confirmed Complete Response (CR) and Partial Response (PR), **CBR** - percentage of subjects experiencing confirmed CR or PR at any time or Stable Disease (SD) for ≥ 24 weeks, **Duration of Response** - time from first CR or PR until tumor progression at any site or death due to breast cancer,

Incidence of CNS progression at any time - proportion of subjects who have relapsed with brain metastases at any time (while on study treatment or in follow up).

Safety Monitoring: Every 3 weeks physical exam, hematology, blood chemistry and every 12 weeks echocardiograms and ECG.

Statistical Plan: Enrollment will be stratified by prior trastuzumab therapy (yes/no) and number of prior treatments for metastatic disease (0 *versus* ≥ 1). The final analysis will take place once all subjects have been followed for a minimum of one year or have otherwise died or withdrawn from study. The primary analysis will be from the independent reviewer's assessment of CNS metastases and the investigator assessment of progression in other sites of disease and will consist of a logistic model adjusted for the protocol pre-specified prognostic factors including stratification factors.

Estimated Start and Completion Dates: Start: January 2009, Complete: estimated for primary endpoint 2013.

Protocol Outline (1 page for each pivotal protocol)

Protocol number /Title: EGF106708 / ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study A randomised, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer

Objectives:

Primary: To compare disease-free survival (DFS) in patients with HER2 overexpressing and/or amplified breast cancer randomised to trastuzumab for one year versus lapatinib for one year versus trastuzumab (12 or 18 weeks, according to assigned design) followed by a six-week treatment-free interval followed by lapatinib (28 or 34 weeks, according to assigned design) versus trastuzumab in combination with lapatinib for one year. **Secondary:** To compare overall survival (OS) in patients randomised to trastuzumab for one year versus lapatinib for one year versus trastuzumab (12 or 18 weeks, according to assigned design) followed by a six-week treatment-free interval followed by lapatinib (28 or 34 weeks, according to assigned design) versus trastuzumab in combination with lapatinib for one year;

To compare time to recurrence (TTR) in treatment groups;

To compare time to distant recurrence (TTDR) in treatment groups;

To evaluate the safety and tolerability of all four treatment groups;

To compare the cumulative incidence of brain metastases as the first site of breast cancer recurrence in treatment groups;

To conduct all analyses separately for cohorts defined by the presence or absence of cMyc gene amplification;

To conduct all analyses separately for cohorts defined by the expression levels of PTEN;

To conduct all analyses separately for cohorts defined by the presence or absence of p95 HER2 domain.

Design:

Four-arm, randomised, open-label and multicentre study in women or men with primary breast

cancer that over expresses or amplifies HER2.

Design 1: For patients eligible to complete all (neo) adjuvant chemotherapy – prior to administration of targeted therapy - randomisation after (neo) adjuvant chemotherapy:

Treatment Arm 1: trastuzumab 8 mg/kg IV loading dose followed by 6 mg/kg IV every 3 weeks for a total duration of 52 weeks.

Treatment Arm 2: oral lapatinib 1500 mg daily for a total duration of 52 weeks.

Treatment Arm 3: trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly for a total of 12 weeks followed by a six-week wash out period followed by oral lapatinib 1500 mg daily for 34 weeks (total duration of 52 weeks).

Treatment Arm 4: lapatinib 1000 mg daily in combination with trastuzumab 8 mg/kg load followed by 6 mg/kg IV every 3 weeks for a total duration of 52 weeks.

Design 2: For patients who will receive a taxane in the adjuvant setting together with the targeted agents - randomisation after anthracycline-based (neo) adjuvant chemotherapy:

Treatment Arm 1: weekly paclitaxel 80mg/m² IV for 12 doses OR three weekly docetaxel 75 mg/m² IV for 4 cycles over 12 weeks, concomitant with trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly. After finishing paclitaxel or docetaxel, trastuzumab should be continued at the dose of 6mg/kg IV every 3 weeks (with radiotherapy, when indicated) for a total duration of 52 weeks.

Treatment Arm 2: weekly paclitaxel 80mg/m² IV for 12 doses OR three weekly docetaxel* 75 mg/m² IV for 4 cycles over 12 weeks concomitant with oral lapatinib 1500 mg (if concomitant with paclitaxel) or 1250 mg (if concomitant with docetaxel) daily. After finishing paclitaxel or docetaxel cycles, lapatinib should be continued at the dose of 1500 mg daily (with radiotherapy, when indicated) for a total duration of 52 weeks.

Treatment Arm 3: weekly paclitaxel 80mg/m² IV for 12 doses OR three weekly docetaxel 75 mg/m² IV for 4 cycles over 12 weeks concomitant with trastuzumab 2 mg/kg IV weekly (after 4 mg/kg IV loading dose) for a total of 12 doses followed by a six-week wash out period followed by oral lapatinib 1500 mg daily for 34 weeks (total duration of 52 weeks).

Treatment Arm 4:

With concurrent paclitaxel: weekly paclitaxel 80mg/m² IV for 12 doses concomitant with trastuzumab 2 mg/kg IV weekly (after 4 mg/kg IV loading dose) plus oral lapatinib 750 mg daily. After completing paclitaxel, oral lapatinib 1000 mg daily in combination with trastuzumab 6 mg/kg IV every 3 weeks (with radiotherapy, when indicated) will be administered to complete 52 weeks of treatment.

OR

With concurrent docetaxel*: three weekly docetaxel 75 mg/m² IV for 4 cycles over 12 weeks concomitant with trastuzumab 2 mg/kg IV weekly (after 4 mg/kg IV loading dose) plus oral lapatinib 1000 mg daily. After completing docetaxel, oral lapatinib 1000 mg daily will be continued in combination with trastuzumab 6 mg/kg IV every 3 weeks (with radiotherapy, when indicated) to complete 52 weeks of treatment.

* For treatment arms 2 and 4, when docetaxel-based chemotherapy is used concurrently, it is mandatory to use prophylactic G-CSF support.

Design 2B: For patients who will receive a non-anthracycline platinum containing adjuvant chemotherapy (docetaxel and carboplatin) together with the targeted agents - randomisation before chemotherapy and targeted therapy:

Treatment Arm 1: three weekly docetaxel 75 mg/m² IV and carboplatin AUC 6 IV for 6 cycles over 18 weeks**, concomitant with trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly. After finishing docetaxel and carboplatin cycles, trastuzumab should be continued at the dose of 6 mg/kg IV every 3 weeks (with radiotherapy, when indicated) for a total duration of 52 weeks.

Treatment Arm 2: three weekly docetaxel 75 mg/m² IV and carboplatin AUC 6 IV for 6 cycles over 18 weeks**, concomitant with oral lapatinib 1000 mg daily. After finishing docetaxel and carboplatin cycles, lapatinib should be continued at the dose of 1500 mg daily (with radiotherapy, when indicated) for a total duration of 52 weeks.

Treatment Arm 3: three weekly docetaxel 75 mg/m² IV and carboplatin AUC 6 IV for 6 cycles over 18 weeks**, concomitant with trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly. After finishing docetaxel and carboplatin cycles, a six-week wash out period is followed by oral lapatinib 1500 mg daily for 28 weeks (total duration of 52 weeks).

Treatment Arm 4: three weekly docetaxel 75 mg/m² IV and carboplatin AUC 6 IV for 6 cycles over 18 weeks**, concomitant with trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly plus oral lapatinib 1000 mg daily. After finishing docetaxel and carboplatin cycles, oral lapatinib 1000 mg daily in combination with trastuzumab 6 mg/kg IV every 3 weeks (with radiotherapy, when indicated) will be administered to complete 52 weeks of treatment.

** The use of prophylactic G-CSF support is mandatory for all treatment arms in Design 2B, during the first 18 weeks of treatment (chemotherapy concomitantly with targeted therapy).

Timing of chemotherapy use (Design 1 versus Design 2) is a stratification variable in the study. A balance between the two designs regarding patient numbers is necessary, and was assumed when the protocol was originally developed. Thus at some timepoint, one design might be closed to recruitment in order to achieve this balance.

There is an increasing importance of non-anthracycline regimens in the treatment of breast cancer, and subsequently an increase in the use of such regimens in the clinical setting today. As ALTTO is a true global trial, there is an obligation to make the results of this trial applicable to all regions of the world. Thus at some timepoint, recruitment to anthracycline-based regimens might be closed and patients will be included in a non-anthracycline chemotherapy regimen given concurrently with the targeted therapy (Design 2B) in order to address this question.

Patient Population: Approximately 8000 women (2000 per treatment arm) with ErbB2-overexpressing and/or amplified, early breast cancer who have adequately excised and histologically confirmed invasive adenocarcinoma of the breast will be enrolled. Subjects enrolled in Design 1 or 2 must have received prior systemic (neo-) adjuvant anthracycline-based chemotherapy for primary breast cancer. In cases for which a taxane is indicated, it should be given concomitantly with the targeted therapy and after anthracycline-based chemotherapy (Design 2). For Design 2B, patients must have been treated with definitive surgery and be prepared to receive docetaxel and carboplatin concurrently with targeted therapies. Patients should not have received any prior anti-HER therapy, which includes agents that target other members of the HER family of receptors, e.g. gefitinib (Iressa). Patients may receive adjuvant hormonal therapy per standard of care. Women must have completed definitive surgery, adjuvant radiotherapy (if applicable), and received at least four cycles of an approved (neo-)adjuvant anthracycline-based chemotherapy for primary breast cancer. In cases where women are eligible for a taxanes, it should be given concomitantly with the targeted therapy and after anthracycline-based chemotherapy. Patients should not have received any prior anti-ErbB2 therapy. Patients may receive adjuvant hormonal therapy as per standard of care.

- **Efficacy Endpoints:** **Primary:** Disease free survival. **Secondary:** Overall survival (OS), Time to recurrence (TTR), Time to distant recurrence (TTDR), Safety and tolerability, Cumulative incidence of brain metastases as the first site of breast cancer recurrence, Presence or absence of cMyc gene amplification Expression levels of PTEN, Presence or absence of p95 HER2 domain.

Definition of Endpoints: **DFS** - the time from randomization until the first occurrence of breast cancer recurrence at any site, a second primary cancer or death from any cause as first event. **OS**

- the time from randomization until death from any cause. **TTR** - the time from randomization to breast cancer recurrence, excluding second primary cancers, and censoring deaths without recurrence. **TTDR** – the time from randomization to first distant breast cancer recurrence, excluding locoregional recurrences and second primary cancers, and censoring deaths without recurrence.

Safety Monitoring: All patients will have physical exams (Wk 13, 25, 37, 52, month 18, 24, 26, 28, 60 and then yearly until year 10), blood chemistries (Wk 7, 13, 19, 25, 37, 52, month 18, 24, 26, 28, 60 and then yearly until year 10) and hematology assessed (Wk 25, 52, month 18, 24, 26, 28, 60 and then yearly until year 10). Assessment of left ventricular function (MUGA or echocardiogram) will occur at weeks 25, 37 and 52 during the treatment and in the follow up at months 18, 24, 36, 48 and 60 and then yearly until year 10.

Statistical Plan: the data analysis plan includes 6 monthly safety reviews, three interim analyses and a final analysis. The three interim analyses will occur at approximately 400, 700 and 1000 total DFS events, with review exclusively by the IDMC. The final analysis will take place when 1386 events have occurred.

Enrollment Start Date: 17 May 2007

Estimated Enrollment Complete Date: June 2010

Estimated Final Analysis Complete Date: August 2012

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

12/10/2009

Finalized December 7, '09 T-con Mins. re: sNDA 022059/SE1-007 Tykerb + Letrozole

JENNIE T CHANG

12/11/2009

PATRICIA CORTAZAR

12/15/2009



Professor Xavier Pivot, M.D.
CHU-Hôpital Jean Minjoz 3
Boulevard Fleming
25030 Besançon, France

Dear Professor Pivot:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. On September 14-18, 2009, Ms. Ingrid A. Zambrana, representing the FDA, met with you and your staff to review your conduct of a clinical investigation (Protocol #EGF30008 "A randomized, double-blind, placebo-controlled, multicenter, Phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer), of the investigational drug lapatinib (Tykerb), performed for GlaxoSmithKline.

We understand that you conducted this study under a U.S. Investigational New Drug Application (IND) and thus, is subject to the U.S. Code of Federal Regulations (CFR). Therefore, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under U.S. IND.

We provide these comments based on our review of the establishment inspection report, the documents submitted with that report. The provisions of the U.S. CFR that were violated for the study conducted under an IND are provided below for future reference. We wish to emphasize the following:

You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. Per Protocol EGF30008 Section 9.9, prompt reporting of serious adverse events (SAEs) to the sponsor (GSK) was required. The time frame required that "SAE data collection tool" was to be processed as part of the initial report within 24 hours after awareness of the event; however, there was a delay in submission of the SAE reports to the sponsor. Specifically,

1. Subject (b) (6) was diagnosed with adenocarcinoma of the left kidney on (b) (6). However, per the facsimile transmission to the sponsor, the SAE was not submitted until (b) (6).
2. Subject (b) (6) had Crohn's enteritis on (b) (6). However, per the facsimile transmission to the sponsor, the SAE was not submitted until (b) (6).

3. Subject (b) (6) developed a cardiovascular event on (b) (6). However, per the facsimile transmission to the sponsor, the SAE was not submitted until (b) (6)

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Zambrana during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Bldg. 51, Rm. 5358
Office of Compliance
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

TEJASHRI S PUROHIT-SHETH
12/02/2009



Prof. Mikhail Lichinitser M.D., Ph.D.
Russian Cancer Research Center
Dep.-Moscow-Russian Federation 24
Kashirskoye Shosse
115478 Moscow, Russia

Dear Professor Lichinitser:

Between September 21 and 24, 2009, Ms. Ingrid A. Zambrana, representing the FDA, met with you to review your conduct of a clinical investigation (Protocol EGF30008 entitled "A randomized double blind, placebo-controlled, multicenter, Phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer,") of the investigational drug lapatinib (Tykerb), performed for GSK.

This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected.

At the conclusion of the inspection, Ms. Zambrana presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge that during the inspection you indicated that you plan to implement corrective actions to prevent the recurrence of the inspectional findings, and we expect that these actions will be implemented.

We appreciate the cooperation shown Investigator Zambrana during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5358
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

TEJASHRI S PUROHIT-SHETH
12/02/2009

From: Robertson, Kim
Sent: Tuesday, December 01, 2009 1:57 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb + Letrozole

Importance: High
Hello Richard:

The Agency would like to have a t-con with GSK to further discuss your supplemental application for NDA 22-059; Tykerb + Letrozole. We would need GSK to be prepared to focus the discussions on any ongoing/additional studies, summary of designs of any ongoing studies, and your proposals to fulfill PMRs.

Would GSK be able to accommodate the Agency for a **December 7, 2009, approximately 2:30PM** t-con? If necessary, we have allotted an hour for discussions. If we feel the entire hour is necessary, we will call GSK at 2:00PM, and the meeting would run until 3:00PM.

Please advise.
Thanks,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim

Sent: Wednesday, December 02, 2009 2:25 PM

To: 'Rich.Swenson@gsk.com'

Subject: RE: sNDA 22-059 Tykerb + Letrozole

Yes please. Dr. Cortazar has asked that GSK submit their proposal this week, so that we may review it prior to the December 7 t-con.

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Tuesday, December 01, 2009 4:55 PM

To: Robertson, Kim

Subject: Re: sNDA 22-059 Tykerb + Letrozole

Dear Kim:

Thank you for arranging the t-con so quickly. We will be ready for the discussion on Monday 7 December 2009. Does the Division want GSK to submit a summary of what ongoing/proposed studies we would put forward as candidate PMCs?

We will be ready for a 2 p.m. start to the t-con. Please let us know on Friday what time you expect to start the conference.

Please use the following dialing information:

Toll Free (US):  (b) (4)

Participant Code: 

Chairman: Richard Swenson

Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

From: Robertson, Kim
Sent: Friday, December 04, 2009 2:15 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: sNDA 22-059 Tykerb + Letrozole

Importance: High
Hello Richard:

This is just a follow up e-mail regarding GSK's proposal.....are we going to receive something today? The team would really like to be able to review the proposal prior to Monday's t-con.

Thanks,
Kim

From: Robertson, Kim
Sent: Wednesday, December 02, 2009 2:25 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: sNDA 22-059 Tykerb + Letrozole

Yes please. Dr. Cortazar has asked that GSK submit their proposal this week, so that we may review it prior to the December 7 t-con.

Kim

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Sent: Tuesday, December 01, 2009 4:55 PM
To: Robertson, Kim
Subject: Re: sNDA 22-059 Tykerb + Letrozole

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We will be ready for a 2 p.m. start to the t-con. Please let us know on Friday what time you expect to start the conference.

Please use the following dialing information:

Toll Free (US):

(b) (4)

Participant Code:

Chairman:

Richard Swenson

Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs

From: Robertson, Kim

Sent: Friday, December 04, 2009 4:51 PM

To: 'Rich.Swenson@gsk.com'

Subject: RE: sNDA 22-059 Tykerb + Letrozole

Thank you Richard. I'll forward them to the team at once.

Have a good weekend,

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Friday, December 04, 2009 4:50 PM

To: Robertson, Kim

Subject: RE: sNDA 22-059 Tykerb + Letrozole

Dear Kim:

Apologies for the delay in getting this proposal to you.

In addition to the proposal, we are submitting summaries of several Phase III studies that are ongoing in the lapatinib clinical trial program. Dr. Justice requested a summary of all these ongoing studies.

If you have any question about this submission, please call me on Monday a.m.

Thanks,

rich

Richard Swenson, Ph.D.

Senior Director

Global Regulatory Affairs

From: Robertson, Kim
Sent: Thursday, December 17, 2009 3:04 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb--Clinical Request

Importance: High
Hello Richard:

Please see the following Clinical request for information:

- Please submit the AE narratives for subjects (b) (6)

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

December '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

From: Robertson, Kim
Sent: Thursday, November 19, 2009 3:49 PM
To: 'Rich.Swenson@gsk.com'
Subject: Monday, November 23, 2009 Tykerb Discussion Meeting for sNDA 22-059

Importance: High
Hello Richard:

After speaking with my Office Personnel with regard to your GSK slides for the Tykerb presentation, they have informed me that the absolute latest we can receive your slides is **Monday, November 23, 2009; 7:30AM!!!** Please e-mail your slides to me, and I will forward them on to the office staff that has to distribute them. GSK will need to arrive at our facility and be prepared to be processed by the security staff no later than 10:00AM. GSK should be prepared to present at 10:50AM. We have a presentation that must take place prior to our Tykerb business, but we need ALL GSK representatives to be processed prior to the 10:50AM presentation time.

Also, please be sure to provide me with the names of everyone that will be attending the meeting, so that I may forward them to our Security Staff.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

November '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

From: Robertson, Kim
Sent: Tuesday, October 06, 2009 9:10 PM
To: Rich.Swenson@gsk.com
Subject: sNDA 22-059 Tykerb/Letrozole-Clinical Information Request

Importance: High
Hello Richard:

Please see the following request for information from the reviewers of your sNDA for Tykerb/Letrozole:

- Please submit the serious adverse event reports for the following subjects: [REDACTED] (b) (6) These are not included in the Study EGF30008 Clinical Study Report.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

10/06/2009

Clinical IR for SAEs for Multiple Patients; sNDA 22-059 Tykerb/Letrozole SLR-007

From: Robertson, Kim
Sent: Friday, October 02, 2009 8:15 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059; Tykerb-Clinical Pharmacology Request-IR

Importance: High
Hello Richard:

Please see the following request for information from our Clinical Pharmacology discipline:

- For each analyte (lapatinib and letrozole) in Study EGF10030, please submit the validation of the bioanalytical assay, the results of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis), and the chronology of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis).

We respectfully request that within three business days, GSK informs us of when they anticipate providing the requested information.

Regards,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Tuesday, October 06, 2009 9:10 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole-Clinical Information Request

Importance: High
Hello Richard:

Please see the following request for information from the reviewers of your sNDA for Tykerb/Letrozole:

- Please submit the serious adverse event reports for the following subjects: [REDACTED] (b) (6) These are not included in the Study EGF30008 Clinical Study Report.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

October IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

REQUEST FOR CONSULTATION

TO (Office/Division): HFD-42/DDMAC/Attn: Keith Olin

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/DDOP/Kim Robertson, 6-1441

DATE September 25, 2009	IND NO.	NDA NO. 22-059	TYPE OF DOCUMENT NDA Supplement	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Tykerb (lapatinib) Tablets		PRIORITY CONSIDERATION Standard Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 31, 2009

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: At this time, the DDOP is requesting that DDMAC review the proposed product labeling and any relevant advertising for this sNDA. Please find the submission in the EDR for any other pertinent information you may need to complete your review (path to link:) \\CDSESUB1\EVSPROD\NDA022059

Clinical reviewer: Jennie Chang, Pharm.D.; CSO: Kim Robertson
To facilitate your review, please see the attached label and PPI.

SIGNATURE OF REQUESTOR Kim Robertson, CSO	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

09/25/2009

25September09 DDMAC Consult for sNDA 22-059; SE1/007; Tykerb; hormone sensitive adv. or mets. breast cancer



NDA 22-059/S-007

SUPPLEMENT REQUEST

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

We refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

We have received your submissions dated June 27, 2007 and May 19, 2008 (2) reporting on your postmarketing commitments listed in the approval letter for this application. The numbers below correspond to the numbers used in the March 13, 2007 approval letter:

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 1, 2005
Study Start: Ongoing
Final Report Submission: June 2008

2. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 7, 2002
Study Start: Ongoing
Final Report Submission: June 2007

4. **Description of Commitment:** GSK commits to submitting the results of the survival analysis of Study EGF100151 at 75% of the events.

Protocol Submission: November 2003
Study Start: Ongoing
Final Report Submission: June 2008

We have reviewed the data and conclude that the labeling of your product should be updated. In lieu of submitting a new labeling supplement, you may submit an amended labeling supplement for sNDA 22-059/S-007. The amended supplement should incorporate the following changes:

For PMC 2, the value for half-life of paclitaxel in the current study, approximately 6.5 hours, is lower than those reported in the paclitaxel package insert (13–20 hours) and the literature (17 hours with 24 hour sampling, 86 hours with three week sampling, Baker et al., Clinical Cancer Research Vol. 10: 1976-1983, 2004).

Current package insert	FDA's recommended package insert
7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems Lapatinib inhibits CYP3A4 and CYP2C8 <i>in vitro</i> at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes <i>in vitro</i>, however, the clinical significance is unknown.	7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems Lapatinib inhibits CYP3A4 and CYP2C8 <i>in vitro</i> at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes <i>in vitro</i>, however, the clinical significance is unknown. PACLITAXEL: In cancer patients receiving TYKERB and the CYP2C8 substrate paclitaxel, 24 h systemic exposure (AUC) to paclitaxel was increased 23%. The increase in paclitaxel exposure may have been underestimated from this <i>in vivo</i> evaluation due to study design limitations.

For PMC 4, the label should include the survival information comparing lapatinib plus capecitabine versus capecitabine alone.

If you have questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.

Director

Division of Drug Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

AMNA IBRAHIM
09/10/2009
For Dr Robert Justice

From: Robertson, Kim
Sent: Wednesday, September 09, 2009 12:11 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb

Importance: High
Hello Richard:

I am following up on my August 31, 2009 e-mail with regard to the CRFs for patients who had a PFS event (disease progression or death of any cause). Dr. Cortazar would like this information this week.

Also, can we still expect GSK's robust rationale as to why they believe this sNDA should NOT go to ODAC, by September 11, 2009? That would be the 2 week date that Dr. Cortazar indicated GSK should have their material(s) to us for review. Then perhaps after reviewing the materials, she will determine if we can accommodate a t-con with GSK for further discussions regarding this sNDA.

Regards,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Wednesday, September 09, 2009 5:37 PM
To: 'Rich.Swenson@gsk.com'
Subject: NDA 22-059 Tykerb-PMC Letters and Labeling Supplement Request

Importance: High

Attachments: Postmarketing Commitment 2 and 4 Fulfilled wAmna to GSK.pdf;
Postmarketing Commitment Not Fulfilled Final wAmna to GSK.pdf;
Postmarketing Commitment Supplement Request Final wAmna to GSK.pdf

Hello Richard:

Please see the attached .pdf documents, as they pertain to GSK's NDA 22-059 for Tykerb (lapatinib) Tablet. The documents contain information with regard to the status of the PMCs that were originally outlined in the March 13, 2007 Approval Letter, as well as a request to amend labeling.

These are courtesy copies. You will receive copies via USPS mail also.

Regards,
Kim



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*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*



NDA 22-059/S-007

SUPPLEMENT REQUEST

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

We refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

We have received your submissions dated June 27, 2007 and May 19, 2008 (2) reporting on your postmarketing study commitments listed in the approval letter for this application. The study numbers below correspond to the numbers used in the March 13, 2007, approval letter:

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 1, 2005
Study Start: Ongoing
Final Report Submission: June 2008

2. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 7, 2002
Study Start: Ongoing
Final Report Submission: June 2007

4. **Description of Commitment:** GSK commits to submitting the results of the survival analysis of Study EGF100151 at 75% of the events.

Protocol Submission: November 2003
Study Start: Ongoing
Final Report Submission: June 2008

We have reviewed the data and conclude that the labeling of your product should be updated. In lieu of submitting a new labeling supplement, you may submit an amended labeling supplement for sNDA 22-059/S-007. The amended supplement should incorporate the following changes:

For PMC 2, the value for the half-life of paclitaxel in the current study, approximately 6.5 hours, is lower than those reported in the paclitaxel package insert (13–20 hours) and the literature (17 hours with 24 hour sampling, 86 hours with three week sampling, Baker et al., Clinical Cancer Research Vol. 10: 1976-1983, 2004).

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For PMC 4, the label should include the survival information comparing lapatinib plus capecitabine versus capecitabine alone.

If you have questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

AMNA IBRAHIM
09/08/2009



NDA 22-059

**FULFILLMENT OF
POSTMARKETING COMMITMENTS**

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

We have received your submissions dated June 27, 2007, and May 19, 2008, reporting on the following postmarketing commitments:

2. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 7, 2002

Study Start: Ongoing

Final Report Submission: June 2007

4. **Description of Commitment:** GSK commits to submitting the results of the survival analysis of Study EGF100151 at 75% of the events.

Protocol Submission: November 2003

Study Start: Ongoing

Final Report Submission: June 2008

We have reviewed your submissions and conclude that the above commitments were fulfilled.

The following commitments acknowledged in our March 13, 2007, letter are open:

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 1, 2005
Study Start: Ongoing
Final Report Submission: June 2008

3. **Description of Commitment:** Based upon the ability of lapatinib to act as a Pgp inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

Protocol Submission: September 2007
Study Start: November 2007
Final Report Submission: December 2009

If you have any questions, call Kim J. Robertson, Regulatory Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

AMNA IBRAHIM
09/09/2009



NDA 22-059

**POSTMARKETING COMMITMENTS
NOT FULFILLED**

SmithKlineBeecham Corporation d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

Our letter of March 13, 2007, acknowledged your commitment to conduct the following postmarketing study:

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Protocol Submission: October 1, 2005
Study Start: Ongoing
Final Report Submission: June 2008

We have reviewed your submission and conclude that the terms of the commitment were not met. It appears that the pharmacokinetics of intravenously administered midazolam was not significantly affected by lapatinib. However, the analysis of the data, and possibly the conduct of the study, do not allow for a reliable estimation of the magnitude of effects.

1. We recommend that the data from Study EGF10015 be re-analyzed in the following manner:
 - a. Two analyses, one for oral data and one for IV data, using all available data with no modification or imputation of data, should be performed (90% confidence intervals on log transformed constructed) for the effect of lapatinib on midazolam.

- b. An analysis (90% confidence intervals on log transformed constructed), without data modification or imputation, of the effect of lapatinib on midazolam in patients with CVP should be performed. A duplicate analysis in patients without CVP should be performed.
 - c. An analysis (90% confidence intervals on log transformed constructed), without data modification or imputation, of the effect of lapatinib on midazolam in patients with CVP, excluding two minute samples, should be performed. A duplicate analysis in patients without CVP should be performed.
 - d. Additional analyses of datasets with data omissions made at your discretion can be considered, but analyses should not modify or impute data. Any such analysis should specify the criteria used to select data for omission and the rationale for the criteria.
2. The submission of the re-analyzed data should include electronic datasets for each group which is analyzed. The validation of the bioanalytical assay, the results of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis), and the chronology of the actual analytical runs (all values: standards, samples, blanks, QC samples, dilutions, re-assays, and incurred sample analysis) should also be submitted.

If you have any questions, call Kim J. Robertson, Regulatory Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	PMR/PMC-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

AMNA IBRAHIM
09/08/2009
For Dr Robert Justice

From: Robertson, Kim
Sent: Friday, September 11, 2009 6:35 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole--Clinical Request for Information

Importance: High
Hello again Richard:

Please see the following request for information from our clinical discipline:

The clinical reviewers of your sNDA for Lapatinib & Letrozole have the following request for information:

Clinical:

1. Please explain what the significant GCP and protocol compliance issues for center 92244 (Jesus Cardenas, M.D.). It was closed following a "For Cause" investigations. Please provide the patient identification numbers and CRFs for review.
2. For patients with nonmeasurable disease using the lesion.xpt dataset, please state what the baseline disease locations were.
3. Please provide the 44 subject identification numbers (ID) for the subjects according to lesion location, as described within "2. Identification of new lesions" of Study EGF30008 Clinical Study Report. Additionally, please categorize the subjects according to their IDs as detailed within:
 - Identify the subjects that had lesions recognized as new by the investigator that were identified at baseline by the IRC
 - Six subjects that had follow-up imaging that was not available to the IRC
 - Nine subjects that had new lesions were identified by the IRC that were either later identified or not identified by the investigator
4. Please indicate whether cross-over to combination (lapatinib + letrozole) arm was permitted in Study EGF30008. If yes, please provide the subject IDs, timepoints, and outcomes for the patients that crossed over.
5. Please explain the difference in the number of patients with bone-only disease in Table 16 (n=179) and Table 17 (n=165) in Study EGF30008 Clinical Study Report

We need a response from GSK as soon as possible.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Tuesday, September 15, 2009 5:34 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Requests for Information

Importance: High

Attachments: 15September09 Request for Information.pdf
Hello Richard:

Please see the attached .pdf document, as it pertains to GSK's sNDA for Tykerb/Letrozole. Please review promptly, as it contains further requests for information.

Furthermore, the Tykerb review team has had an opportunity to review GSK's *robust rationale* highlighting why the supplement should NOT go to ODAC. They have determined however, that this application should and will go to ODAC for discussion in December.

Thank you,
Kim



15September
Request for In

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Richard Swenson, Ph.D.

From: Kim J. Robertson

Fax:

Fax: 301-796-9845

Phone: (610) 917-6821

Phone: 301-796-1441

Pages, including cover sheet: 3

Date: 15 September 2009

Re: **sNDA#22-059; Lapatinib and Letrozole- Request for Information**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Dear Dr. Swenson:

The reviewers of your sNDA for Lapatinib & Letrozole have the following request for information:

Please provide the narrative summaries and CRFs for the following subjects:

(b) (6)

Please include the following information in the narrative summaries:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing to exposure
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant drugs with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)

- Time course of serum enzyme and bilirubin elevations (consider tabular and/or graphical display of serial laboratory data)
- A summary of all available clinical information including, if known:
 - Prior or current history of ethanol use
 - Presence of risk factors for NASH (e.g., obesity, diabetes, marked hypertriglyceridemia)
 - Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease, pre-study AT values, if available
 - Symptoms and clinical course including follow-up to resolution
 - Special studies (i.e., ultrasound, radiologic examinations, liver biopsy results)
 - Presence or absence of possible confounders, including concomitant illness, use of concomitant drugs that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of the treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

Please submit all narrative summaries for deaths that occurred within 30 days of discontinuation in Study EGF30008. Provide a timeline for the submission also.

We found some inconsistencies on the number of patients with bone disease only:

From the PFSINV dataset, the STRATA summary indicates there are 179 patients with bone disease only. The CSR, page 93, Table 17 indicates there are 165 patients with bone disease only. Please explain the difference.

Thank you for submitting information on the 41 patients who potentially received neoadjuvant therapy. Since the CRFs did not capture any surgeries after starting the study, please contact the study sites for these patients and ask the investigators if any of these patients had breast surgery after randomization or if breast surgery was the cause for patient withdrawal from the study.

Using the Lesion dataset we found 966 patients with measurable disease and 314 patients with non-measurable disease that adds up to a total of 1280 patients. Please explain why there is a difference on 5 patients.

September 15, 2009

Regards,

Kim J. Robertson
Consumer Safety Officer

APPEARS THIS WAY ON ORIGINAL

From: Robertson, Kim
Sent: Friday, September 18, 2009 1:51 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole

Importance: High

Attachments: 18September09 Request for Information.doc
Hello Richard:

Please see the following request for information below, as it pertains to your sNDA for Tykerb/Letrozole:



18September
Request for In

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Richard Swenson, Ph.D.

From: Kim J. Robertson

Fax:

Fax: 301-796-9845

Phone: (b) (6)

Phone: 301-796-1441

Pages, including cover sheet: 1

Date: 18 September 2009

Re: **sNDA#22-059; Lapatinib and Letrozole- Request for Information**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Dear Dr. Swenson:

The review team of your sNDA for Lapatinib & Letrozole has the following request for information:

REQUEST:

Please explain how treatment discontinuation due to an adverse event was captured in Study EGF30008 Clinical Study Report. Datasets ae.xpt and trlmed.xpt appear to record differing information on this variable. Trlmed.xpt (n=124) captures treatment discontinuation on p. 117 of the CRFs, and ae.xpt (n=130) captures it on p. 127.

Regards,

Kim J. Robertson
Consumer Safety Officer

From: Robertson, Kim
Sent: Friday, September 18, 2009 1:57 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: sNDA 22-059 Requests for Information

Importance: High
Hello Richard:

The review team mentioned that the one requested is:

(b) ALL deaths that have occurred regardless if SAE related or not

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Thursday, September 17, 2009 3:33 PM
To: Robertson, Kim
Subject: Re: sNDA 22-059 Requests for Information

Dear Kim:

With regard to the FDA request of 15 September 2009 "Please submit all narrative summaries for deaths that occurred with 30 days of discontinuation in Study EGF30008."

GSK wishes to clarify the request. Is it (a) or (b) that is requested?

(a) all deaths due to "fatal SAEs", or

(b) ALL deaths that have occurred regardless if SAE related or not?

Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs - Oncology

From: Robertson, Kim
Sent: Wednesday, September 23, 2009 1:51 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Information Request

Hello Richard:

Please see the following request for information from the review team of GSK's sNDA for Tykerb/Letrozole:

- Please submit the SAS program for analyses reported in Sections 7.1, 7.2, 7.3 and 7.4 in the clinical study report, including related sensitivity analyses. Please also submit the SAS program used to derive the variables involved in those analyses.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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

/s/

KIM J ROBERTSON

01/20/2010

September '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consult; John Senior, M.D.

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/DDOP/Kim Robertson, 6-1441

DATE September 2, 2009	IND NO.	NDA NO. 22-059	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT March 31, 2009
NAME OF DRUG Tykerb (lapatinib) Tablets/Letrozole		PRIORITY CONSIDERATION Standard Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 30, 2009

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: At this time, the DDOP is requesting that OSE; more specifically Dr. John Senior; hepatologist, reviews the cases of hepatotoxicity of lapatinib (Tykerb) for sNDA 22-059. It is currently labeled for hepatotoxicity (b) (4) in the labeling, but we would like for you to review the cases for the efficacy supplement. This efficacy supplement will be going to ODAC on December 16, 2009. PDUFA is January 31, 2010. Information regarding the sNDA is as follows:

Safety issue: hepatotoxicity

sNDA: 22-059

Drug name: lapatinib (Tykerb)

Initial approval: March 13, 2007

Indication sought: (b) (4)

(b) (4)

Current labeling has been extracted from the Tykerb labeling (see succeeding page after consult form).

Two cases meeting Hy's Law were reported in the applicant's submission (please see relevant attachments). If you should require additional information (i.e., narratives, lab values, etc.), please let us know and we will provide them for you.

The clinical reviewer is Jennie Chang.

Additional information can be found in the EDR.

EDR Location: \\CDSESUB1\EVSPROD\NDA022059

Thank you,

Kim

SIGNATURE OF REQUESTOR Kim Robertson, CSO	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. [See Warnings and Precautions (5.2).]

5.2 Hepatotoxicity

Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin >^{(b) (4)} times the upper limit of normal) has been observed in clinical trials (<1% of patients) and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If changes in liver function are severe, therapy with TYKERB should be discontinued and patients should not be retreated with TYKERB [see Adverse Reactions (6.1)].

Global Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Lapatinib: Hepatotoxicity

Date of review	30-Jun-2008
Drug terms included	Project ID = '016' and/or Drug Preferred Term code = 'AZZ071'
Adverse events (MedDRA*preferred terms) included	MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ, MedDRA v11

*See [Appendix 1](#) for full list of abbreviations

1. EXECUTIVE SUMMARY

- As of April 2008, approximately 13,833 subjects have been enrolled in the lapatinib programme, of which 10,683 subjects are estimated to have received lapatinib.
- Lapatinib was first approved for marketing in the USA on 13 March 2007. It is estimated that approximately 2,095 patient years of lapatinib treatment have been prescribed worldwide as of December 2007. This calculation is based on available sales information volume and assuming a daily dose of 1250mg.
- Amongst an estimated 8,503 subjects receiving lapatinib in metastatic cancer studies, 2 episodes of acute liver failure possibly related to lapatinib were observed (one very atypical).
- In the metastatic cancer studies, a rate of 0.14% possible Hy's law events (ALT >3x ULN and bilirubin >2x ULN) probably, possibly, very likely or definitely related to lapatinib was observed.
- Amongst an estimated total of 1500 subjects who will have received lapatinib in the adjuvant breast cancer study EGF105485, a rate of 0.13-0.27% possible Hy's law events (ALT >3x ULN and bilirubin >2x ULN) has been observed, including one event of severe liver injury with compromised synthetic function, very likely related to lapatinib use, which resolved with lapatinib cessation.
- GSK conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

2. BACKGROUND

A review of hepatobiliary events in the lapatinib clinical program was completed in March 2008 (UM2008/00097/00). This review compared hepatobiliary events from the entire lapatinib programme (all studies regardless of phase or indication), with hepatobiliary events reported from the sub-population of subjects receiving lapatinib as adjuvant breast cancer therapy. Based on the results of this review GlaxoSmithKline (GSK) concluded that an association between hepatotoxicity (specifically severe liver injury and transaminase elevations) and lapatinib could not be ruled out, therefore the lapatinib core safety information (CSI) was updated to include these events.

The purpose of the current review is to provide a status update on lapatinib and hepatobiliary events, and to determine whether any updates to the core safety information (CSI) for hepatobiliary events are required.

3. EXPOSURE TO DRUG

As of April 2008, approximately 13,833 subjects have been enrolled in the lapatinib programme, of which 10,683 subjects are estimated to have received lapatinib.

Of these 13,833 subjects, a total of 3906 have been enrolled in ongoing studies in the adjuvant breast cancer setting. Amongst these adjuvant subjects, a total of 2999 subjects were enrolled in study EGF105485, and 907 were enrolled in EGF106708 as of April 2008. It is estimated that 1500 and 680 respectively of these subjects will have received lapatinib, giving a total estimated lapatinib exposure of 2180 in the adjuvant breast cancer setting. Exposure in the metastatic cancer setting (including breast, colorectal, non small cell, and head and neck cancers) is estimated as 9927 subjects, of which 8503 will have received lapatinib.

Lapatinib was first approved for marketing in the USA on 13 March 2007. It is estimated that approximately 2,095 patient years of lapatinib treatment have been prescribed worldwide as of December 2007. This calculation is based on available sales information volume and assuming a daily dose of 1250mg.

4. SAFETY DATA REVIEWED

This evaluation presents relevant information on reports of hepatotoxicity using laboratory data from the GSK clinical trials database, and serious adverse event (SAE) data from the GSK worldwide safety database.

Reports of possible Hy's law cases, fatal hepatic events and hepatic failure were medically reviewed and adjudicated by GSK's internal liver safety panel.

4.1. Reports from the GSK Clinical Trials database

In a review of hepatotoxicity completed in March 2008 (UM2008/00097/00), laboratory data from 18 completed or ongoing breast cancer studies were reviewed. In the current

review, laboratory data on the clinical trials database from 45 completed or ongoing studies (26 phase I, 19 phase II/III) were reviewed. Completed breast cancer studies included in the previous review were excluded from the current review of laboratory data since all serious hepatobiliary events and possible Hy's law cases are included on the GSK safety database, and are therefore part of the dataset reviewed in section 4.2.

Laboratory data from these 45 studies were reviewed for the incidence of transaminase elevations, and for subjects whose transaminase elevations may meet Hy's law:

- AST or ALT >3x ULN **and** total bilirubin >2x ULN with no initial findings of cholestasis (that is, alkaline phosphatase activity $\leq$ 2x ULN) [FDA, 2007].

Since the majority of reports were in the setting of metastatic cancer, some cases had alkaline phosphatase values higher than 2x ULN, also information on fractionated bilirubin was rarely available. However these reports have been included in the category "possible Hy's law cases" for completeness.

As of April 2008, a total of 7283 subjects have been enrolled in these 45 studies, of which 4736 subjects are estimated to have received lapatinib and 2547 subjects received either placebo or comparator.

4.1.1. Liver Chemistry Elevations

4.1.1.1. Data from Phase I Studies

A review of the clinical trials safety databases from the lapatinib Phase I experience (25 phase I trials plus 1 phase I extension study, 991 subjects in total) was undertaken. The analysis included both lapatinib healthy volunteer trials and cancer patient trials, using lapatinib as monotherapy and in combination with other chemotherapeutic agents. In addition subjects were receiving a variety of concomitant medications. Liver function entry criteria varied from normal (healthy volunteer studies) to up to 5x ULN (subjects with refractory solid tumours with liver metastases). One trial, EGF10014, was conducted in subjects with moderate or severe hepatic impairment.

The overall incidence of AST or ALT elevation above 3x ULN was 5.25% (52/991), without taking into consideration baseline liver function test (LFT) measurements. Twenty of these 52 subjects had normal ALT/AST ($\leq$ 1x ULN) at baseline, but developed AST or ALT >3x ULN post baseline (2%; 20/991) during treatment with lapatinib monotherapy. There were no fatal hepatobiliary events in this group of studies.

Two cases met the liver chemistry criteria of ALT >3x ULN and bilirubin >2x ULN suggesting possible Hy's law events. One patient (██████████^{(b) (6)}) with a history of metastatic breast cancer enrolled on extension study EGF19060, experienced an ALT elevation of 3.2x ULN and total bilirubin 2.3x ULN after 195 days of lapatinib monotherapy (or after a total of 234 days lapatinib therapy in studies EGF10015 and EGF19060). Lapatinib therapy was thereafter discontinued and LFTs subsequently improved. This patient had previously experienced an ALT elevation 4.2x ULN, accompanied by a total bilirubin measurement 1.6x ULN, after 99 days of therapy. At

that point lapatinib was interrupted and liver function tests returned to normal. The patient was then restarted on lapatinib therapy at the original dose of 1500mg. The timing of the events in this case, combined with normalisation of LFTs after interruption of lapatinib, followed by a positive rechallenge, strongly suggest a drug-related effect (see appendix 2 for narrative). The other patient (study EGF10014 subject (b) (6)) exhibited baseline cirrhosis and severe hepatic impairment (Child-Pugh score >9) on enrolment into a pharmacokinetic study of hepatic impairment.

4.1.1.2. Data from Phase II/III Studies

A review of the clinical trials safety databases from the lapatinib Phase II/III experience (19 studies) was undertaken. Approximately 6292 subjects were enrolled in these studies of which 3745 are estimated to have received lapatinib. Data from ongoing blinded studies such as EGF105485 (adjuvant study) and EGF30008 (letrozole +/- lapatinib or placebo) remain blinded.

There were 1703 subjects with LFT abnormalities amongst a total of 3745 (45.5%) subjects who received lapatinib either as monotherapy or in combination with chemotherapy. This is compared to 40.3% of LFT abnormalities (750/1859) that were reported from all studies with a placebo controlled arm. Of these, 34% occurred on lapatinib monotherapy, and 66% occurred in subjects who received lapatinib in combination with other chemotherapies. The majority of LFT abnormalities (45.5%) occurred in subjects with recurrent metastatic breast cancer, who were treated in the 2nd line setting and beyond, followed by subjects who were treated in the 1st line setting (35%), the remaining 19.5% of subjects were treated for other tumour types. This is compared to a total of 6% of LFT abnormalities occurring in the adjuvant breast cancer setting (study EGF105485), and 1.4% of LFT abnormalities occurring in subjects with head and neck cancer treated with curative intent.

A total of 8 subjects (0.2%) were identified from these 19 studies with possible Hy's law cases which occurred on treatment or shortly after. Amongst these 8 subjects, two received lapatinib monotherapy, two received lapatinib in combination with pazopanib, and four reports remain blinded. Four of these eight subjects were treated in adjuvant breast cancer study EGF105485, the remaining four subjects were treated for metastatic breast cancer.

The most common LFT abnormalities were elevation of ALT and/or AST $\geq 3x$ ULN but below $5x$ ULN. Again the majority of LFT abnormalities occurred in subjects with recurrent breast cancer. Most of these LFT abnormalities were observed in subjects who received lapatinib in combination with other chemotherapies. Elevations of ALT and/or AST $\geq 3x$ ULN were very infrequent in the following two groups: breast cancer subjects treated in the adjuvant setting and subjects with head and neck cancer. For ALT and AST $\geq 3x$ ULN, the estimated incidence was 1.06-2.0% amongst subjects being treated in the adjuvant breast cancer setting (study EGF105485), and 1.3-1.9% in subjects with head and neck cancer. The lower figures assume events were split evenly amongst treatment groups and the higher figure assumes all subjects received lapatinib.

Elevation of bilirubin only was seen in 4.8% of subjects with elevations >1.5x ULN (45.6% of subjects were from monotherapy studies), and 2.5% with elevations >2x ULN (33% of subjects were from monotherapy studies).

Elevation of alkaline phosphatase >1.5x ULN accounted for the majority of LFT elevations (537/3745, 14.3%). Of the total LFT elevations, 26.8% occurred with lapatinib monotherapy. Infrequent elevation of alkaline phosphatase was noted in adjuvant breast cancer (3%) and head and neck studies (1.5%).

Based on the above, GSK conclude that:

- A 10-20 fold higher incidence of LFT elevations was observed in advanced disease and in combination with chemotherapy in subjects receiving lapatinib in comparison to approximately 4,000 patients in earlier GSK oncology studies (with and without liver metastases) receiving multiple therapies.
- In comparison to the low level background rate of liver chemistry elevations seen in >18,000 patients in non-oncology clinical trials [Weil, 2008], the lapatinib adjuvant breast cancer studies exhibit >10 fold higher incidence of ALT elevations exceeding 5x ULN (Grade 2-4) in adjuvant therapy studies compared with non-oncology studies

4.1.2. Possible Hy's law cases

Review of the laboratory data from these 45 studies identified a total of three possible Hy's law cases which were not included in the GSK safety database:

- Subject (b) (6), study EGF104900 received lapatinib plus trastuzumab for metastatic breast cancer. Baseline laboratory values were: ALT 57 IU/l (normal range 0-48 IU/l), AST 94 IU/l (normal range 0-42 IU/l), alkaline phosphatase 205 IU/l (normal range 20-125 IU/l), and total bilirubin 12 umol/l (normal range: 0-22 umol/l). On (b) (6), 28 days after starting lapatinib and trastuzumab the subjects liver function tests were: ALT 145 IU/l (normal range: 0-48 IU/l), AST 216 IU/l (normal range: 0-42 IU/l), alkaline phosphatase 828 IU/l (normal range: 20-125 IU/l), and total bilirubin 76 umol/l (normal range: 0-22 umol/l). She was diagnosed with febrile neutropenia which resolved after 4 days. Lapatinib was discontinued and the subject withdrawn due to disease progression. Laboratory values for ALT and total bilirubin normalized following study withdrawal (b) (6), AST 46 IU/l (normal range: 0-42 IU/l), alkaline phosphatase 210 IU/l (normal range: 20-125 IU/l). GSK's internal liver safety panel adjudicated this case as: possible drug-induced *cholestatic* liver injury for which lapatinib was the most likely suspect.
- Subject (b) (6), a 39 year old female received blinded medication (lapatinib or placebo) in study EGF105485 for the treatment of breast cancer in the adjuvant setting. AST, ALT and total bilirubin were elevated at baseline (AST 75 U/l, normal range 0-42 U/l; ALT 110 U/l, normal range 0-48 U/l; and total bilirubin 30 umol/l, normal range: 0-22 umol/l). During treatment the subject experienced two episodes of non-serious diarrhoea, and an increase in blood

bilirubin. Ninety three days after the start of investigational product liver function tests were: AST 112 U/l (normal range 0-42 U/l), ALT 121 U/l (normal range 0-48 U/l), alkaline phosphatase 91 U/l (normal range 20-125 U/l), and total bilirubin 40 umol/l (normal range: 0-22 umol/l). Laboratory values were increased at the next study visit. Follow-up of this event is ongoing. GSK's internal liver safety panel adjudicated this case as: inadequate information available for an adjudication.

- Subject (b) (6), a 75 year old female, was enrolled in study VEG20007 for the treatment of metastatic breast cancer. The subject received oral pazopanib (a VEGFR inhibitor) with oral lapatinib. Concomitant medications included simvastatin, which was initiated prior to the study. Baseline laboratory values were: AST 46 IU/l (normal range 14-36 IU/l), ALT 36 IU/l (normal range 9-52 IU/l), alkaline phosphatase 73 IU/l (normal range 38-130 IU/l), and total bilirubin 0.7 mg% (normal range 0.2-1.3mg%). Twenty five days after treatment onset, transaminases and bilirubin had risen to meet Hy's law, however, direct bilirubin was 0.2 (total 2.8). Laboratory values were: AST 544 IU/l (normal range 14-36 IU/l), ALT 379 IU/l (normal range 9-52 IU/l), alkaline phosphatase 148 IU/l (normal range 38-130 IU/l), and total bilirubin 2.8 mg% (normal range 0.2-1.3 mg%). Investigational products were discontinued; simvastatin was continued. Transaminases and bilirubin subsequently improved: AST 244 IU/l (normal range 14-36 IU/l), ALT 303 IU/l (normal range 9-52 IU/l), alkaline phosphatase 105 IU/l (normal range 38-130 IU/l), and total bilirubin 1.1 mg% (normal range 0.2-1.3 mg%). GSK's internal liver safety panel adjudicated this case as: Possible drug-induced liver injury due to co-suspect medications lapatinib or pazopanib.

Narratives for all possible Hy's law cases are provided in [appendix 2](#).

4.2. Reports from the GSK Worldwide Safety database (OCEANS)

4.2.1. Database Search Strategy

The GSK worldwide clinical safety database was searched on *17-Apr-2008* using the following criteria:

- **Data lock point(s):** *all reports as of 10-Apr-2008*
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and serious clinical trial reports (attributable and non-attributable). *Lapatinib* was reported as a suspect drug, or the case was from a lapatinib study, or a study where lapatinib was used.
- **MedDRA preferred term(s):** *MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ, MedDRA v11.*

4.2.2. Summary of Overall Dataset

A total of 252 reports were retrieved from the GSK worldwide safety database. Of these reports:

- 232 cases (92%) had a healthcare professional (HCP) as a report source.
- The majority were received from USA, 28.6% and France, 10.3%.
- 231 cases (91.7%) met the criteria for a serious adverse event report, although seriousness may have been the result of an event other than hepatotoxicity.
- Subject profile – the majority (92%) of subjects were female, this is because the majority of lapatinib studies are in the breast cancer indication. Subjects ranged in age from 22 to 88 years (median age 53 years).
- The most frequently reported hepatobiliary events were: jaundice (55 events), blood bilirubin increased (39 events), hyperbilirubinemia (32 events), and hepatic enzymes increased (28 events).

4.2.3. Case Evaluation

When conducting an evaluation, it is GSK practice to review all reports of an adverse event retrieved from the GSK worldwide safety database. This section presents a detailed summary of this evaluation, however, copies of all reports can be made available upon request in CIOMS I report format.

Due to the nature of spontaneous reporting there will always be some cases that contain insufficient information for assessment, despite adequate follow-up measures. Also, there will be other cases for which it becomes evident on clinical review of the information provided by the reporter, that the reported event is not consistent with the diagnostic criteria for that term (the latter category does not include reports for which there is no accompanying description of the event). [Table 1](#) summarises the number of unassessable cases of *hepatotoxicity* associated with *lapatinib* therapy and also those that are considered inconsistent with the diagnostic criteria/definition for a possible drug-induced hepatic event.

Table 1 Cases containing insufficient information for assessment and cases inconsistent with the reported term (16 reports)

Reason	Number of Reports
Very poorly-documented cases providing no details about the event (i.e., no time to onset, duration, or outcome) AND no details about the patient other than age or gender AND no dechallenge or rechallenge information or otherwise clinically unevaluable cases due to inadequate documentation	11
Description of the event is inconsistent with diagnostic criteria/definition	5

A total of 16 cases were therefore screened out of the dataset. Eleven cases were very poorly documented and therefore clinically unevaluable, chiefly due to lack of information on the reported liver events, e.g. no liver function test data. In five cases the reported event (haemangioma, hepatitis B infection, hypoalbuminemia (2), and oesophageal varices) was inconsistent with a diagnosis of a drug-induced liver event.

Similarly, there are cases which document other **very much more likely** causes of the adverse event (e.g., concurrent medical conditions or other treatments), when time to onset, dechallenge/rechallenge, or other clinical observations are taken into account. These are summarised in [Table 2](#).

Table 2 Cases with other very much more likely causes than treatment with lapatinib (163 reports)

Reason*	Number of Reports
Time to onset is inconsistent with a possible effect of <i>lapatinib</i>	0
Alternative diagnosis or concurrent disease is <i>very much more likely</i> to have caused the event, based on reported time to onset or other clinical observations	135
Concurrent drug is <i>very much more likely</i> to have caused the event, based on reported time to onset or other clinical observations	28

* Although theoretically some reports could have been assigned to more than one category, only one was allocated to each case and this was the first appropriate reason as listed above.

A total of 135 cases were considered to be confounded by an alternative diagnosis or concurrent disease. Examples included tumour-related confounding factors (e.g., progression of liver metastases, biliary cholestasis (due to tumour compression of the biliary ducts), complications of the underlying cancer (e.g. multi-organ failure, sepsis and shock causing liver injury due to blood stasis), and elevated alkaline phosphatase

4.2.3.1. Hepatobiliary events with fatal outcome

Fourteen of the total 252 hepatobiliary cases had a fatal outcome. Twelve cases were from clinical trials, and two cases were from post-marketing surveillance. There were no reports of fatal hepatobiliary events from adjuvant breast cancer trials, or from spontaneous/ marketed use. Eight subjects received lapatinib as monotherapy, six subjects received lapatinib in combination with either capecitabine (5 cases) or letrozole (1 case). There were no reports of fatal hepatobiliary events from subjects who received either placebo or comparator. This may reflect the fact that most subjects participating in lapatinib trials will have received lapatinib, and only 23% (3,150/13,833) will have received placebo or comparator alone.

Fatal hepatobiliary events reported included hepatitis, hepatic failure, elevated gamma glutamyltransferase, jaundice and hepatorenal syndrome. Nine of these 14 cases were confounded, the majority (7/9) by progressive disease and/or liver metastases (new or progressive). In addition, one subject had obstructive jaundice and the ninth subject had chronic hepatopathy, likely liver cirrhosis.

There were 5 fatal outcomes for which an association with lapatinib could not be ruled out:

- Subject (b) (6) a 59-year-old female received lapatinib and letrozole in metastatic breast cancer study EGF30008. Two hundred and five days after initiating lapatinib and letrozole the subject developed moderate hepatic dysfunction: ALT 29 U/L (normal range 6 to 30), alkaline phosphatase 569 IU/L (normal range 35 to 105), AST 719 U/L (normal range 9 to 31), bilirubin 13.15 mg/dL (normal range 0.1 to 1.0). Stable liver metastasis was confirmed by MRI and CT. Lapatinib and letrozole were discontinued. The investigator indicated that the hepatic dysfunction was related to lapatinib, letrozole and the subject's liver failure. Three weeks later the subject developed encephalopathy and died. GSK's internal liver safety panel adjudicated this case as: possible drug-induced liver injury for which lapatinib was the probable suspect, and letrozole was unlikely.
- Subject (b) (6) a 36-year-old female received lapatinib in metastatic breast cancer study VEG20007. Approximately 382 days after starting lapatinib, the subject developed liver failure. Relevant liver function tests: alanine aminotransferase 113 U/L, aspartate aminotransferase 310 U/L, total bilirubin 1.7 mg/dL and alkaline phosphatase 513 U/L. The subject's prior CT scan showed a solitary ill-defined liver lesion. Treatment with lapatinib was interrupted and the subject later died. The investigator considered there was no reasonable possibility that the liver failure may have been caused by lapatinib due to shrunken, cirrhotic liver on ultrasound, prevalence of viral hepatitis in the region and fulminant course. The subject had chronic liver disease/cholecystitis but no history of alcohol abuse. GSK's internal liver safety panel adjudicated this case as: possible drug-induced liver injury but very atypical.
- Subject (b) (6) a 70 year-old female received lapatinib and capecitabine in metastatic breast cancer study EGF103659. Approximately 87 days after

(suggestive of a space occupying cancer in the liver, or biliary compression). These cases were confounded on the basis of the subject's disease course while on treatment, rather than the presence of pre-existing liver metastases at baseline.

Of the 252 cases in the overall dataset, 179 fulfilled the criteria for inclusion in [Table 1](#) or [Table 2](#) and were therefore excluded from the analysis. The remaining 73 cases have been further reviewed and the available data are summarised in [Table 3](#).

Table 3 Characteristics of Remaining Cases (73)

Patient Age (n, %)	Range	years	22-88
(71, 97)	Median	years	54
Patient Gender (n, %)	Male	n (%) ²	5 (7)
(73, 100)	Female	n (%) ²	68 (93)
Report Type	Spontaneous Reports	n (%)	5 (7)
	Serious Clinical Trial Reports	n (%)	58 (79)
	Post Marketing Surveillance Reports	n (%)	10 (14)
Report Source	Health Care Professional	n (%)	73 (100)
Time to Onset of Event (n, %) ¹	Range	days	2-382
(63, 86)	Median	days	56
Outcome (n, %) ¹	Fatal (due to event)	n (%) ²	5 (7.8)
(64, 87.7)	Unresolved	n (%) ²	19 (29.7)
	Resolved	n (%) ²	31 (48)
	Improved	n (%) ²	9 (14.5)
Rechallenge (n, %) ¹	Positive	n (%) ²	9 (69)
(13, 17.8)	Negative	n (%) ²	4 (31)
Dechallenge (n, %) ¹	Positive	n (%) ²	40 (83)
48 (65.8)	Negative	n (%) ²	8 (17)

1. Number and percentage of reports with available data
2. Number of reports with available data was used as the denominator

Amongst these 73 remaining cases, 67 subjects are known to have received lapatinib, 23 as monotherapy, and 44 in combination with other chemotherapeutic agents (capecitabine, letrozole, paclitaxel, pazopanib, or trastuzumab). The daily dose of lapatinib ranged from 750mg to 1500mg once daily. Six cases remain blinded.

Of the 73 cases, 58 were from clinical trials, 10 from post-marketing surveillance (the French Authorisation for Temporary Use/ATU programme), and 5 were spontaneous reports. The estimated incidence of hepatobiliary events is 0.5% (58/10,683) for the entire lapatinib clinical programme. This estimate assumes the six subjects which remained blinded received lapatinib. The estimated incidence of hepatobiliary events on the French ATU study (PMS cases) is 0.8% (10/1250) as of April 2008.

The estimated incidence of hepatobiliary events from marketed use of lapatinib (spontaneous reports) is 0.2% (5/2,095 *patient years*). This estimate assumes a daily dose of 1250mg lapatinib.

treatment onset the subject developed grade 3 or severe increased bilirubin (290 umol/L). Abdominal CT showed decreased liver metastases, however two nodes in the left lobe had consolidated and there was evidence of biliary dilation. MRI showed no metastatic or other obstruction. Treatment with lapatinib and capecitabine was discontinued. The subject was withdrawn from the study for palliative care due to disease progression and subsequently died. Cause of death was reported as hyperbilirubinemia, secondary to liver failure due to advanced breast cancer. Bilirubin was 511 umol/l the day before the subject's death. GSK's internal liver safety panel adjudicated this case as: unlikely drug-induced liver injury.

- Subject (b) (6) a 33-year-old female received lapatinib and capecitabine in metastatic breast cancer study EGF103659. Approximately 6 weeks after treatment onset the subject presented with jaundiced skin and eyes, and increased liver enzymes: ALT 7 u/l, alkaline phosphatase 671 u/l, AST 382 u/l and bilirubin 496 micromol/l. Treatment with lapatinib and capecitabine was discontinued. The subject died approximately 4 days later. Cause of death was reported as jaundice and increased liver enzymes. The investigator attributed the event to the disease under study and no post-mortem was carried out. GSK's internal liver safety panel adjudicated this case as: unlikely drug-induced liver injury, lapatinib unlikely suspect but cannot be ruled out.
- Subject (b) (6) a 73-year-old female received oral lapatinib in metastatic breast cancer study EGF104900. Approximately 27 days after starting lapatinib the subject was hospitalised due to liver failure and renal failure. The subject was asymptomatic. The subject also had a fractured femoral neck. Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study. The subject died on (b) (6) due to hepatic and renal failure. The investigator noted the subject was lost to follow up and no further information was available. The investigator considered that there was no reasonable possibility the liver failure, renal failure and fractured femoral neck may have been caused by lapatinib. GSK's internal liver safety panel adjudicated this case as: inadequate information but a case of interest.

All five subjects were female with metastatic breast cancer, median age 59 years (range 33-73 years). Two subjects received lapatinib at 1250mg daily in combination with capecitabine, and three subjects received 1500mg daily (two as monotherapy, one in combination with letrozole). The median time to onset of the fatal hepatic event was 146 days (range: 27-382 days).

The approximate incidence of fatal hepatobiliary events on the lapatinib clinical programme was 0.05-0.1% (5 where lapatinib association could not be ruled out or 12 total clinical trial cases/10,683). Narratives for all 14 fatal hepatobiliary events are provided in [Appendix 3](#).

4.2.3.2. Hepatic Failure

Approximately 1-3 cases/million/year of non-acetaminophen acute liver failure are reported in U.S. and E.U. [[Bower, 2007](#); [Escorsell, 2007](#)]. Seventy five percent of

patients with non-acetaminophen-induced acute liver failure die without liver transplantation [Polson, 2005]. Disseminated cancer is seldom associated with liver failure. In a large U.K. retrospective dataset, 0.1% (4/4040) subjects presenting with acute liver failure (ALF) at King's College (1978-1995) exhibited infiltrating liver metastases due to metastatic carcinoma [Rowbotham, 1998]. In this U.K. dataset, median AST of 358 IU/l was lower than acute liver failure of other aetiologies and encephalopathy progressed within 7 days of jaundice. Within a retrospective Spanish review, only 3.7% (10/267) were attributed to disseminated cancer in (1992-2000) [Escorsell, 2007].

There were seven cases of hepatic failure amongst the total 252 case dataset, all seven cases were from the metastatic setting. Six cases were from clinical trials, and one case was from spontaneous/ marketed use. There were no reports of hepatic failure from adjuvant breast cancer trials, or from post-marketing surveillance. Four subjects received lapatinib as monotherapy, the remaining three subjects received lapatinib as combination therapy, two with capecitabine, one with letrozole. Three of these seven cases were confounded: one spontaneous report was poorly documented, one case by advanced disease with liver metastases, and in one subject due to chronic hepatopathy, likely liver cirrhosis. An association with lapatinib could not be ruled out in the remaining four cases (b) (6) all of which were fatal and have been summarised in section 4.2.3.1.

These seven reports of hepatic failure were reviewed by GSK's internal liver safety panel and adjudicated as follows:

- Possible drug-induced liver injury – two cases (one very atypical)
- Unlikely drug-induced liver injury – two cases (one of which was likely due to liver cirrhosis, the second was likely due to disease progression)

There were three cases of hepatic failure for which there was insufficient information available to make an adjudication. Narratives for all seven hepatic failure cases are provided in appendix 4.

4.2.3.3. Possible Hy's law cases

In follow up of over 900 breast cancer patients, 5% (47/912) developed liver metastases [Hoe, 1991]. In these 47 patients with liver metastases, 71% exhibited mean AST elevations of 4.2 times upper limits of normal, 28% exhibited hyperbilirubinemia and 11% had ascites. In summary, modest liver chemistry elevations were generally evident in patients with liver metastases.

A total of 17 cases (from 252 cases on the safety database) were identified as possible Hy's law cases.

- AST or ALT >3x ULN **and** total bilirubin >2x ULN with no initial findings of cholestasis (that is, alkaline phosphatase activity $\leq$ 2x ULN) [FDA, 2007].

Since the majority of reports were in the setting of metastatic cancer, some cases had alkaline phosphatase values higher than 2x ULN, also information on fractionated

bilirubin was rarely available. However these reports have been included in the category “possible Hy’s law cases” for completeness.

These 17 possible Hy’s law cases were reviewed by GSK’s internal liver safety panel and adjudicated as follows:

- Definite drug-induced liver injury – 2 cases (both cases had a positive rechallenge with lapatinib)
- Probable drug-induced liver injury – 7 cases
- Very likely drug-induced liver injury – 4 cases
- Unlikely drug-induced liver injury – 1 case
- Drug-induced liver injury excluded – 1 case with possible Budd-Chiari Syndrome.

There were two cases for which there was insufficient information available to make an adjudication.

For those 13 cases assessed as definite, probable or very likely drug induced liver injury, all subjects were female, with a median age of 57 years (range 42-74 years). Twelve of the 13 subjects were receiving lapatinib for breast cancer (mostly metastatic but three reports were from the adjuvant breast cancer setting). The remaining subject received lapatinib for non-small cell lung cancer. Two subjects received lapatinib at 1000mg daily, one as monotherapy, the other in combination with pazopanib. Nine subjects received 1500mg daily lapatinib, four as monotherapy, four in combination with paclitaxel, one in combination with letrozole. Two subjects remain blinded. The median time to onset of the liver function test abnormalities in these 13 cases was 163 days (range: 23-351 days). Overall eight of the 13 subjects recovered or improved (for six of these subjects lapatinib was discontinued), three events were ongoing, and the outcome of two events was unknown. Nine of these 13 subjects had a positive dechallenge (event resolved/improved on interruption of lapatinib/blinded medication). Three of these nine subjects subsequently had a positive rechallenge (recurrence of the event) when lapatinib was restarted.

Subject (b) (6) a 58 year old female received lapatinib in study EGF105485 for the treatment of breast cancer in the adjuvant setting. She experienced hepatotoxicity which met the criterion for a possible Hy’s law event approximately five months after treatment onset. The subject recovered following cessation of lapatinib. GSK’s internal liver safety panel adjudicated this case as: very likely drug-induced severe liver injury with ‘compromised synthetic function’, lapatinib probable; anastrozole: lapatinib interaction possible. The remaining two possible Hy’s law cases from the adjuvant breast cancer programme both improved on discontinuation of study medication, and were adjudicated as very likely, and probable drug-induced liver injury. The latter case remained blinded.

Narratives for all possible Hy’s law cases are provided in [Appendix 2](#).

4.3. Disproportionality analysis

Disproportionality analysis (DPA) provides information on the frequency of reporting of a drug-event pair, relative to the background reporting in a given database. The aim of DPA is to detect higher-than-expected reporting of drug-event combinations. The DPA method used at GSK is an empirical Bayes data mining algorithm called MGPS, which computes the adjusted relative reporting ratio (EBGM) and associated 90% confidence interval (EB05, EB95) using stratification for age, gender, and year of report. More detailed information on DPA methodology and interpretation is provided in [appendix 5](#).

Specifications for this evaluation are listed in Table 4.

Table 4 Specifications of Disproportionality analysis

Database	GSK Safety Database (OCEANS)
Data Period	Up to end April 2008
Data mining algorithm	MGPS
Drug(s)	Lapatinib
Event(s) (MedDRA PTs)	MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ
Drug Type	Suspect Only

Results:

Drug	Event (MedDRA PT)	N	EBGM	EB05
Lapatinib	SubSMQ-Possible drug related hepatic disorders - comprehensive search (SMQ)	230	1.453	1.013

GCSP review the available DPA data on a monthly basis. There is limited spontaneous data for lapatinib. The EB05 value expresses a ratio between the two groups under comparison, where it is 1 or close to 1 it indicates there is no difference between the groups. The combined EB05 value for the MedDRA sub-SMQ 'possible drug related hepatic disorders' is 1.013 and therefore quantitatively would not be considered a signal.

5. SUMMARY

An association between lapatinib and hepatotoxicity was identified in a previous review of hepatobiliary events (UM2008/00097/00). The estimated incidence for serious hepatobiliary events was 0.4% across the entire clinical programme. This estimate was based on serious adverse event (SAE) data from the GSK safety database and was consistent with the estimated incidence of hepatobiliary events from the adjuvant breast cancer programme.

The current review, based on data to April 2008 demonstrates reasonably comparable incidences for hepatobiliary events, which range from an estimated 0.5 – 0.8% overall.

Specifically 0.5% (58/10,683) for the entire lapatinib clinical programme, 0.8% (10/1250) for the French ATU programme (PMS cases), and 0.2% (5/2,095 *patient years*) for marketed use. The minor changes in reporting may be attributable to an increased awareness and reporting of hepatobiliary events following the circulation of the Dear Investigator/Healthcare provider letters in March 2008; and the addition of hepatobiliary stopping criteria to the protocols for all ongoing studies. The estimated incidence for hepatobiliary events amongst subjects who received placebo or comparator is 0.4% regardless of event attribution.

Review of laboratory data from the clinical trials database for 26 phase I studies demonstrated an overall incidence of AST or ALT elevation above 3x ULN of 5.25% (52/991), although this does not take into consideration baseline LFT measurements. Twenty of these 52 subjects had normal ALT/AST ($\leq 1x$ ULN) at baseline, but developed AST or ALT $>3x$ ULN post baseline (2%; 20/991). There were no fatal hepatobiliary events in this group of phase I studies. Data from 19 phase II/III studies indicated that the most common LFT elevations were elevation of ALT and/or AST $\geq 3x$ ULN but below 5x ULN. The majority of LFT elevations took place in subjects with recurrent breast cancer. Most of these LFT elevations were observed in subjects who received lapatinib in combination with other chemotherapies. Elevation of alkaline phosphatase $>1.5x$ ULN accounted for the majority of LFT elevations (14.3%; 537/3745). Of the total LFT elevations, 26.8% occurred with lapatinib monotherapy. Infrequent elevation of alkaline phosphatase was noted in adjuvant breast cancer, and head and neck studies (3%, and 1.5% respectively). Elevation of bilirubin only was seen in 4.8% of subjects with elevations $>1.5x$ ULN (45.6% of subjects were from monotherapy studies), and 2.5% with elevations $>2x$ ULN (33% of subjects were from monotherapy studies). These LFT elevations were very infrequent in breast cancer subjects treated in the adjuvant setting or in subjects with head and neck cancer.

Based on this review of laboratory data from 45 ongoing or completed clinical studies, GSK therefore concluded that there was a higher incidence of LFT elevations observed in advanced disease and in combination with chemotherapy. LFT elevations taking place in adjuvant trials, or head and neck cancer trials were very low in general, and mainly due to elevation of ALT and/or AST.

Overall, following review of SAE data from the safety database, the estimated incidences of hepatobiliary events on the entire clinical trial programme (all phases/indications) are:

- Fatal hepatobiliary events 0.05-0.1% (5 where lapatinib association could not be ruled out *or* 12 total clinical trial cases/10,683)
- Hepatic failure 0.02-0.06% (2 possible drug induced per GSK's internal liver safety panel adjudication, *or* 6 total clinical trial cases/10,683)

Based on the total of 20 possible Hy's law cases reported from the entire clinical trials programme (3 new cases from the clinical trials database, 17 from the safety database), the overall incidence of possible Hy's law cases on the lapatinib clinical programme is:

- 0.14% (15/10,683) for cases assessed as definite, probable, very likely or possible drug related liver injury by the GSK internal liver safety panel, *or*

- 0.19% (20/10,683) including all possible Hy's law cases reported from the clinical programme.

In comparison, no Hy's law events observed in >18,000 non-oncology patients in GSK Phase II-III clinical trials [[Weil, 2008](#)].

Approximately 8,503 subjects with metastatic cancer are estimated to have received lapatinib as of April 2008. There were 12 reports of fatal hepatic events (acute liver failure) from the metastatic clinical programme, of which 2 were adjudicated as possible drug-induced liver injury by GSK's internal liver safety panel. This gives an estimated incidence of 0.02-0.14% (2 possible drug induced *or* total of 12 clinical trial cases/8,503). There were six reports of hepatic failure in the metastatic clinical programme, of which 2 were adjudicated as possible drug-induced liver injury by GSK's internal liver safety panel (the same two fatal cases discussed above). This gives an estimated incidence of 0.02-0.06% (2 possible drug induced *or* total of 6 clinical trial cases/8,503). A total of 16 possible Hy's law cases were identified from the metastatic cancer programme. Twelve of these cases were adjudicated as very likely, possible, probable or definite drug related liver injury by the GSK internal liver safety panel. This gives an estimated incidence range of 0.14 to 0.2% (12 or 16 total clinical trial cases/8,503) for lapatinib subjects in the adjuvant breast cancer setting.

Approximately 2180 subjects are estimated to have received lapatinib in the adjuvant breast cancer setting as of April 2008, 1500 of these in study EGF105485. Fifteen of the original 215 hepatobiliary cases originated from adjuvant studies EGF105485 and EGF106708. Amongst these 15 cases were 11 for which an association with lapatinib could not be ruled out. There were no reports of fatal hepatic events or hepatic failure in the adjuvant breast cancer setting. A total of four possible Hy's law cases were identified from adjuvant breast cancer study EGF105485: two subjects received lapatinib and two cases remain blinded. Three of these four cases were adjudicated as very likely/probable drug related liver injury by the GSK internal liver safety panel, giving an estimated incidence range of 0.13 to 0.27% (2 or 4/1500) for lapatinib subjects in the adjuvant breast cancer study EGF105485. By comparison, there were no possible Hy's Rule events reported from 18,000 subjects in non-oncology clinical trials [[Weil, 2008](#)]. When liver chemistries from the lapatinib adjuvant breast cancer studies were compared to prior GSK Phase II-III clinical trial datasets from >18,000 patients, a >10-fold increase of ALT >5x ULN (Grade 2-4) was observed [[Weil, 2008](#)].

Amongst the 73 hepatobiliary cases where an association with lapatinib cannot be excluded, there were no obvious trends or risk factors. Most subjects (93%) were female, however the majority of lapatinib studies are in the breast cancer setting, and it is known that women are more susceptible to hepatotoxicity [[Navarro, 2006](#)]. The subjects median age is 54 years, and a similar distribution is seen when looking at fatal hepatobiliary events, hepatic failure, or the possible Hy's law cases.

In terms of the events themselves, there was no evidence of a dose related effect. The daily dose of lapatinib ranged from 1000mg to 1500mg once daily (QD), or 500mg to 750mg twice a day (BID). The fatal hepatobiliary events occurred in subjects who received lapatinib at doses of 1250mg or 1500mg, and an approximately equal distribution between the number of subjects who received lapatinib as monotherapy or in

combination with other therapies. The cohort of subjects who were possible Hy's cases received lapatinib at doses from 1000 to 1500mg, with 55% (11/20) subjects receiving lapatinib at 1500mg. Again there was an approximately equal distribution between the number of subjects who received lapatinib as monotherapy or as combination therapy.

Of note, the median time to onset was 56 days for the 73 case dataset. However the median time to onset for fatal hepatobiliary events was longer, at 21 weeks (146 days), and longer again (23 weeks/163 days) for potential Hy's cases. The time to onset for these hepatobiliary events (range = 56-163 days) is consistent with that of a drug induced effect.

Other tyrosine kinase inhibitors (TKI's) have been associated with hepatotoxicity, however the mechanism for this hepatotoxicity is currently unknown. Possible mechanisms for TKI associated hepatocellular damage include inhibition of the transporters P-glycoprotein or BCRP, and possibly BSEP and MDR3, which could, in addition, be exacerbated by enterohepatic recycling. It is also possible that EGFR inhibition may impair hepatocyte regeneration.

It has been reported that genetic variability may be the most important factor in predicting susceptibility to drug-induced hepatotoxicity [Navarro, 2006]. Pharmacogenetic studies are ongoing to identify markers for patients who are susceptible to hepatotoxicity when given lapatinib.

Lapatinib associated hepatotoxicity appears idiosyncratic in nature and may occur early or later in the course of therapy. There are currently no specific patient sub-populations identified at disproportionate risk and, therefore no criteria for excluding such patients from treatment. Hepatotoxicity and hyperbilirubinemia are included in the lapatinib CSI with a frequency of 'uncommon' (incidence ≥ 0.1 to $< 1\%$). In addition, the CSI for lapatinib includes the warning that "*Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment* (b) (4) (b) (4) *as clinically indicated*" and instructs that "*Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated*". GSK therefore conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

6. CONCLUSION

- Amongst an estimated 8,503 subjects receiving lapatinib in metastatic cancer studies, 2 episodes of acute liver failure possibly related to lapatinib were observed (one very atypical).
- In the metastatic setting, a rate of 0.14% possible Hy's law events (ALT >3x ULN and bilirubin >2x ULN) probably, possibly, very likely or definitely related to lapatinib was observed.
- In the adjuvant breast cancer study EGF105485, a rate of 0.13-0.27% possible Hy's law events (ALT >3x ULN and bilirubin >2x ULN) has been observed.
- GSK conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

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APPENDIX 1 LIST OF ABBREVIATIONS

Abbreviations	
AE	Adverse event
AERS	(FDA) Adverse Event Reporting System
ALT	Alanine transaminase
AST	Aspartate transaminase
ATU	Authorisation for Temporary Use
CSI	Core Safety Information
DPA	Disproportionality analysis
EBGM	Empiric Bayes Geometric Mean
EB05	Lower bound of 2-sided 90% confidence interval around EBGM
FDA	(US) Food and Drug Administration
GSK	GlaxoSmithKline
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MGPS	Multi-item Gamma Poisson Shrinker
OCEANS	GSK's worldwide safety database
PT	Preferred term
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal

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APPENDIX 2 NARRATIVES FOR POSSIBLE HY'S LAW CASES

Protocol Id: EGF104900

Subject Number: (b) (6)

Suspect Drugs: Lapatinib, trastuzumab

This 41 year old female subject was enrolled in an open-label study EGF104900 for the treatment of metastatic breast cancer. The subject was diagnosed with lung metastases in (b) (6). Baseline laboratory values on (b) (6) were: ALT 57 IU/l (normal range 0-48 IU/l), AST 94 IU/l (normal range 0-42 IU/l), alkaline phosphatase 205 IU/l (normal range 20-125 IU/l), and total bilirubin 12 umol/l (normal range: 0-22 umol/l). The subject received oral lapatinib from (b) (6) at dose 1000 mg daily, and intravenous trastuzumab (Herceptin) at 2mg/kg. She was receiving concomitant Ativan and oxycodone. At the week four visit on (b) (6) 28 days after the start of lapatinib and trastuzumab the subjects liver function tests were: ALT 145 IU/l (normal range: 0-48 IU/l), AST 216 IU/l (normal range: 0-42 IU/l), alkaline phosphatase 828 IU/l (normal range: 20-125 IU/l), and total bilirubin 76 umol/l (normal range: 0-22 umol/l). She was diagnosed with serious febrile neutropenia on (b) (6) which resolved on (b) (6).

Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study due to disease progression. Laboratory values following study withdrawal (b) (6) were: ALT 33 IU/l (normal range: 0-48 IU/l), AST 46 IU/l (normal range: 0-42 IU/l), alkaline phosphatase 210 IU/l (normal range: 20-125 IU/l), and total bilirubin 8 umol/l (normal range: 0-22 umol/l). The subject died on (b) (6) (b) (6).

GSK's internal liver safety panel adjudicated this case as: possible drug-induced *cholestatic* liver injury for which lapatinib was the most likely suspect.

Protocol Id: EGF105485
 Subject Number: (b) (6)
 Suspect Drugs: Blinded

This 39 year old female subject was enrolled in blinded study EGF105485 for the treatment of breast cancer. Baseline laboratory values on (b) (6) were: AST 75 U/l (normal range 0-42 U/l), ALT 110 U/l (normal range 0-48 U/l), alkaline phosphatase 96 U/l (normal range 20-125 U/l), and total bilirubin 30 umol/l (normal range: 0-22 umol/l).

The subject received investigational product from (b) (6). While receiving investigational product the subject experienced two episodes of non-serious diarrhoea, and during (b) (6) had increased blood bilirubin. On (b) (6), 93 days after the start of investigational product the subjects liver function tests were: AST 112 U/l (normal range 0-42 U/l), ALT 121 U/l (normal range 0-48 U/l), alkaline phosphatase 91 U/l (normal range 20-125 U/l), and total bilirubin 40 umol/l (normal range: 0-22 umol/l). Laboratory values on (b) (6) were: AST 179 U/l (normal range 0-42 U/l), ALT 204 U/l (normal range 0-48 U/l), alkaline phosphatase 106 U/l (normal range 20-125 U/l), and total bilirubin 46 umol/l (normal range: 0-22 umol/l).

	Subject	Visit	Date	Test	Value		Normal range low	Normal range high
254128	(b) (6)	Screening	(b) (6)	AST_PLC	75.0000	U/L	0.0000	42.0000
254129	(b) (6)	Screening	(b) (6)	ALT_PLC	110.0000	U/L	0.0000	48.0000
254130	(b) (6)	Screening	(b) (6)	ALP_PLC	96.0000	U/L	20.0000	125.0000
254131	(b) (6)	Screening	(b) (6)	BILT_PLC	30.0000	UMOL/L	0.0000	22.0000
254158	(b) (6)	Month 3	(b) (6)	AST_PLC	47.0000	U/L	0.0000	42.0000
254159	(b) (6)	Month 3	(b) (6)	ALT_PLC	56.0000	U/L	0.0000	48.0000
254160	(b) (6)	Month 3	(b) (6)	ALP_PLC	89.0000	U/L	20.0000	125.0000
254161	(b) (6)	Month 3	(b) (6)	BILT_PLC	56.0000	UMOL/L	0.0000	22.0000
254187	(b) (6)	Unscheduled	(b) (6)	AST_PLC	112.0000	U/L	0.0000	42.0000
254188	(b) (6)	Unscheduled	(b) (6)	ALT_PLC	121.0000	U/L	0.0000	48.0000
254189	(b) (6)	Unscheduled	(b) (6)	ALP_PLC	91.0000	U/L	20.0000	125.0000
254190	(b) (6)	Unscheduled	(b) (6)	BILT_PLC	40.0000	UMOL/L	0.0000	22.0000
254199	(b) (6)	Unscheduled	(b) (6)	AST_PLC	179.0000	U/L	0.0000	42.0000
254200	(b) (6)	Unscheduled	(b) (6)	ALT_PLC	204.0000	U/L	0.0000	48.0000
254201	(b) (6)	Unscheduled	(b) (6)	ALP_PLC	106.0000	U/L	20.0000	125.0000
254202	(b) (6)	Unscheduled	(b) (6)	BILT_PLC	46.0000	UMOL/L	0.0000	22.0000

GSK's internal liver safety panel adjudicated this case as: inadequate information available for an adjudication.

Protocol Id: VEG20007
 Subject Number: (b) (6)
 Suspect Drugs: Lapatinib, pazopanib

This 75 year old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral pazopanib at a starting dose of 400mg per day and oral lapatinib at a starting dose of 1000mg per day. Baseline laboratory values on (b) (6) were: AST 46 IU/l (normal range 14-36 IU/l), ALT 36 IU/l (normal range 9-52 IU/l), alkaline phosphatase 73 IU/l (normal range 38-130 IU/l), and total bilirubin 0.7 mg% (normal range 0.2-1.3mg%). Concomitant medications included simvastatin, which was initiated June 18, 2007 (prior to the study).

The subject received investigational product from (b) (6) By (b) (6) (b) (6) 25 days after treatment onset, transaminases and bilirubin had risen to meet Hy's Rule, however, a direct bilirubin at that time was 0.2 (total 2.8). Laboratory values on (b) (6) were: AST 544 IU/l (normal range 14-36 IU/l), ALT 379 IU/l (normal range 9-52 IU/l), alkaline phosphatase 148 IU/l (normal range 38-130 IU/l), and total bilirubin 2.8 mg% (normal range 0.2-1.3 mg%). Investigational product was discontinued on (b) (6) due to the liver toxicity; simvastatin was continued. Transaminases and bilirubin were improved at the time of the study withdrawal visit on (b) (6) AST 244 IU/l (normal range 14-36 IU/l), ALT 303 IU/l (normal range 9-52 IU/l), alkaline phosphatase 105 IU/l (normal range 38-130 IU/l), and total bilirubin 1.1 mg% (normal range 0.2-1.3 mg%).

Parameter (ULN)	Baseline (21-Aug-07)	D8 (28-Aug-07)	Week 4 (16-Sep-07)	IP disc (07-Oct-07)
ALT (52)	36	38	379	303
AST (36)	46	57	544	244
Bilirubin (1.3)	0.7	---	2.8	1.1
Bilirubin, direct (0.3)	---	---	0.2	---
AP (130)	73	103	112	105

GSK's internal liver safety panel adjudicated this case as: Possible drug-induced liver injury due to co-suspect medications lapatinib or pazopanib.

Protocol Id: EGF100151
 Investigator Number: (b) (6)
 Subject Number:
 Treatment Number:
 Case Id: (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Hyponatraemia

This 50-year-old female subject was enrolled in an open-label study for the treatment of advanced or metastatic breast cancer. The subject received oral lapatinib at 1250 mg per

day in combination with oral capecitabine at 4000 mg per day (to be confirmed) from (b) (6) (b) (6). The dose of capecitabine was reduced to 3000mg from (b) (6) (b) (6) until (b) (6) (b) (6) and was further reduced to 2500mg from (b) (6) (b) (6) until (b) (6) (b) (6). Concomitant medications included oxazepam and spironolactone.

The cumulative dose of lapatinib at the time of the event was 456250 mg. The cumulative dose of capecitabine at the time of the event was 630000 mg. The subject's ECOG at baseline was grade 0 (100%).

On (b) (6) (b) (6), 367 days after the start of lapatinib and capecitabine, the subject developed dizziness, fatigue and ascites. The subject was diagnosed with grade 4 hyponatremia and was hospitalised. Total bilirubin on (b) (6) (b) (6) was 2.9mg/dl (normal range: 0.1-1.1). The subject was treated with fluids with improvement. Treatment with lapatinib and capecitabine was discontinued on (b) (6) (b) (6). The subject was withdrawn from the study. The subject died due to disease progression on (b) (6) (b) (6) an autopsy was not preformed.

The investigator considered that there was no reasonable possibility that the hyponatremia may have been caused by lapatinib and capecitabine and that the event was possibly due to the disease under study.

Follow-up information received from the medical monitor on (b) (6) (b) (6):

54-year-old Caucasian woman, was initially diagnosed with Stage IV, HER2-positive, ER/PgR-positive breast cancer on (b) (6) (b) (6). She received 1 cycle of FAC on (b) (6) (b) (6) followed by various hormonal therapies. She received radiotherapy to her left breast in (b) (6) (b) (6) and (b) (6) (b) (6). On (b) (6) (b) (6) she started treatment with trastuzumab plus paclitaxel followed by vinorelbine and subsequently experienced progression of her disease on (b) (6) (b) (6). Prior to randomization, she had metastases to the bone, breast, lung, lymph nodes, and liver. Patient was randomly assigned to lapatinib 1250mg PO QD plus capecitabine 2000 mg/m² on (b) (6) (b) (6) and administered first dose of the combination on (b) (6) (b) (6).

The patient's performance status at the time of enrolment was 0 on the ECOG scale. Her height and weight were 150.0cm and 61.5kg, respectively. She reported Grade 2 anxiety and Grade 3 hypertension and was taking the following medications at baseline: Aredia (pamidronate disodium), Cardiloc (bisoprolol fumarate), Ooscar Plus (hydrochlorothiazide and losartan potassium), and Vaben (oxazepam). Prior to administration of combination therapy, she experienced Grade 1 ALP and Grade 2 AST and ALT.

On (b) (6) (b) (6) AST and ALT values decreased to Grade 1 and ALP had remained unchanged from baseline (Grade 1). On (b) (6) (b) (6) 265 days after the start of lapatinib plus capecitabine therapy, the patient experienced Grade 2 AST and hyperbilirubinemia; ALP and ALT values remained the same at Grade 1. Other AEs reported around the time of the elevated liver functions tests included Grade 1 ascites

(b) (6) (b) (6) Grade 1 diarrhea (b) (6) (b) (6) Grade 1 abdominal pain (b) (6) (b) (6); and Grade 2

fatigue ([REDACTED] ^{(b) (6)}). All AEs, except ascites, were considered by the investigator to be possibly related to study drug.

On [REDACTED] ^{(b) (6)} 355 days after starting combination therapy, the patient experienced Grade 1 hepatic cirrhosis and Grade 3 ascites. Laboratory results on [REDACTED] ^{(b) (6)} showed that liver function tests remained unchanged with Grade 2 AST and hyperbilirubinemia and Grade 1 ALP and ALT (refer to Table 5 for laboratory results). Grade 2 hypoalbuminemia was also reported. Eosinophils remained within normal range.

On [REDACTED] ^{(b) (6)} 367 days after the start of lapatinib and capecitabine, she was hospitalized for dizziness, fatigue, and ascites and was diagnosed with Grade 4 hyponatremia with reported sodium value of 125mmol/L (normal range: 136 - 148mmol/L). Patient was treated with fluids and improved.

The patient permanently discontinued combination therapy on [REDACTED] ^{(b) (6)} due to hepatic cirrhosis, ascites, hyperbilirubinemia, and hyponatremia, none of which were considered to be related to study drug by the investigator. The patient was on the combination of lapatinib plus capecitabine for duration of approximately 12.5 months. Her last tumor response as assessed by the independent review panel in [REDACTED] ^{(b) (6)} indicated SD. Tumor assessments performed by the investigator also indicated SD through [REDACTED] ^{(b) (6)}. No new lesions or progressions were noted at this time. She later died due to disease progression on [REDACTED] ^{(b) (6)} an autopsy was not preformed. Hyponatremia was reported by the investigator as a fatal event.

GSK's internal liver safety panel adjudicated this case as: inadequate information.

Protocol Id: EGF103009

Investigator Number:

Subject Number: (b) (6)

Treatment Number:

Case Id: (b) (6)

Suspect Drugs: Lapatinib

Serious Events:

Patient (b) (6) 44-year-old Caucasian woman, was initially diagnosed with inflammatory breast cancer on (b) (6) and was treated with fluorouracil, epirubicin, and cyclophosphamide for approximately 4 months followed by radiotherapy to left chest wall and supraclavicular area. She then received docetaxel followed by trastuzumab with last dose received on (b) (6). At the time of screening, she had ER/PgR-positive, Stage IV disease with dermal lymphatic invasion and overexpression of ErbB1 and ErbB2 (IHC 2+). Patient entered the study and began treatment with lapatinib 1500mg PO QD on (b) (6). The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 156.0cm and 76.4kg, respectively. She reported Grade 1 pain due to an ulcerated lesion on her chest wall and metastatic bony disease and was receiving acetaminophen (Tylenol) and pamidronate disodium at the time of study entry.

On (b) (6) 6 days after the start of lapatinib, the patient experienced Grade 2 hypersensitivity and dermatitis acneiform. Lapatinib was reduced to 1250mg QD from (b) (6). Hypersensitivity resolved on (b) (6) and the patient resumed full dose thereafter. The outcome of dermatitis acneiform remains unknown.

On (b) (6) 84 days after the start of lapatinib, the patient reported Grade 2 hyperbilirubinemia. Other relevant liver-related laboratory results included Grade 2 ALT and Grade 1 AST. Subsequent laboratory tests performed every 4 weeks up until her last dose of lapatinib on (b) (6) showed that ALT, AST, and TBL remained elevated (refer to Table 16 for laboratory results). Hyperbilirubinemia was considered by the investigator to be possible related to study drug. The other laboratory findings (elevated ALT and AST) were not recorded as AEs; therefore, investigator's assessment of relationship to study drug is not known.

On (b) (6), the patient experienced worsening of erythema which was considered progressive disease according to the protocol-defined criteria for clinically evaluable skin disease. Further progression was noted in the chest wall on (b) (6). Lapatinib was discontinued on (b) (6) due to disease progression and on that day, the patient started treatment with capecitabine 2000 mg/m². On (b) (6) 200 days after the start of lapatinib and 15 days after the last dose, she was hospitalized with Grade 3 dehydration accompanied by diarrhea, mucositis, nausea, vomiting, decreased oral intake, and dyspepsia. On (b) (6), 18 days after the last dose of lapatinib, the patient developed Grade 3 febrile neutropenia (WBC: 1.8 and ANC: 0.6) and was treated with prophylactic antibiotics, including cefazolin, tobramycin, and metronidazole. Blood and urine cultures were negative. Febrile neutropenia resolved on (b) (6) and dehydration resolved on (b) (6). In the investigator's opinion, both events were possibly related to capecitabine.

The patient was on lapatinib for duration of approximately 7 months. Her overall best tumor response as assessed by the investigator was PR according to RECIST criteria and protocol-defined criteria for clinically evaluable skin disease. Patient was not followed for long-term survival outcome.

GSK's internal liver safety panel adjudicated this case as: inadequate information.

Protocol Id: EGF103009
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Fatigue, Hyperbilirubinaemia

This subject was enrolled in an open-label study for the treatment of refractory breast cancer. The subject received oral lapatinib from (b) (6) to (b) (6).

The subject complained of extreme lethargy and malaise during the past three weeks. On (b) (6) 194 days after the start of lapatinib, the subject developed grade 4 or severe bilirubin increased and grade 2 or moderate fatigue. The subject was hospitalised on the same day. The subject experienced further symptoms of aggravated (worsening) rash, jaundice and increased transaminase. Relevant laboratory results included aspartate aminotransferase (AST): 2316 IU/l, alanine aminotransferase (ALT): 3338 IU/l and bilirubin to be increasing further to 25 ug/dl and stabilising at this figure. Albumin decreased to 2.7 and international normalized ratio (INR) was stable on 1.4-1.5. All viral autoimmune and radiologic tests were negative. The investigator stated a differential diagnosis of 'drug-induced hepatotoxicity'. Treatment with lapatinib was discontinued on (b) (6). On (b) (6) the subject INR peaked to 1.6 after the peak enzyme levels. The subject was treated with prednisone 60mg. The subject was feeling well, bilirubin was to 16, INR 1.05 and liver function tests in the 400 range. The event of fatigue was improved at time of reporting.

The investigator reported the bilirubin increased and fatigue as possibly related to treatment with lapatinib and that the events were possibly due to disease under study. The investigator cited loratadine(Lorastin) was given for a lapatinib induced acneiform rash. The investigator also cited approximately half the bilirubin increase had been unconjugated bilirubin and the bilirubin seemed to have peaked after the peak of liver injury - which, by the enzyme levels, started to return to baseline before steroids were started.

Additional information received on (b) (6)

The subject has been improving and generally feeling much better. Latest laboratory test results include bilirubin 3.3 ug/dl, INR 0.87, AST 56 IU/L, ALT 101 IU/L.

Additional information received on (b) (6)

The onset and max toxicity of bilirubin increase was confirmed as (b) (6) and grade 4 toxicity.

Follow-up information received on (b) (6)

Onset date of fatigue was (b) (6) the event resolved on (b) (6). Bilirubin resolved on (b) (6). Laboratory test alkaline phosphatase was 148.

Lapatinib was stopped on (b) (6) and the subject was hospitalised on (b) (6).

Follow up information received on (b) (6)

Onset date of fatigue was updated to (b) (6). Hepatotoxicity was upgrade to a SAE (onset date (b) (6)). On (b) (6) the hepatotoxicity was reported to be resolved. The investigator considered that hepatotoxicity was related to the investigational product.

Follow up received on (b) (6)

The event term 'increased bilirubin' was changed to 'hyperbilirubinemia'.

Follow up received on (b) (6)

The event drug induced hepatotoxicity was downgraded to non-serious.

Follow up information received from medical monitor (b) (6)

Patient (b) (6) 43-year-old Caucasian woman, was initially diagnosed with inflammatory breast cancer on (b) (6) and was treated with fluorouracil, doxorubicin, and cyclophosphamide for approximately 1 month followed by docetaxel and trastuzumab. She then received capecitabine followed by navelbine with last dose received on (b) (6). At the time of screening, she had ER/PgR-negative refractory Stage IV disease with dermal lymphatic invasion and overexpression of ErbB2 (IHC 3+); ErbB1 expression was unknown. Patient entered the study and began treatment with lapatinib 1500mg PO QD on (b) (6).

The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 157.0cm and 70.0kg, respectively. She reported no significant past or current medical conditions and no concomitant medications at study enrollment.

On (b) (6) 194 days after the start of lapatinib, patient developed Grade 4 hyperbilirubinemia and Grade 2 fatigue. Other liver-related laboratory findings included Grade 4 AST and Grade 1 ALP. Lapatinib was discontinued on (b) (6). She was hospitalized on (b) (6) and experienced further symptoms of aggravated (worsening) rash, jaundice, and increased transaminase. Patient also experienced low serum albumin (2.7 g/dL). International normalized ratio (INR) was stable (1.4-1.5) at this time. Viral autoimmune tests were negative. An ultrasound of the liver performed on (b) (6) showed liver was of normal size and without focal findings; the

gallbladder was without stones or thickening; and bile ducts were not dilated. On (b) (6) (b) (6) an MRI was performed and findings were within normal limits. On (b) (6) (b) (6) INR peaked to 1.6. Treatment with prednisone was initiated at a starting dose of 60mg. The investigator commented that approximately half the bilirubin increase had been unconjugated bilirubin and that the bilirubin peaked after the peak of liver injury which, according to the enzyme levels, started to return to baseline before steroids were initiated. Laboratory findings for AST, ALT and TBL remained elevated throughout (b) (6) (b) (6) (refer to Table 4 for laboratory results).

Another ultrasound of the liver was performed on (b) (6) (b) (6) and showed a small liver without focal findings; open hepatic veins; portal flow in correct direction; no ascites; and IVC open. An abdominal CT, including coronal planes and with contrast, was also performed on (b) (6) (b) (6) and concluded no new findings compared with previous CT on (b) (6) (b) (6) left breast was edematous with thickened skin; no pathological findings within lung bases and stomach; liver and spleen were of normal consistency and size without dilated bile ducts; adrenals were normal size; kidneys were of normal consistency without hydronephrosis; and no evidence of ascites or lymphadenopathy in retroperitoneum or pelvis was noted. The patient was initially withdrawn from the study on (b) (6) (b) (6) however, a waiver was granted to allow the patient to remain on the study and re-start lapatinib; exposure data for the period of re-challenge are forthcoming from the investigative site.

The investigator considered fatigue and hepatotoxicity, including hyperbilirubinemia, to be possibly related to study drug. Her fatigue resolved on (b) (6) (b) (6) and the investigator reported the hepatotoxicity as resolved on (b) (6) (b) (6).

The patient was on lapatinib for duration of approximately +6.5 months. Her overall best tumor response as assessed by the investigator was SD according to RECIST criteria and PR according to protocol-defined criteria for clinically evaluable skin disease. Patient was not followed for long-term survival outcome.

GSK's internal liver safety panel adjudicated this case as: definite drug-induced liver injury, lapatinib – very likely (positive rechallenge).

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number:
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Hepatic enzyme increased, Jaundice

This 33-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 80 mg twice per day from (b) (6). Concomitant medications included prednisolone. Medical conditions included palliation (general condition).

On an unspecified date in (b) (6) the subject developed grade 5 jaundice. On (b) (6) the subject was seen in the out-patient clinic and it was noted that in three weeks she had lost 6kg in weight. She was jaundiced in both skin and eyes. The subject experienced grade 5 hepatic tests increased (increased liver enzymes). Relevant test results included ALAT: 7 u/l, Alkaline phosphatase: 671 u/l, ASAT:382 u/l and Bilirubin: 496 micromol/l. Treatment with lapatinib and capecitabine was discontinued on (b) (6) and the subject was withdrawn from the study. The subject was informed about hospice and terminal care at home. The subject died on (b) (6) at home, cause of death were jaundice and hepatic tests. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the jaundice and hepatic tests increased may have been caused by lapatinib and capecitabine and that the events were possibly due to the disease under study.

GSK's internal liver safety panel adjudicated this case as: unlikely drug-induced liver injury, lapatinib unlikely suspect but cannot be ruled out.

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number:
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Ascites, Hepatic infarction

This 43-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib from (b) (6) to (b) (6) and oral capecitabine from (b) (6) to (b) (6). Medical conditions at the time of the event included liver metastases. Concomitant medications included dexamethasone, omeprazole, paroxetine hydrochloride, spironolactone, diclofenac and unknown.

On (b) (6) 40 days after the start of lapatinib and capecitabine, the subject developed moderate hepatic infarction and grade 3 or severe abdominal ascites. The

subject presented at clinic appointment with elevated enzymes, jaundice and abdominal distension, subject felt well. The subject was hospitalised on (b) (6). The investigator reported final diagnosis liver infarction due to liver necrosis, causing abdominal ascites and no evidence of liver metastases. Relevant test results included on (b) (6) laboratory values creatinine 116umol/L (normal range 58-93), urea 10.7mmol/L (normal range 2.9-6.2), alkaline phosphatase 193 iu/L (normal range up to 115), total bilirubin 102 umol/L (normal range 5-18) and alanine aminotransferase 319iu/L (normal range up to 31). On (b) (6) CT scan showed no evidence of liver metastases and bone scan showed response in left side pf pelvis and no new bone lesions. Abdominal acites drained - 3800ml. The subject was treated with diclofenac, albumin, gelofusin, enoxaparin and ciprofloxacin. Treatment with lapatinib was interrupted on (b) (6). Treatment with capecitabine was interrupted on (b) (6). The events improved on an unspecified date. The investigator considered that there was no reasonable possibility that the hepatic infarction and abdominal ascites may have been caused by lapatinib and capecitabine.

On (b) (6) 52 days after the start of lapatinib and capecitabine, the subject developed abdominal ascites. The subject was hospitalised on (b) (6). Abdominal parecentesis was performed under ultra-sound scan on (b) (6) and 2000ml fluid was drained. An ascitic tap was to remain in situ until satisfactory amount was drained. The subject was discharged on (b) (6) but was re-admitted on (b) (6) as her abdomen was grossly distended. The abdominal ascites was unresolved and the subject was discharged on (b) (6). On (b) (6) the subject was readmitted to hospital for recurrence of abdominal ascites and discharged again on the saem day. Treatment with lapatinib and capecitabine was due to be restarted on (b) (6) and a final diagnosis of liver dysfunction was made which was unresolved. The investigator considered that there was no reasonable possibility that the abdominal ascites may have been caused by lapatinib and capecitabine and that it was probably due to liver infarction, and jaundice.

GSK's internal liver safety panel adjudicated this case as: drug-induced liver injury excluded: Etiology of hepatic infarction unclear; possible Budd-Chiari Syndrome.

Protocol Id: EGF105485

Investigator Number: (b) (6)

Subject Number:

Treatment Number:

Case Id: (b) (6)

Suspect Drugs:

Serious Events: Hepatotoxicity

This 58-year-old female subject was enrolled in a blinded study for the treatment of breast cancer. The subject received oral investigational product per day from (b) (6). The subject was randomized to the lapatinib arm of the study.

On (b) (6) 163 days after the start of investigational product, the subject developed grade 4 hepatotoxicity. The event was clinically significant per protocol of

grade 4 laboratory abnormalities. She also experienced tiredness, nausea, vomiting, diarrhea, weight loss, and jaundice of eyes and skin. Diagnostic tests performed on (b) (6) were notable for total bilirubin of 248 micromol/L (normal range 4 to 22 micromol/L), glutamic-pyruvate transaminase (alanine aminotransferase) 1927 U/L (normal range 10 to 45 U/L), glutamic-oxaloacetic transferase 1507 U/L (normal range 15 to 35 U/L), lactic dehydrogenase 328 U/L (normal range 105 to 205 U/L), alkaline phosphatase 201 U/L (normal range 35 to 105 U/L), platelet count $70 \times 10^9/L$ (normal range 150 to $400 \times 10^9/L$), hepatitis B surface antigen negative, and hepatitis B surface antibody was negative. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the hepatotoxicity may have been caused by investigational product.

Follow-up received (b) (6). The investigator reported that, on (b) (6) (b) (6) an ultrasound of the abdomen revealed a gallbladder with concretion but no liver metastases. On (b) (6) an abdominal CT scan revealed no new information, gallstone, or metastases.

Follow-up received (b) (6). The site reported that, on (b) (6) the Hepatitis A (HAV) IgM and total antibody were both negative. Hepatitis C (HCV) PCR was negative. CMV IgM and IgG both negative. EBV IgM and VCA negative. EBV IgG EBNA positive. EBV IgG VCA positive. On (b) (6) SGOT was 301 U/L, SGPT was 595 U/L, and total bilirubin was 112 umol/L. Treatment medications included cefuroxime, ciprofloxacin, prednisolone, B-combin, and phythomenadione.

Follow-up received (b) (6). The site reported that the subject additionally experienced a non-serious grade 1 fever that began on (b) (6) and resolved later the same day. The subject did not have a rash. The site confirmed that a gallstone (previously reported as 'gallbladder concretion') was seen on CT scan, but had no relevance to the hepatotoxicity. A liver biopsy showed moderate hepatitis and autoimmune hepatitis. A CT of the abdomen was performed on (b) (6) and incipient hepatic failure was suspected. The subject had no history of alcohol use.

Follow-up received (b) (6). The site confirmed that the subject had no history of acetaminophen use.

Follow-up received (b) (6). The site confirmed that the hepatotoxicity resolved with sequelae on (b) (6) and confirmed that the event was not related to study participation.

Follow-up received (b) (6). The site reported that the subject stopped lapatinib on (b) (6). Prior history included a lumpectomy and prior chemotherapy (FEC) from August 2003 to December 2003. Concurrently, the subject received anastrozole.

Follow-up received (b) (6). The site provided additional laboratory values and reported that the subject received prior chemotherapy with FEC (b) (6) and tamoxifen (b) (6) and currently received Arimidex.

GSK's internal liver safety panel adjudicated this case as: very likely drug-induced liver injury, lapatinib probable; anastrozole: lapatinib interaction possible.

Protocol Id: EGF105485
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Alanine aminotransferase increased

This 68-year-old female subject was enrolled in a blinded study for the treatment of breast cancer. The subject received oral investigational product from an unspecified date. The subject was randomized to lapatinib 1500mg daily.

On (b) (6) the subject developed a grade 4 increase in alanine aminotransferase. The event was clinically significant (or requiring intervention). She also experienced nausea, weight loss, diarrhea and fatigue. Treatment with investigational product was interrupted. The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the alanine aminotransferase increased may have been caused by investigational product.

Follow-up received (b) (6) The site reported that the elevated ALT was considered to be life-threatening. Investigational product was discontinued and the subject was withdrawn from the study.

Follow-up investigator comments: "patient came to visit (b) (6) She had a weight loss of 3.9 kg since the last visit, she was terrible tired, had nausea and constant diarrhea. All her liver parametre was increased. the study drug was interrupted and she had new test done (b) (6) which revealed no change in ALAT, increase in alkaline phosphatase, bilirubi stabile, decrease in creatinine. "

Follow-up received (b) (6) The site reported that the event did not meet the criteria to be considered "life-threatening" at the time of presentation. Follow-up investigator comments: "new test done the (b) (6) reveals ALAT still no change, bilirubin increasing, creatinine decreasing and alkaline phosphatase decreasing. We had new tests done both the (b) (6) and finally the ALAT is decreasing from the (b) (6) and furthermore the (b) (6) The same with alkaline phosphatase, bilirubin and creatinine. the ALAT is still a grade 3. It is decided by PI to withdraw patient from study drug."

Follow-up received (b) (6) The site reported that the subject took lapatinib from (b) (6) to (b) (6) The subject had a previous history of a mastectomy and received prior chemotherapy (FEC) from (b) (6) to (b) (6)

GSK's internal liver safety panel adjudicated this case as: very likely drug-induced liver injury, lapatinib probable.

Protocol Id: EGF105485
Investigator Number:
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Blinded trial medication
Serious Events:

Patient (b) (6), a 62-year-old Caucasian woman with Stage IIIa breast cancer, initially diagnosed in (b) (6), was randomly assigned to blinded study drug (lapatinib 1500 mg PO QD or placebo) on (b) (6) and administered first dose on the same day. She has ER-negative/PgR-positive disease with no lymph node involvement.

Prior to randomization, the patient received neoadjuvant fluorouracil, doxorubicin (Adriablastine), and cyclophosphamide for 3 months followed by a mastectomy of the left breast. She also received adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide for 3 months. She has been taking tamoxifen since (b) (6).

The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 168cm and 79.0kg, respectively. She reported no significant past or current medical conditions and no other concomitant medications, except tamoxifen, at the time of screening.

On (b) (6) the patient experienced mild increases of AST and ALT (both Grade 2) and Grade 1 hyperbilirubinemia. On (b) (6) 351 days after the start of blinded study drug, the patient experienced Grade 3 AST and Grade 2 ALT and hyperbilirubinemia. Eosinophils and albumin levels remained within normal range during study treatment. The patient permanently discontinued blinded study drug with the last dose received on (b) (6). She was treated with Essential Forte 1800mg for hyperbilirubinemia for 2 weeks and is currently receiving a daily dose of 900mg. Subsequent laboratory results on 14 and (b) (6) showed mild improvement of AST to Grade 2 and consistent Grade 2 ALT and hyperbilirubinemia. On (b) (6) (b) (6), all liver function tests were Grade 1. Her reported weight on (b) (6) (b) (6) was 75.0kg.

The investigator confirmed that the elevated liver function tests, which were non-serious events, were possibly related to study drug; treatment assignment remains blinded.

The patient was on blinded study drug for duration of approximately 12 months. As of (b) (6) the patient has not reported recurrence of disease and continues to be followed for disease assessment.

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury, blinded drug – probable.

Protocol Id: EGF19060
Investigator Number: (b) (6)
Subject Number: (b) (6)

Treatment Number:

Case Id: (b) (6)

Suspect Drugs: Lapatinib

Serious Events: Hepatic enzyme increased, Transaminases increased

This 48-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject was previously enrolled in study EGF10015 and received oral lapatinib at 1500 mg per day from (b) (6). The subject was then rolled over to study EGF19060 and continued to receive oral lapatinib from (b) (6).

In early January, the subject developed a low-grade fever and skin infection and was prescribed a ten-day course of Augmentin 875 mg twice daily from (b) (6). Results of a computed tomography scan showed lung metastasis but no liver metastasis.

In (b) (6) the subject's liver function test results were as follows: aspartate aminotransferase 28, alanine aminotransferase 28, alkaline phosphatase 89 and total bilirubin 1.5 (units not reported; investigator reported results within normal limits). On (b) (6) the subject developed increased liver function tests. The event was clinically significant (or requiring intervention). She was described as asymptomatic with a normal physical exam. The subject's lapatinib level drawn at 1:00 pm on Tuesday, (b) (6) 29 hours following the preceding dose of 1500 mg taken at 8:00 am on Monday, (b) (6) was 1131 ng/mL. Additional laboratory results drawn on (b) (6) were as follows: aspartate aminotransferase 249, alanine aminotransferase 282, alkaline phosphatase 128 and total bilirubin 1.6 (units and normal ranges not reported). Results of an abdominal computed tomography scan performed on (b) (6) showed a 3.6 x 3.3 x 2.8 centimeter hemangioma, unchanged from (b) (6). No other focal liver lesions were observed. There was no evidence of hepatomegaly or intrahepatic biliary ductal dilatation. The common bile duct, pancreas, visualized abdominal aorta, spleen, both kidneys and gallbladder appeared normal. Treatment with lapatinib was discontinued on (b) (6). Laboratory results drawn on (b) (6) were as follows: aspartate aminotransferase 302, alanine aminotransferase 307, alkaline phosphatase 144, total bilirubin 1.9, direct bilirubin 0.3, indirect bilirubin 1.2, Hepatitis A antibody negative, Hepatitis B antigen and antibody negative, Hepatitis C antibody IgG and IgM negative, Hepatitis E negative, cytomegalovirus negative, Epstein-Barr IgG positive, Epstein-Barr IgM negative, anti-nuclear antibody negative, anti-smooth muscle antibody negative and anti liver-kidney negative. Additional laboratory results drawn on (b) (6) were as follows: aspartate aminotransferase 302, alanine aminotransferase 307, bilirubin 1.90 and alkaline phosphatase 190. On (b) (6) laboratory results were as follows: aspartate aminotransferase 252, alanine aminotransferase 353, bilirubin 1.5 and alkaline phosphatase 150. Repeat laboratory tests drawn on (b) (6) were as follows: aspartate aminotransferase 252, alanine aminotransferase 353, bilirubin 1.5 and alkaline phosphatase 150. Laboratory results drawn on (b) (6) were as follows: aspartate aminotransferase 290, alanine aminotransferase 378, alkaline phosphatase 193, total bilirubin 0.7 and direct bilirubin 0.3. The event was unresolved at time of reporting.

Investigator causality was unknown at the time of reporting but the investigator considered that the event was possibly due to Augmentin.

Follow-up received (b) (6). Increased transaminase levels were reported as toxicity grade 3. Treatment with lapatinib was interrupted on (b) (6) pending normalisation of the elevated liver enzymes, and the subject remained in the study. Additional laboratory results from (b) (6) included gamma glutamyl transferase of 94 Units/L (reference range 0-65), direct bilirubin of 0.3 mg/dL (reference range 0-0.3) and indirect bilirubin of 1.2 mg/dL (reference range 0-0.9). On (b) (6) (b) (6) aspartate aminotransferase was 221 Units/L (reference range 15-37), alanine aminotransferase was 300 Units/L (reference range 30-65), alkaline phosphatase was 148 Units/L (reference range 20-136), total bilirubin was 1.6 mg/dL (reference range 0.3-1.2), direct bilirubin was 0.3 mg/dL and indirect bilirubin was 1.3. On (b) (6) aspartate aminotransferase was 263 Units/L, alanine aminotransferase was 332 Units/L, alkaline phosphatase was 158 Units/L, total bilirubin was 1.2 mg/dL and direct bilirubin was 0.4 mg/dL. On (b) (6) ultrasound of the abdomen showed benign hemangioma, otherwise considered negative. On (b) (6) aspartate aminotransferase was 279 Units/L, alanine aminotransferase was 367 Units/L, alkaline phosphatase was 159 Units/L and total bilirubin was 1.0 mg/dL. On (b) (6) mitochondrial antibody was negative. Hepatitis C virus RNA was not detected. Cytomegalovirus IgM and IgG were negative. Cytomegalovirus viral load and Epstein-Barr viral load were undetectable. Parvovirus B19-G was positive at 6.98 (reference range - positive greater than 1.10) and parvovirus B19-M was negative at 0.26 (reference range less than 0.90); results suggested past infection. On (b) (6) aspartate aminotransferase was 317 Units/L, alanine aminotransferase was 408 Units/L, alkaline phosphatase was 181 Units/L and total bilirubin was 1.0 mg/dL. On (b) (6) aspartate aminotransferase was 346 Units/L, alanine aminotransferase was 449 Units/L, alkaline phosphatase was 167 Units/L and total bilirubin was 2.0 mg/dL. On (b) (6) (b) (6) aspartate aminotransferase was 254 Units/L, alanine aminotransferase was 369 Units/L, alkaline phosphatase was 167 Units/L and total bilirubin was 1.0 mg/dL. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the increased transaminase levels may have been caused by investigational product and that the event was possibly related to Augmentin.

Follow-up received (b) (6). The site reported that the subject had previously been enrolled in study EGF10015 and had actually been receiving oral lapatinib since (b) (6) (b) (6). The elevated liver enzymes began 207 days after first receipt of lapatinib. Upon follow-up, the site also reported that all serology labs were negative.

Follow-up received (b) (6).

The event of increased transaminase levels with an onset date of (b) (6) resolved on (b) (6). The investigator no longer considered that the increased transaminase levels were related to Augmentin. Treatment with lapatinib was restarted on (b) (6). On (b) (6) the subject experienced grade 1 or mild increased transaminase levels. On (b) (6) laboratory results were as follows: aspartate aminotransferase 87, alanine aminotransferase 123, alkaline phosphatase 143, total bilirubin 1.4. Treatment with lapatinib was continued at that time. On (b) (6)

laboratory results were as follows: aspartate aminotransferase 169, alanine aminotransferase 228, alkaline phosphatase 153, total bilirubin 28. Treatment with investigational product was discontinued on (b) (6) and the subject was withdrawn from the study. The event remained unresolved at the time of reporting. The investigator considered there was a reasonable possibility that the increased transaminase levels may been caused by lapatinib.

GSK's internal liver safety panel adjudicated this case as: Definite drug-induced liver injury, lapatinib definite (positive rechallenge).

Protocol Id: EGF20014
Investigator Number: (b) (6)
Subject Number:
Treatment Number:
Case Id: (b) (6)
Suspect Drugs:
Serious Events: Hepatic function abnormal

This 57-year-old female subject was enrolled in an open-label study for the treatment of non small cell lung cancer. Past medical history included post hysterectomy, and knee replacement. Medical conditions at the time of the event included hypertension, intermittent watery diarrhea controlled by medications and gastroesophageal reflux disease. Concomitant medications included oestradiol (Estradiol), metoprolol succinate (Toprol XL) and diclofenac sodium (Voltaren XR).

The subject received oral GW572016 at 500mg twice daily from (b) (6)

On (b) (6) 34 days after the start of GW572016, the subject developed orange urine and icteric sclera and went to the clinic for evaluation. She had a prior history of chills and fever for five to seven days. Relevant tests results included elevated bilirubin 6.4 mg/dl (Reference 0.2-1.2) and elevated alkaline phosphatase 806 U/L(Reference 30-135). The subject was hospitalized and the events were considered life threatening. An ultrasound performed on (b) (6) ruled out cholelithiasis and cholecystitis. She was diagnosed with hepatic dysfunction. Due to her history of fever and chills blood cultures were drawn but returned negative. A computed tomography of the chest, abdomen and pelvis revealed slight enlargement of numerous bilateral pulmonary nodules suggestive progression of metastatic disease, but did not reveal anything remarkable in the liver. All hepatitis markers were negative and the anti-mitochondrial antibody screen was negative. The subject was evaluated by biliary service who felt "the subject had intrahepatic cholestasis secondary to her tyrosine kinase inhibitor which had been discontinued" and recommended monitoring of the prothrombin time, albumin and liver function test. Treatment with GW572016 was discontinued and the subject was withdrawn from the study. Her concomitant medications were continued. On (b) (6) her bilirubin improved to 3.9 U/L from 6.4 U/L and she was discharged from the hospital in stable condition. The liver dysfunction improved (date unknown at time of reporting). On (b) (6) alkaline phosphatase 323 U/L

(Reference 30-135), aspartate aminotransferase 41 U/L and alanine aminotransferase 67 U/L (Reference 10-60). Her condition remained improved but not resolved. The investigator considered there was reasonable possibility that the hepatic dysfunction may have been caused by GW572016.

Upon follow-up the investigator reported the subject continued to have an elevated grade 1 alkaline phosphatase (229 U/L) and grade 1 alanine aminotransferase (85) on (b) (6). The subject started on carboplatin/navelbine chemotherapy as treatment. The elevated alkaline phosphatase and alanine aminotransferase were considered resolved or "normalized" by (b) (6) after 99 days.

GSK's internal liver safety panel adjudicated this case as: Probable drug-induced liver injury, lapatinib very likely.

Protocol Id: EGF30001
Investigator Number: (b) (6)
Subject Number:
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Paclitaxel
Serious Events: Alanine aminotransferase increased

This 45-year-old female subject was enrolled in a blinded study for the treatment of metastatic breast cancer. The subject was noted not to have any relevant medical conditions and relevant risk factors prior to onset. The subject's ECOG score at baseline was zero.

The subject received oral investigational product GW572016 1500 mg from (b) (6) and paclitaxel 175 mg/m² intravenous over three hours every three weeks from (b) (6). The subject received the second cycle of paclitaxel on (b) (6).

On (b) (6) 49 days after the start of investigational product and paclitaxel and 28 days after the last cycle of paclitaxel, the subject was found to have developed an elevated alanine aminotransferase (ALT) level of 1198 U/L (normal value 424 U/L), aspartate aminotransferase (AST) level 412 U/L (normal range 1 - 31); bilirubin 1101 mmol/L (normal range 8.5 - 20.5) and alkaline phosphatase level 326 U/L (normal range 64 - 306). The subject was hospitalised. She was also found to have developed icterus which was not confirmed as serious at the time of reporting by the investigator. The subject was treated with anti-spasmodic drug.

Treatment with paclitaxel was discontinued due to this event on (b) (6). Treatment with investigational product was discontinued due to this event on (b) (6) and the subject was withdrawn from the study. The events resolved with sequelae on (b) (6) after 8 days, with a repeat laboratory result value of ALT 335 U/L. The investigator considered there was reasonable possibility that the event elevated ALT may have been caused by investigational product and paclitaxel.

On receipt of follow-up information, the investigator confirm the event icterus was not a serious event. Hepatitis markers were negative (test date (b) (6)). A biopsy of the liver was not done. On (b) (6) a CT scan showed there was no evidence of progressive disease seen on imaging of the liver. The investigator confirmed the subject did not receive concomitant medication prior to onset and there was no history of any illness prior event onset date. The investigator reconfirmed the subject was not re-challenged with investigational product.

Follow up information received from medical monitor on (b) (6)

a 45-year-old Caucasian woman, was initially diagnosed with Stage III, HER2-negative, ER/PgR-positive breast cancer on (b) (6) no treatment was given at this time. Patient was diagnosed with Stage IV disease on (b) (6) with metastases to the liver, breast, and lymph nodes. Patient was randomly assigned to lapatinib 1500mg PO QD plus paclitaxel 175 mg/m² every 3 weeks on (b) (6) and administered first dose of the combination on the same day.

The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 169.0cm and 66kg, respectively. Written communication received from the site on (b) (6) confirmed that the patient reported a Vitamin C allergy and renal cysts and was taking a dietary supplement, laminolact; an herbal supplement, acorus calamus; and cornsilk. An ECG performed at screening was noted as abnormal, but not clinically significant.

The patient received two doses of paclitaxel administered on 3 and (b) (6) and continued on single-agent lapatinib 1500mg QD. On (b) (6) the patient reported Grade 1 jaundice. On (b) (6) 49 days after the start of the combination of lapatinib and paclitaxel, the patient experienced Grade 4 ALT, Grade 3 AST and hyperbilirubinemia, and Grade 1 ALP (refer to Table 6 for laboratory results). Other laboratory results included Grade 2 hypocalcemia (1.82 mmol/L; normal range: 2.02-2.60 mmol/L). Patient was hospitalized on this day.

Tests for hepatitis markers performed on (b) (6) were negative. On (b) (6) (b) (6) a CT scan showed no evidence of progressive disease in the liver. She was treated with spasmolytics for complaint of pain in right hypochondrium; no evidence of infection or clinical/laboratory signs of renal dysfunction were noted (confirmed by written communication from the site).

The patient permanently discontinued study drug with the last dose of lapatinib on (b) (6) (b) (6). Elevated ALT was reported by the investigator to have resolved with sequelae on (b) (6) laboratory results for ALT and AST were 335 and 207 U/L, respectively. Patient was discharged from the hospital on (b) (6) (confirmed by written communication from site) and jaundice resolved on (b) (6). Eosinophils and albumin level remained within normal range throughout the duration of study treatment. Written communication received from the site confirmed that there have been neither elevated liver-related laboratory results nor jaundice after discontinuing study drug.

The investigator reported that the increased ALT, but not the icterus, was possibly related to lapatinib. The event, Grade 4 ALT, was classified as serious, unexpected, and reportable for lapatinib.

The patient was on the combination of lapatinib plus paclitaxel for duration of 43 days. Her overall best tumor response as assessed by the investigator and independent review panel was partial response (PR) and stable disease (SD), respectively. The patient was still alive as of (b) (6). Written communication from the site noted that the patient has had severe heart failure and progressive disease; however, further attempts to contact the patient have been unsuccessful; the site has considered her to be "lost to follow-up".

GSK's internal liver safety panel adjudicated this case as: very likely drug-induced liver injury; lapatinib probable (most likely of all drugs & herbals).

Protocol Id: EGF30001
Investigator Number:
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Paclitaxel
Serious Events:

Patient 1558, a 42-year-old American Hispanic woman, was initially diagnosed with Stage III, HER2-negative breast cancer on (b) (6) hormone receptor status and prior anti-cancer treatment was not reported. Patient was diagnosed with Stage IV disease on (b) (6) with metastases to the bone, breast, chest wall, skin, and lymph nodes. She was randomly assigned to lapatinib 1500mg PO QD plus paclitaxel 175 mg/m² every 3 weeks on (b) (6) and administered first dose of the combination on the same day. The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 149.0cm and 49.5kg, respectively. She experienced Grade 1 AST, ALT, ALP, and anemia at screening; written communication received from the site on (b) (6) confirmed patient had hepatitis. An ECG performed at screening was noted as abnormal, but not clinically significant. She reported no other significant past or current medical conditions and no concomitant medications.

The patient received prophylactic ondansetron on (b) (6) prior to paclitaxel infusions. On (b) (6) 33 days after the start of the combination of lapatinib and paclitaxel, the patient experienced Grade 2 AST, ALT and hyperbilirubinemia and Grade 1 ALP (refer to Table 20 for corresponding laboratory results). Other reported AEs included intermittent Grade 1/2 exfoliative rash on her face and chest wall reported periodically between March and June 2005; Grade 2 anemia starting on (b) (6) (9.3 g/dL; normal range: (b) (6) g/dL); Grade 1 decreased appetite on (b) (6) and Grade 1 nausea on (b) (6). Because of the anemia, combination therapy was temporarily withheld and the patient was transfused 1 unit of RBCs on (b) (6). Laboratory results on (b) (6) showed an improvement in

AST, ALT and anemia to Grade 1, ALP remained the same, and TBL was within normal range. Her decreased appetite and nausea resolved on (b) (6)

The last dose of paclitaxel was administered on (b) (6). Per protocol, the patient continued treatment with single-agent lapatinib 1500mg QD. On (b) (6) 96 days after starting combination therapy, the patient experienced Grade 2 ALT, AST, and TBL, and ALP remained Grade 1. Eosinophils and albumin values at this time were within normal range. The patient permanently discontinued study drug with the last dose of lapatinib on (b) (6). Grade 2 ALT was reported by the investigator to have resolved on (b) (6) however, corresponding laboratory data were not available.

The investigator reported that all of the aforementioned non-serious AEs, except for decreased appetite, were possibly related to lapatinib.

The patient was on the combination of lapatinib plus paclitaxel for duration of 95 days. Her overall best tumor response as assessed by the investigator and independent review panel was SD. Written communication from the site confirmed that the patient has not had any progression of disease in the liver. The patient was still alive as of (b) (6) (b) (6)

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury (would be very likely drug-induced liver injury if liver chemistries improved within one month after 7June06), lapatinib probable, paclitaxel & ondansetron possible.

Protocol Id: EGF30001
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Paclitaxel
Serious Events:

This 50-year-old female subject was enrolled in an double-blind study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1500mg per day (cumulative dose of 10500mg) from (b) (6) and a single intravenous dose of Paclitaxel at 175mg/m² administered once every three weeks from (b) (6)

50-year-old Asian woman, was initially diagnosed with Stage III, HER2-positive, ER/PgR-negative breast cancer on (b) (6) and received neo-adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide for 3 cycles followed by a modified radical mastectomy. She then received adjuvant chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide for 3 cycles followed by radiotherapy to the left chest wall. Additional written communication received from the site on (b) (6) confirmed that patient received a cumulative dose of 180 mg/m² of doxorubicin in the neoadjuvant and adjuvant settings. The patient was diagnosed with Stage IV disease on (b) (6) with metastases to the lung and liver. Patient was randomly assigned to lapatinib 1500mg PO QD plus paclitaxel 175 mg/m² every 3 weeks on (b) (6) and administered first dose of the combination on the same day.

The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 149.0cm and 87.0kg, respectively. She reported Grade 1 hyperuricemia at baseline. She reported no concomitant medications prior to randomization into the study.

The patient received prophylactic ondansetron, ranitidine hydrochloride, and prednisolone prior to paclitaxel infusions (refer to table above for dates of administration). The last dose of paclitaxel was (b) (6). Per protocol, the patient continued treatment with single-agent lapatinib 1500mg QD. On (b) (6) 218 days after the start of lapatinib-based therapy, the patient experienced Grade 3 AST and ALT and Grade 1 hyperbilirubinemia (refer to Table 8 for laboratory results). Subsequent laboratory results reported on (b) (6) showed AST and ALT resolved to Grade 1 and TBL was within normal range.

Beginning (b) (6) the patient reported Grade 1 anorexia and vomiting which resolved on (b) (6) and (b) (6) respectively. On (b) (6) 514 days after the start of lapatinib-based therapy, the patient reported Grade 2 AST, ALT and TBL. Eosinophils and albumin values at this time were within normal range. Subsequent laboratory results reported in (b) (6) showed AST and ALT resolved to Grade 1 and TBL was either within normal range or Grade 1. These laboratory findings were not recorded as AEs; therefore, investigator's assessment of relationship to study drug is not known. The patient permanently discontinued lapatinib monotherapy because of radiological disease progression (new lesions in both lungs and new lymph nodes); her last dose was on (b) (6). Written communication received from the site on (b) (6) site confirmed that no progression or new lesions were noted in the liver at this time.

Other clinically significant AEs included Grade 3 diarrhea and Grade 1 mucositis reported on (b) (6) 6 days after the start of lapatinib and paclitaxel. The patient was hospitalized and treated with intravenous fluids and antibiotics. Combination therapy was temporarily held and the AEs resolved on (b) (6). The investigator considered both events to be related to lapatinib and paclitaxel. On (b) (6) 49 days after the start of lapatinib and paclitaxel, the patient developed diarrhea, epistaxis, and petechiae on the body and arms which was later diagnosed as scabies. The subject was hospitalized and treated with ciprofloxacin and metronidazole (note: metronidazole was administered for 3 days only and 6 months prior to evaluation of liver function test). Lapatinib was temporarily held. All events resolved by (b) (6) and all, but scabies, were considered to be related to the combination therapy.

The patient was on the combination of lapatinib plus paclitaxel for duration of approximately 5 months and on single-agent lapatinib for another 14 months. Her overall best tumor response as assessed by the investigator and independent review panel was SD and PR, respectively. The patient was still alive as of (b) (6).

Follow up information received from site on (b) (6)

Any medical history of hepatitis OR viral hepatitis serology examination results? At the time the patient was enrolled in this study, there was no medical history of Hepatitis. At the time, the hepatobiliary event was experienced during the course of study, viral

hepatitis serology was done for HBsAG, Anti-HCV and Anti-HCV, but the serology was negative. This hepatobiliary event was spontaneously resolved later on.

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury, lapatinib possible.

Protocol Id: EGF30001
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Paclitaxel
Serious Events:

This 64-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1500 mg per day from (b) (6) and intravenous paclitaxel from (b) (6).

A 64-year-old Asian woman, was newly diagnosed with Stage IV, HER2-positive, ER/PgR-positive breast cancer on (b) (6). Patient was determined to have metastases to the breast, liver, lung, lymph nodes, peritoneum, and pleura on (b) (6). She was randomly assigned to lapatinib 1500mg PO QD plus paclitaxel 175 mg/m² every 3 weeks on (b) (6) and administered first dose of the combination on the same day.

The patient's performance status at the time of enrollment was 1 on the ECOG scale. Her height and weight were 151.0cm and 52.0kg, respectively. She reported current medical conditions of Grade 1 upper abdominal pain, Grade 1 breast mass, Grade 1 hyperuricemia, and Grade 2 diabetes mellitus treated with glibenclamide. At screening, she experienced Grade 1 AST and ALP. Prior to the start of first dose of combination therapy, she had received a short course of cefradine and diclofenac sodium and received allopurinol which continued while on study.

While on combination therapy with lapatinib plus paclitaxel, she received periodic treatment with ondansetron, ranitidine hydrochloride, gabapentin, and dexamethasone. The last dose of paclitaxel was administered on (b) (6). Per protocol, the patient continued treatment with single-agent lapatinib 1500mg QD. She reported Grade 1 vomiting on (b) (6) and Grade 2 anorexia on (b) (6). Both AEs were considered not related to the study drug by the investigator and were reported as resolved on 13 and (b) (6) respectively. On (b) (6) 199 days after the start of the combination of lapatinib and paclitaxel, the patient experienced Grade 3 AST, Grade 2 ALT and Grade 1 ALP (refer to

Table 9 for laboratory results). She also had Grade 2 hypoalbuminemia. Eosinophils remained with normal range. Subsequent laboratory results on (b) (6) showed an improvement in ALT (Grade 1); however, AST and ALP remained the same and TBL was also elevated (Grade 3). The patient discontinued the study on (b) (6) with reason of consent withdrawn. Disease evaluation on (b) (6) showed

progression of disease in the lymph nodes. Additional written communication received from the site on (b) (6) confirmed that patient also had progression of disease in the liver. On (b) (6) TBL and ALT values were within normal range and AST improved to Grade 1; however, ALP value had increased (Grade 2). These laboratory findings were not recorded as AEs; therefore, investigator's assessment of relationship to study drug is not known. Additional written communication received from the site of (b) (6) confirmed that according to the investigator, the elevated AST was attributed to the progression of disease in the liver.

Patient was on the combination of lapatinib plus paclitaxel for duration of 285 days. Her overall best tumor response as assessed by the investigator and independent review panel was PR. The patient was still alive as of (b) (6)

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury, lapatinib probable, Diclofenac unlikely (5 day course).

Protocol Id: EGF30008
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Letrozole
Serious Events: Alanine aminotransferase increased

This 57-year-old female subject was enrolled in a blinded study for the treatment of metastatic breast cancer. The subject received oral investigational product at 1500 mg per day from (b) (6) and oral letrozole at 2.5 mg per day from (b) (6). Medical conditions at the time of the event included lung metastasis and pleural metastases.

On (b) (6) 113 days after the start of investigational product and letrozole, the subject developed grade 4 elevated alanine aminotransferase (ALAT). The event was clinically significant (or requiring intervention) as it was a CTC grade 4 non-haematologic toxicity. Further symptoms experienced included elevated aspartate aminotransferase (ASAT), elevated bilirubin and elevated gamma glutamyl transferase (GGT). On (b) (6) baseline laboratory results included ALAT: 18 u/l (normal 10 -35), ASAT: 24 u/l (normal 10 -35), Bilirubin: 0.69 mg/dl (normal < 1.10 mg/dl) and GGT: 17 u/l (normal < 39). On (b) (6) relevant laboratory test results included ALAT: 77 u/l (10 -35u/l). Ultrasound taken on (b) (6) revealed liver parenchyma composting. Treatment with investigational product and letrozole was temporarily discontinued on (b) (6) and then permanently discontinued on (b) (6) because hepatitis A & B serology was negative and elevated liver values had dropped down. On (b) (6) relevant laboratory test results included ALAT: 986 u/l (10 -35 u/l), Bilirubin: 1.87 mg/dl (normal < 1.10 mg/dl) and GGT: 267 u/l (normal < 39). On (b) (6) relevant laboratory test results included ALAT: 209 u/l (normal 10 - 35), ASAT: 119 u/l (normal 10 - 25), Bilirubin: 1.23 mg/dl (normal <1.10) and GGT: 203 u/l (normal <39).

On [REDACTED] (b) (6) alanine aminotransferase was 37.00 u/L, bilirubin was 0.79 mg/dL, alkaline phosphatase was 97.00 u/L and serum creatinine was 0.70 mg/dL.

On [REDACTED] (b) (6) the subject experienced bladder infection and was treated with nitroxoline. The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the elevated alanine aminotransferase may have been caused by investigational product and letrozole.

Follow-up received on [REDACTED] (b) (6)

The investigator stated that the subject was not a drinker. The subject was receiving no further concomitant medications. The subject was not taking any further antibiotic medications prior to the SAE. The investigator confirmed that the subject was not transfused with platelets/blood/Fresh frozen plasma (FFP), prior to the SAE. During the elevated enzymes, the subject experienced further symptoms of Nausea CTC grade 1. Ultrasound taken on [REDACTED] (b) (6) revealed parenchyma composting (not liver parenchyma composting). No further CT or MRI scan was done, to later evaluate the liver for mets. No Hepatic C serology was tested.

Follow-up received on [REDACTED] (b) (6)

Ultrasound taken on [REDACTED] (b) (6) showed the change of liver parenchyma: parenchymal opacities. The investigator updated the term "parenchyma composting" to parenchymal opacity. The subject had no liver mets. The investigator stated liver function had resolved on an unspecified date (the values were outside the normal range which was provided).

Follow-up received on [REDACTED] (b) (6)

The principal investigator reviewed the ultrasound taken on [REDACTED] (b) (6) and consequently updated the term "parenchyma composting (opacities)" to steatosis hepatis. The investigator stated liver function had resolved on [REDACTED] (b) (6). On [REDACTED] (b) (6) [REDACTED] (b) (6) Alanine aminotransferase (ALAT) was 40 U/l (normal 10 - 35).

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury, lapatinib very likely.

Protocol Id: EGF30008

Investigator Number:

Subject Number: [REDACTED] (b) (6)

Treatment Number:

Case Id: [REDACTED] (b) (6)

Suspect Drugs: Blinded trial medication, Letrozole

Serious Events:

This 74-year-old female subject was enrolled in a blinded study for the treatment of metastatic breast cancer. The subject received oral investigational product at 1500 mg

per day from (b) (6) and oral letrozole at 2.5 mg per day from (b) (6)

A 74-year-old Caucasian woman, was initially diagnosed with Stage II, ER/PgR-positive breast cancer on (b) (6) and underwent a modified radical mastectomy of the right breast on (b) (6). Patient was diagnosed with Stage IV disease on (b) (6). Sites of metastatic disease were pleura, bone, lung, and lymph nodes. She was randomly assigned to blinded study drug (lapatinib 1500 mg PO QD or placebo) plus letrozole 2.5mg QD on (b) (6) and administered first dose of the combination on the same day. The patient had not received any prior anti-cancer therapy or radiation therapy.

The patient's performance status at the time of enrollment was 1 on the ECOG scale. Her height and weight were 152cm and 53.0kg, respectively. At baseline, she reported Grade 2 chest pain and Grade 1 pericardial effusion and was taking the following medications at the time of screening: Seguril®, Adolonta®, Primperan®, Omeprazole, Ibuprofen, Toradol®, and Zometa®.

On (b) (6) 158 days after starting combination therapy, the patient experienced Grade 2 ALT and hyperbilirubinemia, and Grade 1 AST. On (b) (6) patient reported a Grade 1 weight (loss of 5kg from baseline). On (b) (6) 190 days after starting combination therapy, the patient experienced Grade 3 ALT and AST, and Grade 2 hyperbilirubinemia. On (b) (6) lapatinib/placebo was held and restarted on (b) (6). On (b) (6) the patient experienced Grade 2 ALT, AST, and hyperbilirubinemia. On (b) (6) ALT and AST increased (Grade 3) and hyperbilirubinemia remained the same (Grade 2). Patient also complained of Grade 1 diarrhea. Lapatinib/placebo was then held (b) (6) and restarted on (b) (6) at a reduced dose of 1250mg QD. On (b) (6) the ALT and AST improved to Grade 2. Patient continued on lapatinib/placebo at 1250mg and letrozole at 2.5mg QD. On (b) (6) the patient's weight had increased to 50.6 kg and no longer met grading criteria. The patient continued to have elevated ALT, AST, and TBL at subsequent lab visits from September 2005 to October 2005. Patient also reported Grade 2 asthenia and anorexia. On (b) (6) lapatinib/placebo was held and diarrhea from July resolved. A week later on (b) (6) patient experienced Grade 1 ALT and Grade 2 AST and hyperbilirubinemia. Lapatinib/placebo was permanently discontinued. Patient continued on letrozole alone until (b) (6) when the asthenia and anorexia resolved. Patient was discontinued from study due to disease progression on (b) (6) in the lung, pleura, and lymph nodes. Patient's ECOG status was 1 throughout the entire study. Eosinophils and albumin values remained within normal range during study treatment.

During the course of the study, patient discontinued the following concomitant medications that were started pre-study: Seguril® (discontinued on (b) (6)), Adolonta® (discontinued on (b) (6)), Primperan® (discontinued on (b) (6)), Omeprazole (discontinued on (b) (6)), Ibuprofen (discontinued on (b) (6)), and Toradol® (discontinued on (b) (6)). The following medications were started while the patient was on study: Fortasec® ((b) (6)), Almax® ((b) (6)), Influenza vaccine

(b) (6), and Auxina A+E (b) (6) and than again on (b) (6)

The investigator confirmed that the elevated liver function tests, which were non-serious AEs, were related to study drug; treatment assignment remains blinded.

The patient was on blinded study drug and letrozole for the duration of approximately 14 months. The patient is still alive as of (b) (6)

GSK's internal liver safety panel adjudicated this case as: probable drug-induced liver injury, lapatinib probable.

Protocol Id: VEG20007
Investigator Number:
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Pazopanib
Serious Events:

Patient 241, a 45-year-old Hispanic woman, was initially diagnosed with Stage III, poorly differentiated adenocarcinoma of the breast on (b) (6) no prior anti-cancer treatment was reported. At the time of screening, she had ER/PgR-positive, HER2-positive Stage IIIc disease without visceral involvement. Patient entered the study and began treatment with lapatinib 1000mg PO QD plus pazopanib 400mg QD on (b) (6) (b) (6)

The patient's performance status at the time of enrollment was 0 on the ECOG scale. Her height and weight were 144.0cm and 63.4kg, respectively. She reported the following medical conditions at baseline: obesity, hypertension, age-related macular degeneration, hyperbilirubinemia, hypocalcemia, decreased urea and increased chloride levels. She reported no concomitant medication at the time of study entry.

On (b) (6) 23 days after the start of lapatinib and pazopanib, the patient experienced slight elevations of ALT and AST (Grade 1) and Grade 2 hyperbilirubinemia. Liver function tests were further elevated in February 2007 with Grade 3 AST, Grade 2 ALT, and Grade 1 ALP reported on (b) (6) TBL was within normal range and was considered by the investigator to be resolved on (b) (6) (b) (6). The patient also reported Grade 3 neutropenia on (b) (6). The administration of study treatment was temporarily interrupted due to the elevated ALT level and neutropenia, both of which were considered by the investigator to be possible related to study treatment. The investigator reported Grade 1 ALP as resolved on (b) (6) (b) (6)

On (b) (6) lapatinib was decreased to 750mg QD and pazopanib to 200mg QD because of Grade 3 neutropenia which resolved on (b) (6)

In the beginning of [REDACTED] (b) (6) approximately 2.5 months after the start of lapatinib and pazopanib, the patient experienced hyperbilirubinemia (Grade 2) which continued to worsen to Grade 3 in [REDACTED] (b) (6) (refer to Table 23 for laboratory results). During these months, AST and ALT were also slightly elevated (Grade 1- 2). Of note, eosinophils and albumin level were within normal range throughout the duration of study treatment.

Lapatinib plus pazopanib was discontinued on [REDACTED] (b) (6). Hyperbilirubinemia was resolved on [REDACTED] (b) (6) however, AST and ALT levels remained slightly elevated (Grade 1) and the outcome is unknown. The patient experienced progression of disease in her left breast on [REDACTED] (b) (6).

The patient was on lapatinib plus pazopanib for duration of approximately 6 months. The patient was still alive as of [REDACTED] (b) (6).

GSK's internal liver safety panel adjudicated this case as: very likely drug-induced liver injury, lapatinib and pazopanib probable.

APPENDIX 3 NARRATIVES FOR 14 HEPATOBILIARY EVENTS WITH FATAL OUTCOME

Protocol Id: EGF100642

Investigator Number:

Subject Number:

Treatment Number:

Case Id:

Suspect Drugs: Lapatinib

Serious Events: Blood bilirubin increased, Gamma-glutamyltransferase increased

This 54-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. Medical conditions at the time of the event included liver metastases and metastatic breast cancer. Concomitant medications included biolactis, levofloxacin (Cravit), teprenone (Selbex), indomethacin (Inteban), gentamicin sulfate (Eltacin) and chlorhexidine gluconate (Hexizac). The subject's baseline ECOG performance status was 4. The subject received oral GW572016 at 1500mg per day from

On (b) (6) 7 days before starting GW572016, the subject had developed metastasis to the liver, pleural effusion and intrathoracic infiltration at registration. Laboratory test results showed increased alanine aminotransferase level 46 IU/L (normal range 7 - 30), increased aspartate aminotransferase level 62 IU/L (normal range 11 - 30), elevated blood alkaline phosphatase 1099 IU/L (normal range 115 - 359) and bilirubin levels of 0.5 mg/dL (normal range 0.3 - 1.0). The investigator did not consider these values to be serious however the subject was hospitalised at the start of the study. The subject received her first dose of investigational product GW572016 on (b) (6) On (b) (6) (b) (6) the subject was discharged at her own request.

On (b) (6) the subject's blood alkaline phosphate level was 6628 IU/L, CTC grade 3 and total bilirubin level was 3.9 mg/dL. The investigator did not consider a causality with the investigational drug, however progression of disease metastasis to the liver was suspected from the alkaline phosphatase level. Investigational product was temporarily suspended pending the CT results. Results of the CT scan showed a marked enlargement of metastasis to the liver and increased pleural effusion, which both led to progression.

On (b) (6) 62 days after the start of GW572016, the subject developed CTC grade 4 total bilirubin. This case was assessed as medically serious by GSK. Repeat test results showed total bilirubin level to be 12.4 mg/dL, blood alkaline phosphatase 6063 IU/L, alanine aminotransferase 89 IU/L, aspartate aminotransferase 152 IU/L. Gait disturbance was PS4 (performance status 4).

Investigational product GW572016 was interrupted on an unspecified date. The subject was treated with electrolytes (Electrolyte solution). Outcome was unknown at time of reporting. The investigator reported the grade 4 increased total bilirubin as unrelated to

treatment with GW572016. The investigator also considered the event to be possibly associated with the exacerbation of the underlying disease metastasis to the liver.

On receipt of follow-up the subject Gait disturbance was PS4 (performance status 4) on [REDACTED] (b) (6). On [REDACTED] (b) (6) the subject died of hepatic failure as a result of lung metastases exacerbation which was found prior to the study. The investigator commented that the symptoms of the abnormal biochemistry parameters the subject developed prior to death were an exacerbation of the underlying disease and unrelated to study medication GW572016.

On receipt of further follow-up (dated [REDACTED] (b) (6)) the investigator confirmed the subject had also developed elevated gamma-glutamyl transpeptidase levels on [REDACTED] (b) (6) (GGTP 986 IU/L; normal range 10 - 47), approximately 5 weeks after commencing investigational product. The event outcome was fatal. The investigator considered the event elevated gamma-glutamyl transpeptidase levels to be unrelated to GW572016.

On receipt of follow-up date [REDACTED] (b) (6) the investigator confirmed the event disease progression was not considered a serious event as per the protocol.

Protocol Id: EGF103009
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Abdominal sepsis, Hepatitis acute

This 37-year-old female subject was enrolled in an open-label study for the treatment of inflammatory breast cancer. The subject received oral lapatinib at 1500 mg per day from (b) (6). Concomitant medications included salbutamol sulphate.

On (b) (6) the subject complained of intermittent diarrhea and abdominal pain. Laboratory results from (b) (6) showed an aspartate aminotransferase of 393, an alanine aminotransferase of 247 and a lactate dehydrogenase of 3572 (normal ranges and units not reported). On (b) (6) 48 days after the start of lapatinib, the subject was hospitalized with differential diagnoses of abdominal sepsis, possible acute hepatitis and possible progression of disease. She also experienced diarrhea, intermittent abdominal pain and a low grade fever. The subject's bilirubin was within normal limits, but the lactate dehydrogenase and liver enzymes remained elevated. Relevant test results included a liver ultrasound performed on an unspecified date that showed a massive infiltration of the liver with a small amount of ascites. Treatment with lapatinib was interrupted on (b) (6). The events had not resolved at the time of reporting. The investigator considered that there was a reasonable possibility that the differential diagnoses of abdominal sepsis, possible acute hepatitis and possible progression of disease may have been caused by lapatinib and that the events were possibly due to the disease under study.

Follow-up information received (b) (6). The subject was admitted to the hospital on (b) (6) with elevated liver enzymes, hepatomegaly, ascites, dyspnea, fatigue and fever. A computed tomography scan showed multiple liver metastases, moderate ascites, and small pleural and pericardial effusions. The findings were considered to be consistent with progressive metastatic breast cancer. The subject was treated with antibiotics and anticoagulants. On (b) (6) her liver enzymes and bilirubin increased further, and the subject developed oliguric renal failure and worsening dyspnea. She then developed multi-system organ failure and expired on the evening of (b) (6).

Follow-up was received on (b) (6). The outcome of the abdominal sepsis, possible acute hepatitis and disease progression was reported as fatal. The subject expired on (b) (6) from the events.

Follow-up received on (b) (6). Disease progression was removed as an SAE.

Protocol Id: EGF103009
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Jaundice

This 41-year-old female subject was enrolled in an open-label study for the treatment of inflammatory refractory breast cancer. The subject received oral lapatinib 1500mg/day from (b) (6). Concomitant medications included thyroxine sodium, hexamidine isethionate, dexchlorpheniramine maleate and morphine sulphate.

On (b) (6) 145 days after the start of lapatinib, the subject developed Grade 4 icterus. The subject was hospitalised. She also experienced hepatic disease progression. Relevant test results included elevated transaminases with ALT value of 102U/L (normal value <50), AST value of 222U/L (normal value <50), raised alkaline phosphatase, 1180 U/L (normal range 60-275), GGT value of 380 U/L (normal range 11-64), total bilirubin value of 105 mg/l (normal value <10), lactate dehydrogenase value of 1182 UI/L (normal range of 200-480). Treatment with lapatinib was interrupted on (b) (6). The subject died on (b) (6). The investigator considered that there was a reasonable possibility that the icterus may have been caused by lapatinib and that the events were possibly due to progression of underlying disease and lack of efficacy of study medication.

Follow-up information, notes that a CT scan of the abdomen shows an increase in number and size of metastatic lesions in the liver with no segment of the liver considered free of lesions.

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Ascites, Jaundice

This 36-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject entered the study on (b) (6). The subject started treatment with oral lapatinib at 1250 mg once per day in combination with oral capecitabine at 3650 mg/m² once per day cyclically (days 1 to 14, every 21 days) on (b) (6).

On (b) (6) six days after the start of lapatinib and capecitabine, the subject developed ascites. On (b) (6) 12 days after the start of lapatinib and capecitabine, the subject developed jaundice. She also experienced hyperbilirubinemia, dyspnea, wide spread liver metastases and impaired liver function. Treatment with capecitabine was discontinued on (b) (6). Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study. On (b) (6) relevant test results included white blood cell count 18.7 k/ug, absolute neutrophil count 16, AST 2053 IU/L and ALT 474 IU/L. The subject died on (b) (6). (b) (6) cause of death was ascites and jaundice. An autopsy was not performed. Investigator causality was unknown at the time of reporting but the investigator considered that the events were possibly due to disease under study.

Follow-up received on (b) (6)

The events, ascites and jaundice were considered not to be related to the investigational product.

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Hepatic enzyme increased, Jaundice

This 33-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 80 mg twice per day from (b) (6). Concomitant medications included prednisolone. Medical conditions included palliation (general condition).

On an unspecified date in (b) (6) the subject developed grade 5 jaundice. On (b) (6) the subject was seen in the out-patient clinic and it was noted that in three weeks

she had lost 6kg in weight. She was jaundiced in both skin and eyes. The subject experienced grade 5 hepatic tests increased (increased liver enzymes). Relevant test results included ALAT: 7 u/l, Alkaline phosphatase: 671 u/l, ASAT:382 u/l and Bilirubin: 496 micromol/l. Treatment with lapatinib and capecitabine was discontinued on (b) (6) and the subject was withdrawn from the study. The subject was informed about hospice and terminal care at home. The subject died on (b) (6) at home, cause of death were jaundice and hepatic tests. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the jaundice and hepatic tests increased may have been caused by lapatinib and capecitabine and that the events were possibly due to the disease under study.

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Blood bilirubin increased

This 70-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 800 mg twice per day from (b) (6). The subject has no history of liver disease, did not smoke or drink, no history of drug abuse. Concomitant medications included aspirin and amoxicillin trihydrate.

On (b) (6) routine blood test revealed normal bilirubin of 17 umol/l (normal range less than 25). On (b) (6) 87 days after the start of lapatinib and capecitabine, the subject developed grade 3 or severe increased bilirubin. The subject's condition was good (she was asymptomatic) but her bilirubin slowly increased to 290 umol/L. Computed tomography of thorax and abdomen performed on (b) (6) showed that liver metastases were less than before, however two nodes in the left lobe had consolidated. The subject was hospitalised following the investigational CT and the event was disabling and life-threatening. An endoscopic retrograde cholangiopancreatography (ERCP) was attempted on (b) (6) but failed due to an oedema. ERCP was successfully performed on (b) (6) and showed no sign of obstruction. Liver MRI showed no metastatic or other obstruction. As investigations did not reveal any obstruction, the cause of increased bilirubin was considered to be a liver failure due to the tumour / disease progression.

Treatment with capecitabine and lapatinib were discontinued on (b) (6) and the subject was withdrawn from the study on (b) (6) due to disease progression. The subject has become more somnolent and was now bedbound (transition to palliative care on (b) (6) Investigations did not reveal any obstruction.

The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the increased bilirubin may have been caused by

lapatinib and capecitabine and that the event was possibly due to the disease under study and liver metastases.

The subject died on [REDACTED] (b) (6) Cause of death was not specified and it was unknown if an autopsy was performed.

Follow-up information received [REDACTED] (b) (6)

The subject's cause of death was reported to be hyperbilirubinemia, secondary to liver failure due to advanced breast cancer. An autopsy was not performed. Further information received from the CT imaging of the liver showed was convoluted, due to metastases, volume reduction of the right liver lobe and displacement. This in addition to ascites made the evaluation difficult. It was however evident that the biliary pathways in the left lobe are dilated and biliary paths were measured up to 8 mm in diameter centrally, probably due to tumor pressure centrally, though this could be confirmed from the CT images for definite. There was no dilation of the biliary system in the right liver lobe and the coledochus was normal. No sure sign of gallstones could be found. The investigator confirmed increased bilirubin was a factor in the subject's death. Bilirubin on [REDACTED] (b) (6) was 290 umol/l, on [REDACTED] (b) (6) 378 umol/l and on the day before the subject's death [REDACTED] (b) (6) 511 umol/l.

Follow up received [REDACTED] (b) (6)

This case was published in a literature article. There was no new information.

Published: De Placido S et al. Lapatinib Expanded Access Program (LEAP): Design, operation and initial safety data. Breast Cancer Research & Treatment 2007; 106:S273 Abstr. 6077.

GSK's internal liver safety panel adjudicated this case as: unlikely drug-induced liver injury.

Protocol Id: EGF103659
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Capecitabine, Lapatinib
Serious Events: Disease progression

This 61-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 1500 mg twice per day from (b) (6).

On (b) (6) 49 days after the start of lapatinib and capecitabine, the subject developed grade 5 disease progression. The subject was hospitalised with candidiasis. Treatment with lapatinib was discontinued on (b) (6). Treatment with capecitabine was discontinued on an unknown date. The subject died on (b) (6) due to liver failure and metastatic cancer. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the disease progression may have been caused by lapatinib and capecitabine and that the event was possibly due to disease under study.

GSK's internal liver safety panel adjudicated this case as: inadequate information.

Protocol Id: EGF104900
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Femoral neck fracture, Hepatic failure, Renal failure

This 73-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib from (b) (6) at dose 1500 mg daily.

On (b) (6) 27 days after the start of lapatinib the subject was hospitalised due to liver failure and renal failure. The subject was asymptomatic. The subject was also noted to have a fractured femoral neck. Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study. The subject died on (b) (6) due to hepatic and renal failure. It was unknown whether an autopsy was performed. The fractured femoral neck was ongoing at the time of death. The investigator noted that the subject was lost to follow up and no further information was available. The investigator considered that there was no reasonable possibility that the liver failure, renal failure and fractured femoral neck may have been caused by lapatinib.

Investigator text:

Patient is hospitalized due to hepatic and renal failure, further information will be provided when available. I am sorry, but the patient was lost to follow up as well as her relatives. Therefore no additional information can be provided. Furthermore: yes, I confirm, start date of Lapatinib was (b) (6)

Follow up information received from medical monitor on (b) (6)

A 73-year-old Caucasian woman was initially diagnosed with Stage IIIa ER/PgR-positive, HER2-positive (IHC 3+) adenocarcinoma of the breast on (b) (6). She was treated with neo-adjuvant FAC, left mastectomy, and then adjuvant paclitaxel and radiotherapy (b) (6). She underwent a resection of metastatic liver segment on (b) (6) and was treated with several chemotherapy agents. Her last dose of trastuzumab was on (b) (6). Patient was randomly assigned to lapatinib 1500mg PO QD and administered first dose on (b) (6).

The patient's performance status at the time of enrolment was 1 on the ECOG scale. Her height and weight were 160.0cm and 72.6kg, respectively. She reported hypokalemia, chronic kidney insufficiency, and coronary artery disease treated with antihypertensives and potassium. At screening, she had Grade 2 AST/ALT, Grade 3 ALP, and Grade 1 hyperbilirubinemia.

On (b) (6) she reported Grade 1 anorexia and fatigue, and Grade 2 diarrhea; anorexia and diarrhea were considered related to study drug by the investigator. On (b) (6) (b) (6) 22 days after starting lapatinib, she experienced Grade 1 pruritus and

weight loss, both of which were also considered related to study drug. On (b) (6) (b) (6) 28 days after the start of lapatinib, the patient was hospitalized with hepatic and renal failure. It was noted that she also had a fractured femoral neck. Lapatinib was discontinued on (b) (6) and she was withdrawn from the study. Patient subsequently died on (b) (6) due to hepatic and renal failure. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that these SAEs (hepatic failure, renal failure and fractured femoral neck) were related to lapatinib.

The patient was taking lapatinib for duration of 28 days. Two metastatic liver lesions were noted at screening; however, a subsequent tumor response assessment was not performed after baseline.

GSK's internal liver safety panel adjudicated this case as: inadequate information but a case of interest.

Protocol Id: EGF20008
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Gamma-glutamyltransferase increased

This 47-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. Medical conditions at the time of the event included liver metastases. The subject received oral lapatinib at 1500mg once daily from (b) (6) (b) (6)

On (b) (6) 58 days after the start of lapatinib, the subject developed increased gamma glutamyl transferase (GGT) of grade 4 toxicity (she had a baseline level of grade 3 toxicity for GGT). A laboratory value of 916U/L for GGT was noted (normal range of 5-46). Treatment with lapatinib was discontinued due to these events on (b) (6). The subject died on (b) (6). It is unknown whether an autopsy was performed. The investigator considered there was no reasonable possibility that the elevated GGT may have been caused by lapatinib. The investigator also considered the event to be possibly associated with progression of underlying disease.

Follow up received on (b) (6)

The outcome of increased GGT was fatal.

Protocol Id: EGF20009
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib

Serious Events: Hepatic failure, Hepatorenal syndrome, Peritonitis bacterial, Urinary tract infection

This 73-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. Medical conditions at the time of the event included liver metastases and a chronic non-alcoholic hepatopathy. The subject had no prior surgery, radiotherapy or systemic therapy for her cancer which was diagnosed (b) (6). No concomitant medications were taken during the clinical trial. The subject received oral lapatinib at 1000mg/day from (b) (6). Cumulative dose was 222,000mg.

On (b) (6) 62 days after the start of lapatinib, the subject presented with grade 2 diarrhea, grade 2 abdominal pain, grade 2 nausea, and grade 1 vomiting. The subject was hospitalized. On physical examination the subject's abdomen was painful on palpation in the renal ureteral zone. Relevant test results included a urinalysis that showed white blood cells in urine and several microorganisms. Other laboratory tests were within normal limits. She was diagnosed with urinary tract infection. Treatment with lapatinib was interrupted due to these events. The subject as treated with intravenous ceftriaxone, ranitidine and a anti-spasmodic (unspecified). Her abdominal pain improved 24 hours after treatment with ceftriaxone was begun. She was discharged from the hospital in stable condition on (b) (6) after which time ceftriaxone was to be continued until (b) (6). The events were considered resolved on (b) (6) after 2 days. The investigator considered there was no reasonable possibility that the urinary tract infection may have been caused by lapatinib.

The subject had interrupted lapatinib on (b) (6) due to the urinary tract infection and restarted study drug on (b) (6). On (b) (6) 66 days after the start of lapatinib, the subject developed spontaneous bacterial peritonitis. She was treated with intravenous cefepime at fixed doses once a day due to her liver and renal function. On (b) (6) (b) (6) 71 days after the start of lapatinib, the subject developed grade 2 abdominal pain and grade 2 jaundice. On (b) (6) she went to the emergency room where she was found to also have abdominal distension, and was admitted to the hospital. Computed tomography (CT) scan of the abdomen and thorax done on (b) (6) did not indicate any disease progression. However, laboratory evaluations revealed grade 3 liver dysfunction and she was diagnosed with liver failure. Albumin was 22 g/L (normal range: 38-50 g/L), conjugated bilirubin was 73 mcml/L (normal range: 0-5 mcml/L), unconjugated bilirubin was 60 mcml/L (normal range: 2-7 mcml/L), alamine aminotransferase was 117 u/L (normal range: 10-35 u/L), and asparate aminotransferase was 337 u/L (normal range: 10-40 u/L). She was treated with multiple medications. It was determined that the abdominal pain and jaundice as well as ascites which developed on (b) (6) were all related to the subject's liver failure which remained unresolved at the time of reporting. The ascitic fluid showed on microscopic examination gram negative bands. The fluid was cultured and the results were negative until after 72 hours. During hospitalization the subject's creatinine rose to 1.3 U/L on (b) (6) (b) (6). Her baseline creatinine was within normal limits. The subject also started to have oliguria. Due to the ascites, the subject needed oxygen supplementation. The investigator stated that, prior to starting lapatinib and at randomization on (b) (6) (b) (6) the subject had abnormal laboratory values for AST 346 U/L (Reference 0-55),

ALT 189 U/L (Reference 0-48) and alkaline phosphatase 254 U/L (Reference 20-125) which were grade 3. The samples were retested at an institutional laboratory before entering into the study and were grade 1. On review of the subject's laboratory work at screening, the AST value was 199 U/L, ALT 144 and alkaline phosphatase 187 U/L (all grade 2). The subject's liver enzymes remained at grade 1 until Week 34 when the subject was hospitalized for a urinary tract infection. On (b) (6) the subject developed hepatorenal syndrome and received medical management. She subsequently died at 22:00 hours on (b) (6) due to progressive hepatic disease. In the investigator's opinion, the event of liver failure was possibly attributable to lapatinib. The investigator also considered the liver failure to be possibly associated with treatment failure.

Upon follow-up the investigator reported the subject had received ceftriaxone daily from (b) (6) for a urinary tract infection that was not considered drug-related. She restarted lapatinib on (b) (6). The investigator stated the subject had non-alcoholic chronic hepatopathy prior to study entry. The subject received treatment for her liver metastases and her the liver enzymes decreased to the point where she had some values that were within the normal range. However, the chronic hepatopathy worsened and the subject developed liver cirrhosis, then ascites and portal hypertension, spontaneous bacterial peritonitis and hepatorenal syndrome all relating to the chronic hepatopathy.

Additional follow-up stated that the bacterial peritonitis and hepatorenal syndrome were also considered serious adverse events but were not related to the use of lapatinib.

Follow-up received (b) (6). The site confirmed that the spontaneous bacterial peritonitis began (b) (6).

Follow-up received on (b) (6). The start date of Lapatinib was corrected to (b) (6). The liver failure occurred 222 days after the start of investigational product and resulted in the permanent discontinuation of Lapatinib. The liver failure, bacterial peritonitis and hepatorenal syndrome were considered grade 5 and contributed to the subject's death, which occurred 250 days after the start of Lapatinib. On (b) (6) (b) (6) the subject also experienced hepatic encephalopathy.

GSK's internal liver safety panel adjudicated this case as: Unlikely drug-induced liver injury (likely liver cirrhosis).

Protocol Id: EGF30008
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number: (b) (6)
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Letrozole
Serious Events: Hepatic function abnormal

This 59-year-old female subject was enrolled in a blinded study for the treatment of metastatic breast cancer. The subject received oral investigational product per day from

(b) (6) and oral letrozole at 2.5 mg per day from (b) (6)

The subject was randomised to GW572016 arm of the study.

On (b) (6) 205 days after the start of investigational product and letrozole, the subject developed grade 2 or moderate hepatic dysfunction. The event was life-threatening. The subject also experienced deterioration of performance status. Laboratory test results showed increased alkaline phosphatase (1047 U/L), aspartate aminotransferase (AST) increased (216 U/L), alanine aminotransferase (ALT) increased (108 U/L) and hyperbilirubinemia (52 umol/L). Relevant test results on (b) (6) were elevated for alkaline phosphatase (1440 U/L, reference range 35-104); AST (528 U/L, reference range 9-31); ALT (253 U/L, reference range 6-30); bilirubin (8.99 mg/dL, reference range 0.1-1); direct bilirubin (5.74 mg/dL, reference range less than 3) and direct bilirubin (3.25 mg/dL, reference range 0.1-1). An MRI scan of liver revealed liver metastasis and edema. Treatment with investigational product and letrozole was discontinued on (b) (6). The subject has no concomitant medication. The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the hepatic dysfunction may have been caused by investigational product and letrozole and that the event was possibly due to liver failure.

Follow-up received (b) (6). The investigator reported that he believes the hepatic dysfunction was related to lapatinib because progression of disease had been ruled out after a computed tomography scan and liver magnetic resonance imaging showed stable liver metastases and parenchymal edema.

Follow-up received (b) (6). The site reported that the subject presented with nausea and lower extremity edema on (b) (6). The subject's liver enzymes remained elevated. The subject was hospitalized and treated with hydration, furosemide, albumin, and ranitidine. On (b) (6) the subject was evaluated by a gastroenterology specialist who suggested she avoid hepatotoxic drugs. Omeprazole was added to her treatment regimen. On (b) (6) the subject developed moderate pain in the right hypochondrium and was treated with ketoprofen. On (b) (6) the pain was under control and the edema had decreased. The subject remains hospitalized.

Follow-up received (b) (6). Laboratory results on (b) (6) included alkaline phosphatase of 569 IU/L (reference range 35-104), alanine aminotransferase of 169 U/L (reference range 6-30), aspartate aminotransferase of 530 U/L (reference range 9-31), total bilirubin of 44.4 mg/dL (reference range 0.1-1), direct bilirubin 36.9 mg/dL and indirect bilirubin of 7.2 mg/dL. The subject presented with symptoms of encephalopathy on (b) (6). She experienced clinical deterioration and died on (b) (6) at 06:40 am. No autopsy was performed.

Follow-up received on (b) (6)

The investigator considered an event of possible liver obstruction but could not confirm since there was no information related to biliary obstruction.

GSK's internal liver safety panel adjudicated this case as: possible drug-induced liver injury for which lapatinib was the probable suspect, and letrozole was unlikely.

Protocol Id: LAPAATU

Investigator Number:

Subject Number: (b) (6)

Treatment Number:

Case Id: (b) (6)

Suspect Drugs: Lapatinib

Serious Events: Disease progression, Hepatocellular injury, Respiratory distress

This female subject (subject number (b) (6)), received via cohort ATU ("temporary authorisation for use") oral lapatinib (Tykerb) for the treatment of metastatic breast carcinoma. She had disease progression following one prior chemotherapy with anthracycline, taxane and trastuzumab containing regimens.

The subject received lapatinib tablets (daily dose not specified) from an unspecified date.

At an unknown time after the start of lapatinib, the subject developed disease progression. Then, on (b) (6) treatment with lapatinib was discontinued. On (b) (6) (b) (6) the subject died due to disease progression.

The last information was received on (b) (6)

The investigator considered the event as unrelated to treatment with lapatinib.

Follow up received on (b) (6)

This case has been assessed as unexpected according to the French ATU cohorte SmPC.

Additional information received on (b) (6) after data reconciliation (from subject's CRF, as the subject was included in LAPS study) :

On (b) (6) the subject developed disease progression with respiratory distress and hepatocellular insufficiency. She was hospitalised.

The subject died on (b) (6)

The investigator considered the events as related to the subject's breast cancer.

Protocol Id: LAPAATU

Investigator Number:

Subject Number: (b) (6)

Treatment Number:

Case Id: (b) (6)

Suspect Drugs: Capecitabine, Esomeprazole, Lapatinib, Lithium carbonate, Lormetazepam, Morphine

Serious Events: Cytolytic hepatitis, Encephalopathy, Febrile neutropenia, Jaundice cholestatic, Sepsis

This 51-year-old female subject (subject number (b) (6)), received via cohort ATU ("temporary authorisation for use") oral lapatinib (Tykerb) and oral capecitabine (Xeloda) for the treatment of metastatic breast carcinoma. It was reported that the subject was polymedicated (self-medication) with lithium carbonate (Teralithe), morphine (Skenan), lormetazepam (Noctamide) and esomeprazole (Inexium). She had disease progression following several prior chemotherapy with anthracycline, taxane and trastuzumab containing regimens.

The subject received oral lapatinib, 1250 mg daily, from (b) (6) and oral capecitabine, 2000 mg daily (cyclic), from (b) (6)

On (b) (6) approximately 15 weeks after the start of lapatinib and capecitabine, the subject was found at home. She had hyperthermia, encephalopathy and obstructive jaundice. Arterial blood pressure was at 90/70 mmHg and she had tachycardia. Microbiological investigations and general check-up were performed. The subject had cytolysis with transaminases upper than 1000 IU/l, total bilirubin increased and neutrophils at 90 /mm³. The patient was transferred in intensive care unit. All drugs were discontinued. Treatment by triple antibiotherapy and rehydration was initiated.

On (b) (6) the subject died. The death was related to the reported adverse effects. The investigator reported liver cytolysis, obstructive jaundice and encephalopathy as possibly related to treatment with lapatinib and/or polymedication.

According to the reporter the relation between lapatinib and febrile neutropenia and sepsis was unknown. Febrile neutropenia and sepsis might have been due to chemotherapy.

Follow up received on (b) (6)

This case has been assessed as unexpected according to the French ATU cohorte SmPC.

Protocol Id: VEG20007
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Hepatic failure

This 36-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1500 mg per day from (b) (6)

On (b) (6) 382 days after the start of lapatinib, the subject developed grade 5 liver failure. The subject was hospitalised. She also experienced nausea, vomiting, abdominal pain (with no tenderness), pallor, decreased appetite, ECOG 2 and worsening of general condition. Relevant test results on (b) (6) included hemoglobin of 7.6 gm%, alanine aminotransferase of 113 U/L, aspartate aminotransferase of 310 U/L, total bilirubin of 1.7 mg/dL and alkaline phosphatase of 513 U/L. The subject's prior CT scan on week 52 visit showed a solitary ill-defined liver lesion and her liver function test have mild derangement (results not provided). Treatment with lapatinib was interrupted. The outcome of the event was fatal as the subject died on (b) (6). It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the liver failure may have been caused by lapatinib.

Follow-up received on (b) (6)

The subject's ultrasound showed evidence of chronic liver disease with chronic calculus cholecystitis and also had mild liver enzymes elevation prior to her death. The subject died of fulminant hepatitis/hepato-renal syndrome which was due to viral hepatitis. The subject was on lapatinib therapy until the time of death. In the absence of serology tests, the investigator considered that it was viral hepatitis because of the combination of shrunken, cirrhotic liver on ultrasound and the prevalence of viral hepatitis in the region and the fulminant course. The subject had no history of alcohol abuse to account for the cirrhosis.

Follow-up was received on (b) (6)

The subject died at a local hospital. No autopsy was performed.

GSK's internal liver safety panel adjudicated this case as: possible drug-induced liver injury but very atypical.

APPENDIX 4 NARRATIVES FOR 7 CASES OF HEPATIC FAILURE

See appendix 3 for narratives for the following cases:

(b) (6) EGF20009/Subject (b) (6)
(b) (6) EGF30008 (b) (6)
(b) (6) VEG20007/Subject (b) (6)
(b) (6) EGF103659/Subject
(b) (6) EGF103659/ Subject
(b) (6) EGF104900/Subject

Case Id: (b) (6)
Suspect Drugs: Lapatinib
Serious Events: Hepatic failure

This case was reported by a physician and described the occurrence of liver failure in a 59-year-old female patient who received Lapatinib (Tykerb) tablet for breast cancer.

On an unknown date, the patient started Lapatinib (oral) at 1250 mg daily. In (b) (6) (b) (6) Lapatinib, the patient experienced complete liver failure. The patient was hospitalised and placed in the intensive care unit. The physician considered the event to be disabling and clinically significant (or requiring intervention). Treatment with Lapatinib was discontinued. At the time of reporting, the event was unresolved.

Physician reported that the patient presented to their emergency department approximately one week prior to reporting with complete liver failure. Tykerb was discontinued in this patient one week prior to reporting and has not been reinstated. The physician did not know whether Tykerb was the cause of this patient's liver failure. There was no additional information provided.

GSK's internal liver safety panel adjudicated this case as: inadequate information.

APPENDIX 5 DISPROPORTIONALITY ANALYSIS

Spontaneously reported adverse event data are difficult to assess quantitatively because they are derived from voluntary reports and lack a reliable denominator. Statistical methods based on disproportionality of adverse event reporting are applied to spontaneous reporting databases to assess the relative reporting of a drug-event combination against the background of the entire database.

Data Mining Algorithm: MGPS

MGPS (Multi-Item Gamma Poisson Shrinker)^{1,2} is an empirical Bayes data mining algorithm and GSK's preferred method for disproportionality analysis (DPA) of post-marketing adverse event data in spontaneous reporting databases. MGPS uses information for all drugs and all events in a given database to compute the Empiric Bayes Geometric Mean (EBGM) for each observed drug-event combination in that database. EBGM values are adjusted estimates of relative reporting ratios (i.e., observed reporting rate / expected reporting rate) after Bayesian "shrinkage." An EBGM value of 5 is interpreted to mean that a drug-event combination has been reported at least 5 times as frequently as would be expected if reports involving the drug and reports of the event were independent (i.e., no reporting association). MGPS also computes the 2-sided 90% confidence interval (EB05, EB95) for each EBGM value.

The computations within MGPS are internally stratified, using a Mantel-Haenszel approach,³ by age, gender, and year of report. Stratification minimizes the detection of apparent drug-event associations that may be due to independent relationships between a drug and a stratum variable and an event and the same stratum variable. (An example is the reporting association between a drug used commonly in the elderly and an event commonly reported in the elderly.) Stratification by year of report reduces the chance of detecting signals that might arise due to "trendiness" in the reporting of specific drugs and/or events.

MGPS can compute EBGM values in two ways on the basis of how the reporter classified the drug at the time of reporting - as "suspect" or "concomitant." The "Suspect Only" computation includes drugs identified by the reporter as suspect. The "Suspect and Concomitant" computation includes all drugs in the adverse event report.

Adverse Event Reporting Databases: OCEANS and AERS

¹ DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system (with discussion). *Am Stat* 1999; 53 (3): 177-202.

² DuMouchel W, Pregibon D. Empirical Bayes screening for multi-item associations. *Proc KDD 2001*, San Diego, CA, ACM Press.

³ Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-48.

OCEANS is GlaxoSmithKline's worldwide safety database. OCEANS contains spontaneous adverse event reports from worldwide sources for GSK's marketed products, as well as serious adverse event reports from clinical trials of GSK compounds in development. Disproportionality analyses of OCEANS data are applied only to spontaneous adverse event reports for marketed non-vaccine products; clinical trials reports are not considered in the analyses.

AERS (Adverse Event Reporting System) is the safety database of the U.S. Food and Drug Administration (FDA). AERS is a passive surveillance system that relies on voluntary reporting of adverse events to FDA by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufacturers. AERS includes all spontaneous reports from US sources; serious and unlabeled spontaneous reports from non-US sources; and serious, unlabeled, and attributable post-marketing clinical trial reports from all sources. At GSK, DPA is run against quarterly public-release versions of AERS, as provided by a third-party vendor. The public-release versions of AERS may not contain all reports received by the FDA due to delays in data entry and prioritization of data entry.

Interpretation and Limitations of Disproportionality Analysis

DPA provides information about the relative reporting of adverse events in the post-marketing setting. DPA does **not** provide estimates of the incidence of adverse events.

A high relative reporting ratio (high EBGM value) indicates that there is an *association* between a drug and an event in a given database. A causal relationship between the drug and the event is only one of the possible explanations for the association; DPA alone cannot identify the nature of the association. High relative reporting ratios may be seen when events are actually related to medical conditions or co-prescribed drugs, or when adverse event reporting has been stimulated in some way (e.g., publicity, Dear Doctor letters, litigation). For these reasons, high relative reporting ratios are interpreted as hypotheses regarding potential causal associations between drugs and events. The U.S. FDA has used $EB05 \geq 2$ as a threshold for signal detection.⁴

A low relative reporting ratio indicates that a drug-event pair has not been reported more frequently than expected. It does not guarantee the absence of a causal relationship between a drug and an event.

Comparisons of relative reporting ratios between drugs should be made cautiously and should be interpreted as hypothesis-generating rather than confirmatory. A number of factors other than causality may affect the reporting frequencies of adverse events for a drug of interest or drugs in the same class, including the length of time on the market, labelling changes, and publicity. Awareness of potential reporting biases is critical when making comparisons.

⁴ Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* 2002; 25 (6): 381-92.

Global Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Lapatinib: Hepatotoxicity

Date of review	30-Sep-2008
Drug terms included	Project ID = '016' and/or Drug Preferred Term code = 'AZZ071'
Adverse events (MedDRA*preferred terms) included	MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ, MedDRA v11

*See Appendix 1 for full list of abbreviations

1. EXECUTIVE SUMMARY

- As of August 2008, approximately 16,251 subjects have been enrolled in the lapatinib programme, of which 12,309 subjects are estimated to have received lapatinib.
- Lapatinib was first approved for marketing in the USA on 13 March 2007. It is estimated that approximately 3599 patient years of lapatinib treatment have been prescribed worldwide as of June 2008. This calculation is based on available sales information volume and assuming a daily dose of 1250mg.
- Laboratory data from 24 ongoing studies (all phases) indicated that the most common LFT elevations were elevation of ALT and/or AST $\geq 3x$ ULN but below 5x ULN. The majority of LFT elevations took place in subjects with first line or recurrent breast cancer, and in subjects who received lapatinib in combination with other chemotherapies.
- A small increase in reporting of serious hepatobiliary adverse events is evident from all report sources. These changes may be attributed to an increased awareness and reporting of hepatobiliary events following the circulation of the Dear Investigator/Healthcare provider letters, and the addition of hepatobiliary stopping criteria to study protocols leading to an increase in reporting of hepatobiliary events.
- Amongst an estimated 8,597 subjects receiving lapatinib in metastatic cancer studies:
 - There were a total of seven cases of hepatic failure, an association with lapatinib was adjudicated as possible in two of these cases, although one case was very atypical. This gives an estimated incidence of 0.02 to 0.08% (2 or 7 total cases/8597) for hepatic failure in the metastatic cancer setting.

- The estimated incidence of possible Hy's law cases was 0.13 to 0.2% (11 or 16 total clinical trial cases/8597) for lapatinib subjects in the metastatic setting.
- These figures are consistent with those previously reported for lapatinib subjects treated in the metastatic setting.
- Amongst an estimated 3336 subjects who will have received lapatinib in the adjuvant cancer setting there were a total of seven possible Hy's law cases, of which three have been adjudicated as possibly drug related. This gives an estimated incidence of 0.1 to 0.2% (3 or total 7/3336) for possible Hy's law cases amongst subjects treated in the adjuvant setting. This includes one event of severe liver injury with compromised synthetic function, very likely related to lapatinib use, which resolved with lapatinib cessation.
- An external Advisory Board composed of hepatologists and oncologists reviewed safety data from the adjuvant breast cancer programme, including data from lapatinib and pazopanib combination studies. They concluded that the benefit:risk remained favourable in both cases. The advisory board was comfortable with the hepatic monitoring and stopping criteria which have been implemented across the study programmes.
- A retrospective epidemiological study of LFT elevations from completed oncology studies (iNET) demonstrated that elevated liver enzymes were rare. Cumulative incidence of new Hy's Law cases (defined as AST or ALT >3 xULN & BILI >2 xULN, normal ALP) occurring during study treatment was 0.09% in subjects without liver metastases, and 0.37% in subjects with liver metastases. The 0.1 to 0.2% incidence of possible Hy's law cases on the lapatinib clinical programme is consistent with the findings from these epidemiological studies.
- GSK conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

2. BACKGROUND

A review of hepatobiliary events as well as hepatobiliary laboratory abnormalities in the lapatinib clinical program was completed in March 2008 (UM2008/00097/00). The review demonstrated that hepatobiliary events associated with lapatinib monotherapy had a time to onset suggestive of a drug related effect. Furthermore there was evidence of positive dechallenge on treatment discontinuation and a small number of positive rechallenges when lapatinib was reintroduced. Hepatic laboratory abnormalities possibly meeting Hy's law were also present although most were confounded by study disease and concomitant medications. There was a comparable incidence of hepatobiliary events in the metastatic cancer setting and the adjuvant breast cancer setting. Based on these results GlaxoSmithKline (GSK) concluded that there was a possible causal association between hepatotoxicity (specifically severe liver injury and transaminase elevations) and lapatinib treatment, therefore the lapatinib core safety information (CSI) was updated to include these events.

The purpose of the current review is to provide a status update on lapatinib and hepatobiliary events, and to determine whether any updates to the core safety information (CSI) for hepatobiliary events are required.

3. EXPOSURE TO DRUG

As of August 2008, approximately 16,251 subjects have been enrolled in the lapatinib programme, of which 12,309 subjects are estimated to have received lapatinib. An additional 615 subjects are estimated to have received lapatinib whilst enrolled in studies as part of the pazopanib programme.

Of these 16,251 subjects, a total of 5314 have been enrolled in ongoing studies in the adjuvant breast cancer setting. Amongst these adjuvant subjects, it is estimated that 3193 subjects will have received lapatinib. Exposure in the metastatic cancer setting (including breast, colorectal, gastric, non small cell lung, and head and neck cancers) is estimated as 10,287 subjects, of which 8597 will have received lapatinib.

Lapatinib was first approved for marketing in the USA on 13 March 2007. It is estimated that approximately 3599 patient years of lapatinib treatment have been prescribed worldwide as of June 2008. This calculation is based on available sales information volume and assuming a daily dose of 1250mg.

4. SAFETY DATA REVIEWED

This evaluation presents relevant information on reports of hepatotoxicity using laboratory data from the GSK clinical trials database, and serious adverse event (SAE) data from the GSK worldwide safety database. Data presented was received after the cut off used for the previous hepatobiliary review update (UM2008/00234/00).

Reports of possible Hy's law cases, fatal hepatic events and hepatic failure were medically reviewed and adjudicated by GSK's internal liver safety panel.

4.1. Reports from the GSK Clinical Trials database

In the current review, laboratory data on the clinical trials database from 24 completed or ongoing studies (5 phase I, 19 phase II/III) were reviewed. Completed studies included in the previous review were excluded from the current review of laboratory data unless additional data was received. All serious hepatobiliary events and possible Hy's law cases from these studies are included on the GSK safety database, and are therefore part of the dataset reviewed in section 4.2.

Laboratory data from these 24 studies were reviewed for the incidence of transaminase elevations, and for subjects whose transaminase elevations may meet Hy's law:

- AST or ALT >3x ULN and total bilirubin >2x ULN with no initial findings of cholestasis (that is, alkaline phosphatase activity $\leq$ 2x ULN) [FDA, 2007].

Since the majority of reports were in the setting of metastatic cancer, some cases had alkaline phosphatase values higher than 2x ULN, also information on fractionated bilirubin was rarely available. These reports have been included in the category “possible Hy’s law cases” for completeness.

As of August 2008, a total of 3,920 subjects have been enrolled in these 24 studies, of which 2,568 subjects are estimated to have received lapatinib and 1352 subjects will have received either placebo or comparator.

4.1.1. Data from Phase I Studies

A review of the clinical trials safety databases from five ongoing lapatinib Phase I studies was undertaken (4 phase I trials plus 1 phase I extension study, 88 subjects in total). All five studies were in cancer patients (including breast, colorectal and solid tumours), using lapatinib as monotherapy and in combination with other chemotherapeutic agents. Subjects were also receiving a variety of concomitant medications. Liver function entry criteria varied from normal (healthy volunteer studies) to 5x ULN (subjects with refractory solid tumours with liver metastases).

The overall incidence of AST or ALT elevation above 3x ULN in these five studies was 5.7% (5/88), without taking into consideration baseline liver function test (LFT) measurements. Four of these five subjects had normal ALT/AST ($\leq 1x$ ULN) at baseline, but developed AST or ALT $>3x$ ULN post baseline (4.5%; 4/88) during study treatment.

There were no fatal hepatobiliary events, or reports of hepatic failure in this group of studies. There were no new cases which met the liver chemistry criteria of ALT $>3x$ ULN and bilirubin $>2x$ ULN suggesting possible Hy's law events.

4.1.2. Data from Phase II/III Studies

A total of 2738 LFT abnormalities were reported from a total of 3845 subjects ([See appendix 2](#)). Of these 3845 subjects, 1297 are known to have received lapatinib either as monotherapy or in combination with chemotherapy. In terms of events, 14.4% of these LFT abnormalities occurred in subjects who received lapatinib as monotherapy, and 85.6% occurred in subjects who received lapatinib as combination therapy. The majority (90.4%) of LFT abnormalities occurred in subjects with 1st line or recurrent metastatic breast cancer, as compared to a total of 3.2% LFT abnormalities occurring in patients with head and neck cancer treated with curative intent. The remaining 6.4% of events occurred in subjects with other tumours.

Nine subjects (0.2%) from these 19 studies had LFT abnormalities which possibly meet Hy’s law. Six subjects, received lapatinib as combination therapy (bevacizumab, capecitabine, pazopanib, paclitaxel, or trastuzumab), none received lapatinib as monotherapy. One subject received blinded study medication in combination with cisplatin. The remaining two events occurred during study screening before the subjects were treated. One of these nine subjects was treated for first line advanced breast cancer, seven subjects were treated for metastatic breast cancer, and the remaining subject was treated for head and neck cancer.

The most common LFT abnormalities were elevation of ALT &/or AST $\geq 3x$ ULN but below $5x$ ULN (7.7% and 8.7% respectively). Again the majority of the LFT abnormalities took place in subjects with breast cancer. Amongst subjects who received lapatinib monotherapy, the estimated incidences of these LFT abnormalities were 5% and 4.7% respectively.

Elevation of bilirubin only (evidence of cholestatic injury) was seen in 8.5% (327/3845) of subjects with bilirubin $>1.5x$ ULN, and 4.3% (176/3845) of subjects with bilirubin $>2x$ ULN, regardless of treatment. However, of these bilirubin abnormalities 15% and 9% respectively were reported from lapatinib monotherapy studies.

The most frequent LFT abnormality was elevation of ALP $>1.5x$ ULN, which had an incidence of 22.9% (881/3845) in all subjects, regardless of treatment. Of these ALP elevations, 18.3% (162/881) occurred in subjects who received lapatinib monotherapy.

Based on this data, GSK concluded that:

- the incidence of Hy's Law events was similar to that reported in the previous hepatic evaluations, although none of the events occurred with lapatinib monotherapy
- a higher incidence of LFT abnormalities were observed in subjects with advanced disease, and in combination with chemotherapy
- there was generally a low incidence of LFT abnormalities from head and neck cancer trials, mainly elevations of ALT &/or AST.

4.1.3. Possible Hy's law cases

Review of the laboratory data from these 24 studies identified a total of two possible Hy's law cases which were not included in the GSK safety database:

- EGF102988 subject (b) (6) a 74 year old male received blinded investigational product with cisplatin and radiotherapy, for head and neck cancer. He received concomitant Nexium, Olmetec and Pentalong. Liver function test values began rising at week one. Nine days after the start of investigational product the subjects liver function tests were: ALT 188.2 IU/l, AST 30.6 IU/l, alkaline phosphatase 144 IU/l, and total bilirubin 100.9 umol/l. At the following study visit LFTs were: ALT 33.5 IU/l, AST 21.6 IU/l, alkaline phosphatase 100.7 IU/l, and total bilirubin 19.4 umol/l. Study medication was stopped. GSK consider there is insufficient data to assess this case at present and further information is being sought.
- EGF103890 subject (b) (6) a 50 year old female subject received lapatinib at 1500mg daily with bevacizumab (10mg/kg IV every 2 weeks). Twenty three weeks after the start of investigational product the subjects liver function tests were: ALT 223 IU/l (normal ULN 54 IU/l), AST 164 IU/l (normal ULN 41 IU/l), alkaline phosphatase 189 IU/l (normal ULN <111 IU/l), and total bilirubin 61.6 umol/l (normal ULN 1.3 umol/l). Fatigue and dry skin were ongoing

adverse events. Study medication was stopped. GSK consider this is a possible Hy's law case.

Narratives for these two cases are included in [Appendix 3](#).

In addition one case was identified from a subject (EGF100151/ (b) (6)) who received lapatinib+capecitabine combination in study EGF100151 and met the Hy's law criterion for elevated ALT and bilirubin, however data on ALP was not available. Follow-up on this case is ongoing.

4.2. Reports from the GSK Worldwide Safety Database (OCEANS)

The previous review (UM2008/00234/00) included cumulative SAE data from the safety database up to a cut off of 10-Apr-2008. The current review evaluates data received since the last review, for the period 11-Apr-2008 to 14-Aug-2008.

4.2.1. Database Search Strategy

The GSK worldwide safety database was searched on 21-Aug-2008 using the following criteria:

- **Data lock point(s):** *reports received from 11-Apr-2008 to 14-Aug-2008*
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and serious clinical trial reports (attributable and non-attributable). *Lapatinib* was reported as a suspect drug, or the case was from a lapatinib study, or a study where lapatinib was used.
- **MedDRA preferred term(s):** *MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ, MedDRA v11.*

4.2.2. Summary of Overall Dataset

A total of 84 cases were retrieved from the GSK worldwide safety database during the period covered by this report. Of these reports:

- 98.8% (83/84) had a healthcare professional (HCP) as a report source.
- The majority were received from USA, 16.76% (14/84), Germany and France, both 14.3% (12/84).
- 92.9% (78/84) met the criteria for a serious adverse event report, although seriousness may have been the result of an event other than a hepatobiliary event.
- Subject profile – the majority (91.7%, 77/84) of subjects were female, this is because the majority of lapatinib studies are in the breast cancer indication. Subjects ranged in age from 32 to 83 years (median age 53 years).

- The most frequently reported hepatobiliary events were: alanine aminotransferase increased (19 events), blood bilirubin increased (15 events), aspartate aminotransferase increased (12 events), and jaundice (11 events).

4.2.3. Case Evaluation

When conducting an evaluation, it is GSK practice to review all reports of an adverse event retrieved from the GSK worldwide clinical safety database. This section presents a detailed summary of this evaluation, however, copies of all reports can be made available upon request in CIOMS I report format.

Due to the nature of spontaneous reporting there will always be some cases that contain insufficient information for assessment, despite adequate follow-up measures. Also, there will be other cases for which it becomes evident on clinical review of the information provided by the reporter, that the reported event is not consistent with the diagnostic criteria for that term (the latter category does not include reports for which there is no accompanying description of the event). Table 1 summarises the number of unassessable cases of hepatobiliary events associated with lapatinib therapy and also those that are considered inconsistent with the diagnostic criteria/definition.

Table 1 Cases containing insufficient information for assessment and cases inconsistent with the reported term (5 reports)

Reason	Number of Reports
Very poorly-documented cases providing no details about the event (i.e., no time to onset, duration, or outcome) AND no details about the patient other than age or gender AND no dechallenge or rechallenge information or otherwise clinically unevaluable cases due to inadequate documentation	2
Description of the event is inconsistent with diagnostic criteria/definition	3

A total of 5 cases were therefore screened out of the dataset. Two cases were very poorly documented and therefore clinically unevaluable, chiefly due to lack of information on the reported liver events, e.g. no liver function test data. In three cases the reported event diagnoses (renal failure, anaemia, anorexia) were inconsistent with a diagnosis of a drug-induced liver event.

Similarly, there are cases which document other **very much more likely** causes of the adverse event (e.g., concurrent medical conditions or other treatments), when time to onset or other clinical observations are taken into account. These are summarised in [Table 2](#).

Table 2 Cases with other very much more likely causes than treatment with lapatinib (20 reports)

Reason*	Number of Reports
Alternative diagnosis or concurrent disease is <i>very much more likely</i> to have caused the event, based on reported time to onset or other clinical observations	17
Concurrent drug is <i>very much more likely</i> to have caused the event, based on reported time to onset or other clinical observations	3

* Although theoretically some reports could have been assigned to more than one category, only one was allocated to each case and this was the first appropriate reason as listed above.

A total of 17 cases were considered to be confounded by an alternative diagnosis or concurrent disease. Examples included tumour-related confounding factors (e.g., progression of liver metastases, ascites, and cholelithiasis). These cases were confounded on the basis of the subject's disease course while on treatment, rather than the presence of pre-existing liver metastases at baseline. Three cases concerned clinical trial subjects who received comparator only.

Of the 84 cases in the overall dataset, 25 fulfilled the criteria for inclusion in [Table 1](#) or [Table 2](#). The remaining 59 cases have been further reviewed and the available data are summarised in [Table 3](#).

Table 3 Characteristics of Remaining Cases (N = 59)

Patient Age (n, %)	Range	years	32 - 77
	Median	years	54
Patient Gender (n, %)	Male	n (%) ²	4 (6.8)
	Female	n (%) ²	55 (93.2)
Report Type	Spontaneous Reports	n (%)	8 (13.6)
	Serious Clinical Trial Reports	n (%)	43 (72.9)
	Post Marketing Surveillance Reports	n (%)	8 (13.6)
Report Source	Health Care Professional	n (%)	58 (98.3)
	Consumer	n (%)	1 (1.7)
Time to Onset of Event (n = 56, 94.9%) ¹	Range	days	6 - 673
	Median	days	55.5
Outcome (n, %) ¹ (55, 93.2%)	Fatal (due to event)	n (%) ²	4 (7.3)
	Unresolved	n (%) ²	19 (34.5)
	Resolved	n (%) ²	19 (34.5)
	Improved	n (%) ²	13 (23.7)
Rechallenge (n, %) ¹ (4, 6.8%)	Positive	n (%) ²	3 (75)
	Negative	n (%) ²	1 (25)
Dechallenge (n, %) ¹ (53, 89.8)	Positive	n (%) ²	28 (52.8)
	Negative	n (%) ²	20 (37.7)
	Outcome of dechallenge unknown	n (%) ²	5 (9.5)

1. Number and percentage of reports with available data
2. Number of reports with available data was used as the denominator

Amongst these 59 remaining cases, 55 subjects are known to have received lapatinib, 12 as monotherapy, and 43 in combination with other chemotherapeutic agents (capecitabine, letrozole, paclitaxel, pazopanib, or trastuzumab). The daily dose of lapatinib ranged from 750mg to 1500mg once daily. Four cases remain blinded.

Amongst the 28 cases where there was a positive dechallenge (event resolved/improved) on drug discontinuation, lapatinib alone was discontinued in 10 cases, there were 9 cases with a complicated dechallenge (lapatinib and combination therapy both withdrawn), and 9 cases for which it is unclear whether lapatinib and/or the combination therapy were withdrawn. There were four reports of rechallenges during this reporting period, three came from the French ATU programme (PMS use), and one from a collaborative research study (Cherlob). Three of four rechallenges were positive.

Of these 59 cases where an association with lapatinib was possible, 43 were from clinical trials, 8 from post-marketing surveillance (the French Authorisation for Temporary Use/ATU programme), and 8 were spontaneous reports. When the data from this evaluation is collated with the existing hepatobiliary data, the cumulative totals for cases with a possible association to lapatinib are as follows: 101 clinical trial cases, 18 cases from post-marketing surveillance, and 13 spontaneous reports.

On the basis of these cumulative figures, the current estimated incidence of hepatobiliary events is 0.8% (101/12,309) for the entire lapatinib clinical programme. This estimate assumes the subjects which remained blinded received lapatinib.

The current estimated incidence of hepatobiliary events on the French ATU study (PMS cases) is 1.3% (18/1385) based on enrolment as of August 2008.

The estimated incidence of hepatobiliary events from marketed use of lapatinib (spontaneous reports) is 0.4% (13/3599 *patient years*). This estimate assumes a daily dose of 1250mg lapatinib.

4.2.3.1. Hepatobiliary Events with Fatal Outcome

Five of the total 84 hepatobiliary cases received during the period covered by this report had a fatal outcome associated with the hepatic event. All five cases were from clinical trials. There were no reports of fatal hepatobiliary events from adjuvant breast cancer trials, post-marketing surveillance or spontaneous/marked use. Four subjects received lapatinib in combination with capecitabine. The fifth subject received blinded medication in combination with paclitaxel. There were no reports of fatal hepatobiliary events from subjects who received either placebo or comparator. This may reflect the fact that most subjects participating in lapatinib trials will have received lapatinib, and only 24% (3942/16,251) of subjects will have received placebo or comparator alone.

Fatal hepatobiliary events reported included hepatic failure, jaundice, hyperbilirubinemia and hepatobiliary disease. One of these 5 cases (B0518494A) was confounded by progression of underlying liver metastases.

There were four fatal outcomes for which an association with lapatinib (or blinded medication) was possible:

- Subject (b) (6), a 44-year-old female received blinded medication and paclitaxel in metastatic breast cancer study EGF104535. Approximately 39 weeks after treatment onset the subject presented with severe hepatobiliary disorder and abdominal discomfort. Relevant laboratory data included: increased ALT (3.4xULN) and bilirubin (9xULN). Treatment with blinded medication and paclitaxel was discontinued. The subject was treated with ascorbic acid and Glucuro lactone but died approximately two weeks later. It is not known whether an autopsy was carried out.
- Subject (b) (6), a 49-year-old female received lapatinib and capecitabine in the Expanded Access Programme EGF103659. The subject had mild elevated LFTs at baseline. Approximately 18 weeks after treatment onset the subject developed hyperbilirubinemia. Relevant laboratory data included: direct bilirubin 17xULN, total bilirubin 9xULN, ALP 5.7xULN, ALT 2.6xULN, and AST 2.5xULN. Lapatinib and capecitabine were discontinued, however the subject died approximately three weeks later. No autopsy was carried out.
- Subject (b) (6), a 58-year-old female received lapatinib and capecitabine in the Expanded Access Programme EGF103659. Approximately 23 weeks after

treatment onset the subject presented with obstructive jaundice. Relevant laboratory data included ALT 2xULN, bilirubin 32xULN, and ALP 3.8xULN. An ultrasound showed biliary dilatation. Lapatinib and capecitabine were discontinued. The investigator reported the event continued to progress and the subject died approximately six weeks later. It is not known whether an autopsy was carried out.

- Subject (b) (6), a 65-year-old female received lapatinib and capecitabine in the Expanded Access Programme EGF103659. Approximately 33 weeks after treatment onset the subject presented with obstructive jaundice. The subject died the following day. No autopsy was carried out.

Overall the cumulative total of hepatic events with a fatal outcome is 20 cases as of August 2008 (18 cases from the clinical trials programme, two from PMS). In nine of these 20 cases an association with lapatinib was possible. GSK's internal liver safety panel have adjudicated seven of these cases, two cases were adjudicated as possible drug induced liver injury

The estimated cumulative incidence for hepatobiliary events with fatal outcome on the clinical programme is 0.07 to 0.1% (9 where an association with lapatinib was possible *or* 18 total clinical trial cases/12,309). Narratives for all 5 fatal hepatobiliary events received during the period of this evaluation are provided in [Appendix 4](#).

4.2.3.2. Hepatic Failure

There was one case of hepatic failure amongst the total 84 hepatobiliary cases received during the period covered by this report. This case (b) (6) was a fatal event which occurred in the metastatic breast cancer setting and was confounded by progression of underlying liver metastases. The subject had previously experienced liver insufficiency and had a 6cm hepatic metastasis at baseline before starting treatment with lapatinib and capecitabine. A narrative for this case is included in [Appendix 5](#). There were no reports of hepatic failure from adjuvant breast cancer trials, post-marketing surveillance or spontaneous/ marketed use.

Overall a cumulative total of eight cases of hepatic failure have been reported as of August 2008 (7 cases from the clinical trials programme, one spontaneous report). GSK's internal liver safety panel have previously adjudicated six of these cases, of which two were adjudicated as possible drug induced liver injury.

The estimated cumulative incidence for hepatic failure on the clinical programme is 0.02 to 0.06% (2 where an association with lapatinib was possible based on GSK liver safety panel adjudication *or* 7 total clinical trial cases/12,309).

4.2.3.3. Possible Hy's Law Cases

For the purpose of this evaluation, possible Hy's law cases have been defined as:

- AST or ALT >3x ULN **and** total bilirubin >2x ULN with no initial findings of cholestasis (that is, alkaline phosphatase activity $\leq$ 2x ULN) [FDA, 2007].

Since the majority of reports were in the setting of metastatic cancer, some cases had alkaline phosphatase values higher than 2x ULN, also information on fractionated bilirubin was rarely available. These reports have been included in the category “possible Hy’s law cases” for completeness.

There were five possible Hy’s law cases amongst the total 84 hepatobiliary cases received during the period covered by this report. Two cases were new reports, both subjects received lapatinib as combination therapy:

- Subject (b) (6), a 53-year-old male subject received lapatinib with cisplatin for the treatment of squamous cell carcinoma of head and neck. Thirteen days after the start of investigational product, the subject developed elevated ALT (3.8x ULN) and bilirubin (1.8x ULN). Treatment with trial medication was discontinued. The events were unresolved at time of reporting.
- Subject (b) (6) a 63-year-old male subject received lapatinib and pazopanib for the treatment of relapsed malignant glioma. Approximately 55 days after the start of lapatinib and pazopanib, the subject developed increased LFTs: ALT was 1874 IU/L (normal range 7 to 56), AST was 861 IU/L (normal range 15 to 46), bilirubin was also elevated (value not reported). Alkaline phosphatase was normal. An MRI of the brain revealed tumour progression and study medication was discontinued. The subject was treated with dexamethasone and semisodium valproate. The events were unresolved at time of reporting. The subject experienced rapid tumour progression and passed away on (b) (6)

The remaining three events were added to the safety database based on laboratory data included in the (b) (6) hepatobiliary review (UM2008/00234/00). Narratives for all five of these possible Hy’s law cases are provided in [Appendix 3](#).

Overall a total of 23 possible Hy’s law cases have been reported on the GSK safety database as of August 2008, all from the clinical trials programme. GSK’s internal liver safety panel have previously adjudicated 19 of these cases, of which 14 were adjudicated as definite, probable, very likely or possible drug related liver injury. The incidence for possible Hy’s law events is discussed in section 5, in the context of total numbers regardless of which database was used to identify the event.

4.3. Disproportionality analysis

Disproportionality analysis (DPA) provides information on the frequency of reporting of a drug-event pair, relative to the background reporting in a given database. The aim of DPA is to detect higher-than-expected reporting of drug-event combinations. The DPA method used at GSK is an empirical Bayes data mining algorithm called MGPS, which computes the adjusted relative reporting ratio (EBGM) and associated 90% confidence interval (EB05, EB95) using stratification for age, gender, and year of report. More detailed information on DPA methodology and interpretation is provided in [Appendix 6](#).

Specifications for this evaluation are listed in [Table 4](#).

Table 4 Specifications of Disproportionality analysis

Database	GSK Safety Database (OCEANS)
Data Period	Up to end August 2008
Data mining algorithm	MGPS
Drug(s)	Lapatinib
Event(s) (MedDRA PTs)	MedDRA SMQ: "Possible drug related hepatic disorders", comprehensive SMQ
Drug Type	Suspect Only

Results:

Drug	Event (MedDRA PT)	N	EBGM	EB05
Lapatinib	SubSMQ-Possible drug related hepatic disorders - comprehensive search (SMQ)	299	1.808	1.335

GCSP review the available DPA data on a monthly basis. There is limited spontaneous data for lapatinib. The EB05 value expresses a ratio between the two groups under comparison, where it is 1 or close to 1 it indicates there is no difference between the groups. The combined EB05 value for the MedDRA sub-SMQ 'possible drug related hepatic disorders' is 1.335 and therefore quantitatively would not be considered a signal. However, a qualitative evaluation of the data led GSK to conclude there was a possible causal association between hepatotoxicity (specifically severe liver injury and transaminase elevations) and lapatinib treatment.

4.4. Epidemiology studies

In response to recent concerns about hepatotoxicity in cancer patients enrolled in clinical trials of lapatinib, GSK Worldwide Epidemiology (WWEpi) initiated a series of population-based studies. Along with other safety data analyses provided in previous and the current report, these epidemiological data provide context to better understand the magnitude of hepatic related safety signals emerging from the lapatinib clinical program.

Two studies were conducted to assess hepatotoxicity in different patient populations:

- A study of Liver Function Test (LFT) elevations in aggregated data from completed GSK oncology clinical trials (iNET). The objectives being to frame background rates of LFT elevations among cancer patients and to inform thresholds for "stopping criteria" for cessation of study drugs in instances of suspected hepatotoxicity.
- FDA label review and clinical trial literature review of LFT elevations among users of marketed tyrosine kinase-inhibiting drugs (TKIs). The objective being to frame background rates of LFT elevations among cancer patients who received various TKIs, including lapatinib.

4.4.1. LFT elevations in aggregated data from completed GSK oncology clinical trials (iNET)

This retrospective study was a pooled analysis of completed oncology clinical trials using an aggregated clinical trials database with study data from 1985-2005 (GSK iNET Heritage repository). WWEpi identified all oncology trials in which lab values were recorded to assess the baseline prevalence and incidence of elevated liver function values in nearly 4,000 cancer patients enrolled in clinical trials of GSK oncology products (exclusive of Lapatinib and Pazopanib).

WWEpi then evaluated four liver enzymes, and used the following gender-specific upper limit of normal (ULN) ranges to set various threshold cutpoints (i.e. 2, 3, 5 or 10 times ULN, etc):

- ALT or SGPT (alanine transaminase; ULN: males=40 U/L; females=35 U/L)
- BILI (total bilirubin; ULN =1.3 mg/dl)
- ALP (alkaline phosphatase; ULN=100 U/L)
- AST or SGOT (aspartate transaminase; ULN=35 U/L)

WWEpi calculated two descriptive measures stratified by the presence of liver metastases at baseline:

- Prevalence of liver enzyme elevations at baseline prior to administration of any study-assigned treatment in the trial. Prevalence represents the proportion of clinical trial study subjects with abnormal hepatic values (based on various ULN thresholds) at trial entry.
- Incidence of new elevated LFTs during follow-up (based on various ULN thresholds). Two forms of incidence calculations were presented: (a) cumulative incidence, a measure of risk in a given time period which is calculated as the proportion of subjects who have increased LFTs during follow-up time, and (b) incidence rates, a person-time analysis expressed per 1000 person months of follow-up. Both measures were calculated among patients considered 'at risk' during the follow-up period (i.e. patients who had LFTs below the specific threshold at baseline).

95% confidence intervals (CI) around each of these measures were estimated using the Clopper-Pearson approach.

A total of 3,998 subjects were identified (1,950 females, 2,048 males) from 31 GSK oncology trials (84% Phase II studies, 16% Phase III studies). The cancers in this aggregated dataset included colorectal, breast, ovarian, small cell lung cancer, non-small cell lung cancer, prostate, non-Hodgkin's lymphoma, Kaposi's sarcoma, and leukaemia. The majority of trials were conducted among patients with locally advanced or metastatic disease. All studies had some eligibility criteria related to liver function at baseline. Overall, 2,852 subjects did not have liver metastases and 1,146 subjects had liver metastases at baseline. The median age of the subjects was 61 (range, 18 to 90) years.

A second analysis was performed focusing on the five oncology trials conducted among breast cancer patients. This analysis yielded only 137 female patients, 67 subjects without liver metastases and 70 subjects with liver metastases at baseline. The median age of the subjects was 51 (range, 25 to 78) years. Given these small numbers, meaningful results were not available for most of the LFT thresholds and therefore results are only presented for the full cohort of 3,998 patients. The results presented are focused on ALT, AST and BILI thresholds, alone and in combination, as these were the LFTs considered when determining stopping criteria.

In general, elevated liver enzymes were rare in these cancer patients. Prevalence ([Appendix 7](#)) and incidence ([Appendices 8 and 9](#)) estimates were slightly higher among patients with liver metastases; however, these differences were rarely statistically significant. For example, the prevalence of suspected Hy's Law cases (defined in our analysis as ALT >3 xULN & BILI >2 xULN, normal ALP) was zero in both groups ([Appendix 7](#)). Of note, the prevalence reported here may be lower than the general cancer population, as these patients were enrolled in clinical trials which had varying levels of exclusion criteria around liver function.

One incident case of suspected Hy's law events occurred during follow-up among patients with liver metastases, yielding a cumulative incidence of 0.09% (95% CI: 0.0%, 0.2%) and an incidence rate of 0.2 per 1,000 person-months (95% CI: 0.005, 1.0). Among patients with liver metastases, the cumulative incidence of suspected Hy's Law cases was 0.37% (95% CI: 0.01%, 0.87%) and the incidence rate was 0.7 per 1,000 person-months (95% CI: 0.02, 3.7). ([Appendices 8 and 9](#)).

4.4.2. FDA label review and clinical trial literature review of LFT elevations among users of marketed TKIs

The FDA label review and clinical trial literature review included 12 US marketed TKIs (approved by the FDA during 1998-2007, [see Table 5](#)), classified as Class I (small molecule TKIs) and Class II (humanized monoclonal antibodies directed against receptor target tyrosine kinases and their ligands). LFTs of interest included ALT, AST, ALP and BILI. Elevations of these liver enzymes were graded by the National Cancer Institute (NCI)'s or the World Health Organization (WHO)'s Common Toxicity Criteria for Adverse Events ([Table 6](#)).

Table 5 FDA Label Review: Label information for 12 marketed TKI drugs†

Drug	Initially approved	Recent Label	Cancer Indications	LFT affected	LFT G3 or 4 events (%)
<i>Class I: Small molecule TKIs</i>					
Gleevec (Imatinib)	04/2003	09/2007	Leukemia, MDS, GIST	ALT, AST, BILI	3-6% (grade 4: 0% or <1%)
Iressa (Gefitinib)	05/2003	06/2005	Lung	Asymptomatic increases in liver transaminases	
Tarceva (Erlotinib)	11/2004	04/2007	Lung, Pancreatic	ALT, AST, BILI	Lung: 0% Pancreatic: 10%
Nexavar (Sorafenib)	12/2005	11/2007	Hepatocellular, Renal Cell	ALT, AST (ALP, BILI uncommon)	3%
Sprycel (Dasatinib)	06/2006	11/2007	Leukemia (CML, ALL)	ALT, AST, BILI	1-7%
Sutent (Sunitinib)	01/2006	02/2007	GIST, Renal Cell	AST, ALT, ALP	1-4%
Tykerb (Lapatinib)	03/2007	08/2007	Breast	ALT, AST, BILI	Breast: 2-4%
Tasigna (Nilotinib)	10/2007	10/2007	Leukemia	ALT, AST, BILI	Leukemia: 1-10%
<i>Class II: Humanized monoclonal antibodies directed against receptor target tyrosine kinases and their ligands</i>					
Herceptin (Trastuzumab)	09/1998	01/2008	Breast	<i>Not listed</i>	
Avastin (Bevacizumab)	02/2004	03/2008	Colorectal, Lung, Breast	<i>Not listed</i>	
Erbix (Cetuximab)	02/2004	10/2007	Head/Neck, Colorectal	<i>Not listed</i>	
Vectibix (Panitumumab)	09/2006	11/2007	Colorectal	<i>Not listed</i>	

†Source: United States Food and Drug Administration, Center for Drug Evaluation and Research. (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>, assessed as April 4, 2008).

Table 6 NCI/WHO Common Toxicity Criteria for Adverse Events

LFT (ULN)	Grade			
	1	2	3	4
ALP/ALT/AST	>1 – 2.5 x	>2.5 – 5.0 x	>5.0 – 20.0 x	>20.0 x
BILI	>1 – 1.5 x	>1.5 – 3.0 x	>3.0 – 10.0 x	>10.0 x

[Table 5](#) presents summary information for hepatotoxicity data and/or warnings and precautions abstracted from the current FDA official drug labels for 12 TKIs of interest (Source: United States Food and Drug Administration, Center for Drug Evaluation and Research. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>, assessed as of April, 2008). The FDA labels documented up to 10% Grade 3 or 4 elevations of ALT, AST, and/or BILI for the Class I small molecule TKIs; however, no hepatic events were indicated for the monoclonal antibodies (mAbs) in Class II. The current FDA labels for three of the 12 TKIs included specific medical guidance regarding evaluation of liver function. For example, the label for imatinib specified that patients shall be evaluated against their liver function before beginning treatment and be monitored monthly thereafter or as clinically necessary. The gefitinib or erlotinib labels advised that patients should also be tested for liver function periodically.

A MEDLINE literature review of all clinical trial reports or randomized controlled trial reports, published as of April 2008 (English language literature only), which included any of these 12 TKI drugs of interest for cancer treatment was carried out ([Appendix 10](#)). A total of 383 relevant clinical trials of the 12 TKI drugs were initially identified. Of these, 142 (37%) studies documented some hepatic events. Reported events of hepatotoxicity, particularly, elevations of ALT, AST and/or BILI, were extracted from the reports where available. This information was typically presented in a table or short paragraph in the text listing drug-related toxicities or adverse events. The review then focused on 100 (26%) studies (for references see [Appendix 11](#)) that reported Grade 3 or 4 events on individual ALT, AST, or BILI or combinations.

The majority of included reports provided no baseline (prior to treatment) LFT data, although most excluded patients with Grade 2+ events at enrolment. A large proportion of these studies were small (less than 100 patients) phase I or II clinical trials designed to evaluate efficacy, safety, or dosing of the TKI drugs either alone or in combination with other chemotherapies for selected cancer populations.

Among the Class I small molecule TKIs ([Appendix 10](#)), the highest reports of Grade 3 or 4 ALT or AST elevations were seen for imatinib (up to 19%) and gefitinib (up to 14%), where Grade 3 or 4 BILI was highest for imatinib (up to 19%) and erlotinib (up to 11%). These findings based on the clinical trial reports are generally higher than those documented in the current FDA labels. Among studies for the Class II mAbs, up to 9-10% of Grade 3 or 4 LFT elevations were observed for trastuzumab and cetuximab, and up to 33% of elevations were observed for bevacizumab, despite no liver function information documented in the current FDA labels.

Thirteen of these studies (mostly Phase II, n = 12-70 patients) were breast cancer trials (Appendix E), which reported up to 19% of Grade 3 or 4 LFT elevations: lapatinib (1 trial, 4%), imatinib (1 trial, 19%), gefitinib (2 trials, 7%), cetuximab (1 trial, 0%), and trastuzumab (8 trials, 9%). Higher proportions of LFT events were reported by published clinical trials, as compared with the current FDA labels.

The issue of under-reporting of LFT events in these trials cannot be excluded. Many reports include only adverse events that occurred above a certain percentage of the total study population or focus exclusively on more severe grade 3/4 events. Further, some studies collected only specific events that were commonly suspected to occur as a result of taking these drugs and did not report an exhaustive list of potential adverse events. Adverse events such as liver toxicity that are often asymptomatic may be more likely to be under-reported compared to acute or severe events such as myocardial infarction or stroke. Thus, it is likely that some rare hepatic events were not reported leading to under-estimates of the prevalence for the hepatic events. In addition, discrepancies in results between studies for each selected drug could reflect the use of different laboratory tests to determine liver function, making it difficult to draw comparisons across studies.

4.5. Other information

On 19 July 2008, an external Advisory Board met to review the lapatinib adjuvant breast cancer program and specifically, the continued investigation of lapatinib in the adjuvant setting in light of recent observations of hepatotoxicity possibly associated with its use. The Advisory Board was composed of external hepatologists and oncologists, who were asked to review the following topics:

- The benefit:risk for the continued use of lapatinib in the adjuvant treatment of HER2-positive early-stage breast cancer.
- The benefit:risk for the continued investigation of pazopanib in combination with lapatinib in patients with HER2-positive disease in the adjuvant setting. Given the hepatotoxicity observed with each of these molecules.

Following review and discussion of the data they concluded that the benefit:risk remained favourable in both cases. The advisory board was comfortable with the hepatic monitoring and stopping criteria which have been implemented across the study programmes.

5. DISCUSSION

An association between lapatinib and hepatotoxicity was identified in a previous review of hepatobiliary events (UM2008/00097/00). Hepatobiliary events from the lapatinib programme are reviewed on a regular basis. The data evaluated in the current report was received during the period 11-Apr-2008 to 14-Aug-2008.

Review of laboratory data from the clinical trials database for 5 ongoing phase I studies demonstrated an overall incidence of 4.5% (4/88) for AST or ALT elevation above 3x ULN based on subjects who had normal LFT measurements at baseline, but developed

AST or ALT >3x ULN post baseline. There were no fatal hepatobiliary events or reports of hepatic failure in this group of phase I studies and no new possible Hy's law cases.

Data from 19 phase II/III studies indicated that the most common LFT elevations were elevation of ALT and/or AST $\geq$ 3x ULN but below 5x ULN. The majority of LFT elevations took place in subjects with first line or recurrent breast cancer. Most of these LFT elevations (85.6%) were observed in subjects who received lapatinib in combination with other chemotherapies. Elevation of alkaline phosphatase >1.5x ULN accounted for the majority of LFT elevations 22.9% (881/3845) in all subjects, regardless of treatment. Elevation of bilirubin only was seen in 8.5% (327/3845) of subjects with bilirubin >1.5x ULN, and 4.3% (176/3845) of subjects with bilirubin >2x ULN, regardless of treatment. However, of these bilirubin abnormalities 15% and 9% respectively were reported from lapatinib monotherapy studies. GSK concluded there was a higher incidence of LFT abnormalities in subjects with advanced disease, and in combination with chemotherapy. There was generally a low incidence of LFT abnormalities from head and neck cancer trials, mainly elevations of ALT &/or AST.

A total of 84 cases including hepatobiliary events were retrieved from the GSK worldwide safety database during the period covered by this report. Of these reports, 59 were assessed as possibly associated to administration of study medication, of which 55 subjects are known to have received lapatinib, mostly (43/55) in combination with other chemotherapeutic agents (capecitabine, letrozole, paclitaxel, pazopanib, or trastuzumab). The daily dose of lapatinib ranged from 750mg to 1500mg once daily. Four cases remain blinded.

In the majority of cases received during the period of this review (89%, 53/59), lapatinib was discontinued at the time of the hepatobiliary event, as per the instructions in the global datasheet/core safety information. The combination therapy was also often discontinued at the same time. This represents an increase in lapatinib treatment withdrawal following the onset of a hepatobiliary event from 63.8% in the previous review, to 89% and suggests prescribers are complying with the guidance provided. Similarly, the number of subjects being rechallenged with lapatinib following a hepatobiliary event has decreased from 17.8% in the previous review, to 6.8% during the current period. Again suggesting that prescribers are following the prescribing information which advises that "lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.". Of the four reports of rechallenges during this reporting period, three came from the French ATU programme (PMS use), and one from a collaborative research study. Three of four rechallenges were positive.

No obvious trends or risk factors were identified amongst the cases where an association with lapatinib was possible. Most subjects (93%) were female, with a median age of 55 years, and received lapatinib at a dose of 1250mg or 1500mg.

Cumulative hepatobiliary event data

When cumulated incidence data are compared between the current review and the previous review (UM2008/00234/00) a small increase in reporting of serious

hepatobiliary adverse events is evident from all report sources (Table 7). These changes may be attributable to an increased awareness and reporting of hepatobiliary events following the circulation of the Dear Investigator/Healthcare provider letters in March 2008. In addition hepatobiliary stopping criteria have been added to the protocols for all ongoing studies and this is likely beginning to be reflected in the safety data. The estimated incidence for hepatobiliary events amongst subjects who received placebo or comparator is 0.4% (14/3942) regardless of event attribution.

Table 7 Cumulative incidences for hepatobiliary events reported from the lapatinib programme

Event Source	Incidence to Aug08	Incidence as of Apr08
Clinical trials	0.8% (101/12,309)	0.5% (58/10,683)
PMS (French ATU)	1.3% (18/1385)	0.8% (10/1250)
Spontaneous reports	0.4% (13/3599 <i>patient years</i>)*	0.2% (5/2,095 <i>patient years</i>)*

* Assumes a daily dose of 1250mg

Hepatobiliary events with fatal outcome

As of August 2008, there were a total of 20 hepatic events with a fatal outcome on the programme (18 cases from clinical trials, two from PMS). In nine of these 20 cases an association with lapatinib was possible. GSK's internal liver safety panel have adjudicated seven of these nine cases, two cases were adjudicated as possible drug induced liver injury.

Based on the nine cases where an association with lapatinib was possible, or the total 18 cases reported from clinical trials, the estimated incidence for hepatobiliary events with fatal outcome on the clinical programme is 0.07 to 0.1% (9 *or* 18 total clinical trial cases/12,309) as of August 2008. This figure is comparable with that reported in previous reviews.

Hepatic Failure

Overall a cumulative total of eight cases of hepatic failure have been reported as of August 2008 (7 cases from the clinical trials programme, one spontaneous report). GSK's internal liver safety panel have previously adjudicated six of these cases, of which two were adjudicated as possible drug induced liver injury.

Based on the two cases where an association with lapatinib was adjudicated as possible *or* 7 total clinical trial cases, the estimated incidence for hepatic failure on the clinical programme is 0.02 to 0.06% (2 *or* 7 total clinical trial cases/12,309). These figures are unchanged from the previous review.

Possible Hy's Law Cases

There is a cumulative total of 25 possible Hy's law cases reported from the entire clinical trials programme (2 new cases from the clinical trials database, 23 from the safety database). GSK's internal liver safety panel have previously adjudicated 19 of these cases, of which 14 cases were adjudicated as possible drug related liver injury. Based on

the 14 cases adjudicated as possible drug related liver injury, or the total 25 cases, the overall estimated incidence of possible Hy's law cases on the lapatinib clinical programme is 0.1 to 0.2% (14 or 25 total cases/12309). These figures are comparable with those reported in the previous review (0.14 to 0.19%).

Hepatobiliary Events by treatment setting

An evaluation of the data by treatment setting (metastatic compared to adjuvant treatment) was also carried out. Approximately 8597 subjects with metastatic cancer are estimated to have received lapatinib as of August 2008. It is estimated that approximately 3336 subjects will have received lapatinib in the adjuvant cancer setting.

There were 18 reports of fatal hepatic events (acute liver failure) from the metastatic clinical programme, 9 where an association with lapatinib was possible, giving an estimated cumulative incidence of 0.1 to 0.2% (9 or 18 total cases/8597). There were seven reports of hepatic failure on the metastatic cancer programme, of which two were adjudicated as possible associated with lapatinib. This gives an estimated cumulative incidence of 0.02 to 0.08% (2 or 7 total cases/8597) for hepatic failure on the metastatic clinical programme. A total of 18 possible Hy's law cases were identified from the metastatic cancer programme. Sixteen of these metastatic cases have been adjudicated by the GSK liver safety panel, of which 11 were adjudicated as possible drug related liver injury. This gives an estimated incidence range of 0.13 to 0.2% (11 or 16 total clinical trial cases/8597) for lapatinib subjects in the metastatic setting. These figures are consistent with those reported for the metastatic setting in the previous hepatobiliary review (UM2008/00234/00).

Approximately 3336 subjects are estimated to have received lapatinib in the adjuvant cancer setting as of August 2008, the majority of these (3193 subjects) in adjuvant breast cancer studies EGF105485 and EGF106708. There were no reports of fatal hepatic events or hepatic failure from the adjuvant cancer setting. A total of seven possible Hy's law cases were identified from adjuvant cancer setting, five came from breast cancer study EGF105485. Two subjects received lapatinib monotherapy, one received lapatinib in combination with cisplatin, and four cases remain blinded. Three of these cases were adjudicated as possible drug related liver injury by the GSK internal liver safety panel, giving an estimated incidence range of 0.1 to 0.2% (3 or 7/3336) for possible Hy's law cases from subjects being treated in the adjuvant setting. The incidence of possible Hy's law cases in the adjuvant setting is consistent with that reported from the metastatic setting. In addition, these figures are consistent with those reported for the adjuvant setting in the previous hepatobiliary review (UM2008/00234/00).

Epidemiological data

An epidemiological study of LFT elevations using an aggregated clinical trials database for completed oncology studies (iNET) demonstrated that elevated liver enzymes were rare. Prevalence and incidence estimates were slightly higher among patients with liver metastases; however, these differences were rarely statistically significant. At baseline there were no possible Hy's Law cases (defined in our analysis as ALT >3 xULN & BILI >2 xULN, normal ALP) in either group. It is likely that the prevalence reported here may be lower than the general cancer population, since these patients were enrolled in clinical

trials which had varying levels of exclusion criteria around liver function. Cumulative incidence of new possible Hy's Law cases (defined in our analysis as ALT >3 xULN & BILI >2 xULN, normal ALP) occurring during study treatment was 0.09% in subjects without liver metastases, and 0.37% in subjects with liver metastases. The incidence of possible Hy's law cases on the lapatinib clinical programme is 0.1 to 0.2% so comparable with these figures.

An FDA label review confirmed that hepatobiliary events such as LFT elevations are a class effect with small molecule TKIs. This was supported by review of the clinical trial literature however higher proportions of LFT events were reported by published clinical trials, as compared with the current FDA labels.

Summary

Lapatinib associated hepatotoxicity appears idiosyncratic in nature and may occur early or later in the course of therapy. No specific sub-populations have been identified as at disproportionate risk and therefore no criteria for excluding patients from treatment.

Hepatotoxicity and hyperbilirubinemia are included in the lapatinib CSI with a frequency of 'uncommon' (incidence ≥ 0.1 to $< 1\%$). In addition, the CSI for lapatinib includes the warning that "*Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment [REDACTED] (b) (6) as clinically indicated*" and instructs that "*Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated*". The data shows the number of subjects with treatment withdrawn at the onset of a hepatobiliary event has increased, and that there has been a reduction in the number of subjects being rechallenged with lapatinib following a hepatobiliary event. This suggests prescribers are following the prescribing information. GSK conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

6. CONCLUSION

- Laboratory data from 24 ongoing studies (all phases) indicated that the most common LFT elevations were elevation of ALT and/or AST ≥ 3 x ULN but below 5x ULN. The majority of LFT elevations took place in subjects with first line or recurrent breast cancer, and in subjects who received lapatinib in combination with other chemotherapies.
- A small increase in reporting of serious hepatobiliary adverse events is evident from all report sources. These changes may be attributed to an increased awareness and reporting of hepatobiliary events following the circulation of the Dear Investigator/Healthcare provider letters, and the addition of hepatobiliary stopping criteria to study protocols leading to an increase in reporting of hepatobiliary events.
- Amongst an estimated 8,597 subjects receiving lapatinib in metastatic cancer studies:
 - There were a total of seven cases of hepatic failure, an association with lapatinib was adjudicated as possible in two of these cases, although one case was very

atypical. This gives an estimated incidence of 0.02 to 0.08% (2 *or* 7 total cases/8597) for hepatic failure in the metastatic cancer setting.

- The estimated incidence of possible Hy's law cases was 0.13 to 0.2% (11 or 16 total clinical trial cases/8597) for lapatinib subjects in the metastatic setting.
- These figures are consistent with those previously reported for lapatinib subjects treated in the metastatic setting.
- Amongst an estimated 3336 subjects who will have received lapatinib in the adjuvant cancer setting there were a total of seven possible Hy's law cases, of which three have been adjudicated as possibly drug related. This gives an estimated incidence of 0.1 to 0.2% (3 or total 7/3336) for possible Hy's law cases amongst subjects treated in the adjuvant setting. This includes one event of severe liver injury with compromised synthetic function, very likely related to lapatinib use, which resolved with lapatinib cessation.
- An external Advisory Board composed of hepatologists and oncologists reviewed safety data from the adjuvant breast cancer programme, including data from lapatinib and pazopanib combination studies. They concluded that the benefit:risk remained favourable in both cases. The advisory board was comfortable with the hepatic monitoring and stopping criteria which have been implemented across the study programmes.
- A retrospective epidemiological study of LFT elevations from completed oncology studies (iNET) demonstrated that elevated liver enzymes were rare. Cumulative incidence of new Hy's Law cases (defined as AST or ALT >3 xULN & BILI >2 xULN, normal ALP) occurring during study treatment was 0.09% in subjects without liver metastases, and 0.37% in subjects with liver metastases. The 0.1 to 0.2% incidence of possible Hy's law cases on the lapatinib clinical programme is consistent with the findings from these epidemiological studies.
- GSK conclude no change to the lapatinib core safety information on hepatotoxicity is warranted at this time.

7. REFERENCES

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APPENDIX 1 LIST OF ABBREVIATIONS

Abbreviations	
AE	Adverse event
AERS	(FDA) Adverse Event Reporting System
DPA	Disproportionality analysis
EBGM	Empiric Bayes Geometric Mean
EB05, EB95	Lower and upper bounds, respectively, of 2-sided 90% confidence interval around EBGM
FDA	(US) Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
MGPS	Multi-item Gamma Poisson Shrinker
OCEANS	GSK's worldwide clinical safety database
PT	Preferred term

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APPENDIX 2 SUMMARY OF LFT ABNORMALITIES FROM ONGOING PHASE II AND III STUDIES

Aug 08 Hepatox data summary										
	Lap	Blind	Other	Tot	1st ABC	Recurrent BC	HN Cancer	Other tumours	Mono-Therapy	Combo-Therapy
N=	1297	2136	412	3845	1440	1729	230	446	797	3048
Possible HYs Law: >3x ULN AT & < 2x ULN ALP & > 2x ULN BIL	6	3	0	9	1	7	1	0	0	9
Possible HYs Law: >3x ULN AT & ALP missing > 2x ULN BIL	1	0	1	2	0	2	0	0	0	2
>3x ULN AT & >1.5x ULN BIL	36	31	10	77	24	46	3	4	9	68
>3x ULN AT & >2x ULN BIL	24	17	7	48	12	32	2	2	5	43
>= 3x ULN ALT & AST	84	88	10	182	69	99	7	7	23	159
>= 5x ULN ALT & AST	33	30	3	66	27	33	2	4	8	58
>= 10x ULN ALT & AST	7	4	0	11	4	5	0	2	3	8
>= 20x ULN ALT & AST	1	0	0	1	0	1	0	0	0	1
>= 3x ULN ALT	122	151	22	295	113	153	13	16	41	254
>= 5x ULN ALT	52	58	6	116	49	59	4	4	16	100
>= 10x ULN ALT	15	12	2	29	10	15	1	3	4	25
>= 20x ULN ALT	3	2	0	5	1	2	1	1	1	4
>= 3x ULN AST	148	163	25	336	131	182	10	13	38	298
>= 5x ULN AST	63	67	9	139	57	75	3	4	14	125
>= 10x ULN AST	18	11	3	32	12	18	0	2	5	27
>= 20x ULN AST	4	2	0	6	2	3	0	1	1	5
>1.5x ULN BIL	130	163	34	327	118	171	15	23	49	278
>2x ULN BIL	63	93	20	176	74	87	8	7	16	160
>1.5x ULN ALP	330	467	84	881	390	390	17	84	162	719
	1140			2738	1094	1380	87	177	395	2343
	87.80%			71.20%	76%	79.8%	37.80%	39.70%	49.60%	76.80%

APPENDIX 3 NARRATIVES FOR POSSIBLE HY'S RULE CASES RECEIVED FROM 11-APR-2008 TO 14- AUG-2008

Narratives for cases identified from Phase II/III laboratory data

EGF102988 subject (b) (6)

This 74 year old male subject was enrolled in a study EGF102988 for the adjuvant treatment of head and neck cancer. The subject was diagnosed in (b) (6).

Baseline laboratory values on (b) (6) were: ALT 14.1 IU/l, AST 16.1 IU/l, alkaline phosphatase 96.6 IU/l, and total bilirubin 19.2 umol/l. The subject received blinded investigational product from (b) (6) with cisplatin and radiotherapy. He received concomitant Nexium, Olmetec and Pentalong. Liver function test values began rising at week one.

At the week two visit on (b) (6), 9 days after the start of investigational product the subjects liver function tests were: ALT 188.2 IU/l, AST 30.6 IU/l, alkaline phosphatase 144 IU/l, and total bilirubin 100.9 umol/l (normal range: <17 umol/l). At the following study visit on (b) (6) the subjects liver function tests were: ALT 33.5 IU/l, AST 21.6 IU/l, alkaline phosphatase 100.7 IU/l, and total bilirubin 19.4 umol/l (normal range: <17 umol/l). Study medication was stopped on (b) (6). Laboratory values continued to fluctuate during treatment, results on (b) (6) were: ALT 22.9 IU/l, AST 15.6 IU/l, alkaline phosphatase 82.8 IU/l, and total bilirubin 26.6 umol/l (normal range: <17 umol/l).

EGF103890 subject (b) (6)

This 50 year old female subject was enrolled in a study EGF103890 for the treatment of breast cancer. The subject was diagnosed in (b) (6) and developed liver metastases in (b) (6). Baseline laboratory values on (b) (6) were: ALT 23 IU/l (normal ULN 54 IU/l), AST 27 IU/l (normal ULN 41 IU/l), alkaline phosphatase 58 IU/l (normal ULN <111 IU/l), and total bilirubin 11.97 umol/l (normal ULN 1.3 umol/l). The subject received lapatinib at 1500mg daily from (b) (6) in combination with bevacizumab (10mg/kg IV every 2 weeks).

On (b) (6) 23 weeks after the start of investigational product the subjects liver function tests were: ALT 223 IU/l (normal ULN 54 IU/l), AST 164 IU/l (normal ULN 41 IU/l), alkaline phosphatase 189 IU/l (normal ULN <111 IU/l), and total bilirubin 61.6 umol/l (normal ULN 1.3 umol/l). Fatigue and dry skin were ongoing adverse events. The subject received their last dose of study medication on (b) (6).

Narratives for cases on the safety database

Protocol Id: EGF102988

Investigator Number: (b) (6)

Subject Number: (b) (6)

Treatment Number: (b) (6)

Case Id: (b) (6)

Suspect Drugs: Cisplatin, Lapatinib, Radiotherapy

Serious Events: Alanine aminotransferase abnormal, Blood bilirubin abnormal

This 53-year-old male subject was enrolled in a blinded study for the treatment of squamous cell carcinoma of head and neck. The subject received oral investigational product from (b) (6) intravenous cisplatin at 100 mg/m² cyclic from (b) (6) and topical radiotherapy from (b) (6).

The subject was randomized to receive lapatinib. Concomitant medications included candesartan cilexetil and Co-dydramol.

On (b) (6) 13 days after the start of investigational product, the subject developed grade 2 or moderate abnormal alat (sgpt) and grade 2 or moderate bilirubin abnormal. The events were clinically significant (or requiring intervention). Treatment with blinded trial medication was discontinued on (b) (6). The events were unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the abnormal alat (sgpt) and bilirubin abnormal may have been caused by investigational product.

Protocol Id: EGF104900

Investigator Number: (b) (6)

Subject Number: (b) (6)

Treatment Number: (b) (6)

Case Id: (b) (6)

Suspect Drugs: Lapatinib, Trastuzumab

Serious Events:

This 41 year old female subject was enrolled in an open-label study EGF104900 for the treatment of metastatic breast cancer. The subject was diagnosed with lung metastases in (b) (6). Baseline laboratory values on (b) (6) were: ALT 57 IU/l (normal range 0-48 IU/l), AST 94 IU/l (normal range 0-42 IU/l), alkaline phosphatase 205 IU/l (normal range 20-125 IU/l), and total bilirubin 12 umol/l (normal range: 0-22 umol/l). The subject received oral lapatinib from (b) (6) at dose 1000 mg daily, and intravenous trastuzumab (Herceptin) at 2mg/kg. She was receiving concomitant Ativan and oxycodone. At the week four visit on (b) (6) 28 days after the start of lapatinib and trastuzumab the subjects liver function tests were: ALT 145 IU/l (normal range: 0-48 IU/l), AST 216 IU/l (normal range: 0-42 IU/l), alkaline phosphatase 828 IU/l (normal range: 20-125 IU/l), and total bilirubin 76 umol/l (normal range: 0-22 umol/l). She was diagnosed with serious febrile neutropenia on (b) (6) which resolved on (b) (6) (details recorded in case (b) (6)).

Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study due to disease progression. Laboratory values following study withdrawal ((b) (6)) were: ALT 33 IU/l (normal range: 0-48 IU/l), AST 46 IU/l

(normal range: 0-42 IU/l), alkaline phosphatase 210 IU/l (normal range: 20-125 IU/l), and total bilirubin 8 umol/l (normal range: 0-22 umol/l). The subject died on (b) (6)

Protocol Id: EGF105485
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number: (b) (6)
 Case Id: (b) (6)
 Suspect Drugs: Blinded trial medication
 Serious Events:

This 39-year-old female subject was enrolled in a blinded study for the treatment of breast cancer. The subject received oral investigational product per day from (b) (6)

This 39 year old, Hispanic/Latino female subject with Stage IIa infiltrating breast carcinoma diagnosed (b) (6) was enrolled in blinded study EGF105485 for the treatment of breast cancer. She was randomly assigned to blinded study drug on (b) (6) and was administered the first dose on the same day. She had Er/PgR negative disease without lymph node involvement. Prior to randomization, she underwent a left mastectomy with axilla resection in (b) (6) followed by doxorubicin plus cyclophosphamide from (b) (6) then paclitaxel for one month. She also received radiation to the left costal region during (b) (6). Her performance status was 0 at the time of enrolment. Her height and weight were 150cm and 72.0kg, respectively. She reported the following Grade 1 current medical conditions at baseline: increased glucose, increased AST and ALT, and hyperbilirubinemia. She was not receiving any concomitant medications at the time of study entry. Her baseline laboratory values on (b) (6) were: AST 75 U/l (normal range 0-42 U/l), ALT 110 U/l (normal range 0-48 U/l), alkaline phosphatase 96 U/l (normal range 20-125 U/l), and total bilirubin 30 umol/l (normal range: 0-22 umol/l).

While receiving investigational product the subject experienced two episodes of non-serious Grade 3 diarrhoea (resulting in dose reduction) and Grade 2 rash during (b) (6). She was treated with loperamide (diarrhea) and chlorpheniramine and prednisone (rash). On (b) (6) she was admitted to the hospital with right side abdominal. She was diagnosed with appendicitis and underwent an appendectomy; the investigator reported this event as not related to study drug. During (b) (6) she had increased blood bilirubin; reported as non-serious Grade 2 AE with onset date of (b) (6) and resolution on (b) (6). On (b) (6) 93 days after the start of investigational product the subjects liver function tests were: Grade 2 AST 112 U/l (normal range 0-42 U/l), Grade 2 ALT 121 U/l (normal range 0-48 U/l), alkaline phosphatase 91 U/l (normal range 20-125 U/l), and total bilirubin 40 umol/l (normal range: 0-22 umol/l). Laboratory values on (b) (6) were: AST 179 U/l (normal range 0-42 U/l), ALT 204 U/l (normal range 0-48 U/l), alkaline phosphatase 106 U/l (normal range 20-125 U/l), and total bilirubin 46 umol/l (normal range: 0-22 umol/l). ALT was noted as resolved on (b) (6) and AST on (b) (6). On (b) (6) patient also reported Grade 2 abdominal pain, nausea, and vomiting. She was treated with metoclopramide (N/V). Vomiting resolved

on (b) (6) and abdominal pain and nausea subsequently resolved on (b) (6).
 (b) (6) In early (b) (6) AST and ALT were elevated again (both Grade 2) and at this
 time (b) (6) are still ongoing.

On (b) (6) the pts labs were: AST = 184 (so >4 X ULN), ALT = 173 (> 3 X ULN)

Alk Phos = 110 (WNL), Bili = 40 (1.8 X ULN).

There was no evidence of local labs in the CRFs. We have asked the site if further testing was done since (b) (6) and have not yet received a reply. Since the new amendment is not yet approved at this site, the site was asked to consider discontinuing IP due to these elevations as this is a safety issue.

Follow-up received (b) (6) The site reported that IP was discontinued on (b) (6) 2008.

Protocol Id: VEG102857
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number: (b) (6)
 Case Id: (b) (6)
 Suspect Drugs: Lapatinib, Pazopanib
 Serious Events: Alanine aminotransferase increased, Aspartate aminotransferase increased

This 63-year-old male subject was enrolled in an open-label study for the treatment of relapsed malignant glioma. The subject received oral lapatinib at 1000 mg per day from (b) (6) and oral pazopanib at 400 mg per day from (b) (6)

The subject's past medical history included seizure.

On (b) (6) 55 days after the start of pazopanib and lapatinib, the subject developed grade 4 alanine aminotransferase (ALT) increased and grade 3 or severe aspartate aminotransferase (AST) increased. His ALT was 1874 IU/L (normal range 7 to 56) and his AST was 861 IU/L (normal range 15 to 46). The subject also experienced a grade 2 bilirubin elevation and a normal alkaline phosphatase. The events were clinically significant (or requiring intervention). On (b) (6) an MRI of the brain revealed tumour progression. The subject was taken off study due to the tumour progression and treatment with pazopanib and lapatinib was discontinued on (b) (6). The subject was treated with dexamethasone and semisodium valproate. The events were unresolved at time of reporting. The subject experienced rapid tumour progression and passed away on (b) (6). The investigator considered that there was a reasonable possibility that the alanine aminotransferase increased and aspartate aminotransferase increased may have been caused by pazopanib and lapatinib and that the events were possibly due to the disease under study.

Protocol Id: VEG20007
Investigator Number: (b) (6)
Subject Number: (b) (6)
Treatment Number:
Case Id: (b) (6)
Suspect Drugs: Lapatinib, Pazopanib
Serious Events: Liver function test abnormal

This 75-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral pazopanib at 400 mg from (b) (6) and oral lapatinib at 1000 mg per day from (b) (6)

Concomitant medications included simvastatin, nifedipine, hydrochlorothiazide, Cosopt, Agiolax, omeprazole and prostaglandin f2 alpha.

On (b) (6) 25 days after the start of pazopanib and lapatinib, the subject developed abnormal liver function tests as evidenced by elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated total bilirubin and elevated alkaline phosphatase (AP). The subjects AST was 544 IU/L (normal range 14-36), ALT 379 IU/L (normal range 9-52), AP 148 IU/L (normal range 38-130) and total bilirubin 2.8 mg/dL (normal range 0.2-1.3). On (b) (6) prior to treatment with pazopanib and lapatinib, the subject's baseline laboratory values were AST 46 IU/L, ALT 36 IU/L, AP 73 IU/L and total bilirubin 0.7 mg/dL. Treatment with pazopanib and lapatinib was discontinued due to hepatotoxicity and the subject was withdrawn from the study. Treatment with simvastatin was continued. The event improved on (b) (6). The subject's total bilirubin and alkaline phosphatase were normal at 1.1 mg/dL and 105 IU/L, respectively. The subject's AST was elevated at 244 IU/L and her ALT was elevated at 303 IU/L. Investigator causality was unknown at the time of reporting.

Follow-up received on (b) (6)

Upon review, the event was assessed as medically serious by GSK safety physician.

APPENDIX 4 NARRATIVES FOR HEPATOBILIARY EVENTS WITH FATAL OUTCOME RECEIVED FROM (b) (6)

Narratives for subjects who received lapatinib in combination with other chemotherapies

Protocol Id: EGF103659
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number: (b) (6)
 Case Id: (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Hyperbilirubinaemia

This 49-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day and oral capecitabine at 2500 mg per day from (b) (6)

On (b) (6) 124 days after the start of lapatinib and capecitabine, the subject developed grade 4 hyperbilirubinemia. Treatment with capecitabine was discontinued on (b) (6). Treatment with lapatinib was discontinued on (b) (6) and the subject was withdrawn from the study. The subject died on (b) (6) due to hyperbilirubinemia. An autopsy was not performed. The investigator considered that there was a reasonable possibility that the hyperbilirubinemia may have been caused by lapatinib and capecitabine.

Follow up information was received on (b) (6)

Relevant lab results on (b) (6) included alanine aminotransferase 160 U/L(normal range:9-52), aspartate aminotransferase 83U/L(normal range:14-36), alkaline phosphatase 160U/L(normal range:38-126), Lactate dehydrogenase 1560U/L(normal range:313-618), GGT 152U/L(normal range:12-43), bilirubin total 1.62mg/dL (normal range:0.2-1.3) and bilirubin direct 0.41mg/dL(normal range:0-0.4). Relevant lab results on (b) (6) included alanine aminotransferase 114U/L, aspartate aminotransferase 49U/L, alkaline phosphatase 405U/L, Lactate dehydrogenase 1140U/L, GGT 215U/L, bilirubin total 1.97mg/dL and bilirubin direct 0.30mg/dL. Relevant lab results on (b) (6) included alanine aminotransferase 134U/L, aspartate aminotransferase 62U/L, alkaline phosphatase 507U/L, Lactate dehydrogenase 1603U/L, GGT 333U/L, bilirubin total 6.7mg/dL and bilirubin direct 1.9mg/dL. Relevant lab results on (b) (6) included alanine aminotransferase 138U/L, aspartate aminotransferase 91U/L, alkaline phosphatase 717U/L, Lactate dehydrogenase 1829U/L, GGT 270U/L, bilirubin total 11.7mg/dL and bilirubin direct 6.94mg/dL. Laboratory test for prothrombin time, thrombin time, partial thromboplastin time, albumin and total protein was not performed. Serology for hepatitis A, B and C was not obtained. The subject's family reported the subject had confusion, anorexia and jaundice. She had no ascites. There was no sign of right heart failure. Liver ultrasound showed multiple liver metastasis. A liver biopsy was not performed. The subject did not have any close contact with a person with active hepatitis. She had no recent travel to a developing country. She

had no history of autoimmune disorder, hepatitis, hepatic failure, cirrhosis, Gilbert's disease, diabetes, active gallbladder, active pancreatitis, alcohol abuse, non-steroidal anti-inflammatory drugs use, intravenous drug or acetaminophen consumption.

Protocol Id: EGF103659
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number:
 Case Id: (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Jaundice cholestatic

This 65-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 1800 mg twice a day from (b) (6) for 14 days and at a dose of 1450 mg twice a day from (b) (6). Concomitant medications included nystatin, cefuroxime sodium, metronidazole, lactulose, morphine and midazolam.

On (b) (6) 235 days after the start of lapatinib and capecitabine, the subject developed grade 5 obstructive jaundice. On admission to hospital she was dehydrated for which she was treated with intravenous fluids. The subject's condition however, deteriorated. The subject died on (b) (6) due to the obstructive jaundice. An autopsy was not performed. Investigator causality was unknown at the time of reporting but the investigator considered that the event was possibly due to the disease under study.

Follow up information received on (b) (6)

The investigator reported that the cause of death was liver failure due to the progression of advanced breast cancer. The investigator considered that there was no reasonable possibility that the obstructive jaundice was related to treatment with lapatinib or capecitabine.

Follow up information received on (b) (6)

The subject took the last dose of lapatinib on (b) (6) and the last dose of capecitabine on (b) (6). The investigator reported the final cause of death as obstructive jaundice.

Protocol Id: EGF103659
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number:
 Case Id: (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Confusional state, Jaundice

This 58-year-old female subject was enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received oral lapatinib at 1250 mg per day from (b) (6) and oral capecitabine at 1600 mg from (b) (6)

(b) (6) Concomitant medications included atenolol, bendrofluazide and lamotrigine.

On (b) (6) 161 days after the start of lapatinib and capecitabine, the subject developed grade 4 jaundice. The event was life-threatening and clinically significant (or requiring intervention). The investigator reported that the event was serious but the subject was well. Treatment with lapatinib and capecitabine was discontinued on (b) (6). (b) (6) Relevant assessments included ultrasound - biliary duct dilation. The subject was to have MRCP (Magnetic resonance cholangiopancreatography). The event was unresolved at time of reporting. The investigator considered that there was a reasonable possibility that the jaundice may have been caused by lapatinib and capecitabine and that the event was possibly due to disease under study and biliary stricture.

Follow up information received on (b) (6)

The subject had lung and liver metastasis. The subject did not have any risk factor. Treatment with lapatinib and capecitabine was discontinued due to the progression of disease. MRCP showed: marked dilatation of the bile ducts in the left lobe of the liver, apparently completely obstructed duct as it approaches the confluence. The common hepatic and common bile ducts are also, dilated, up to 13mm, tapering down in the pancreas. The 3 cm metastasis shown in the liver, reported on CT, is demonstrated but posterior in the right lobe.

The relevant lab results on (b) (6) included alkaline phosphatase 464 U/L (normal range 40-120), albumin 39 (units and normal range not specified), bilirubin 558 umol (normal range 2-17) and alanine aminotransferase 121 U/L (normal range 10-60).

Follow-up information received (b) (6)

The investigator updated the causality to lapatinib and capecitabine to not related. The investigator reported that on a CT scan, "there was disease progression elsewhere in chest".

Follow-up information received (b) (6)

On (b) (6) the subject had an endoscopic tetrograde cholangiopancreatography (ERCP) and a size 7 fresh stent was inserted. On (b) (6) 193 days after the start of lapatinib and capecitabine, and approximately 1 month after the last dose, the subject developed grade 4 confusion. The subject was hospitalised. Upon admission, she was treated with Tazocin for biliary sepsis, and also experienced hypolemia. Liver function tests were worse than prior to stenting (results not specified). The subject died on (b) (6) (b) (6) due to confusion. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the confusion may have been caused by lapatinib and capecitabine.

Follow up information received on (b) (6)

The investigator reported that the confusion was due to progressive disease, the subject died of progressive disease and no autopsy was performed. Jaundice was reported to be

unrelated to capecitabine and unlikely to have been caused by lapatinib. Jaundice was reported as unresolved at the time of death.

Follow up information received on [REDACTED] (b) (6)

The investigator reported that jaundice was due to progressive disease and unlikely to be related to investigational product. Confusion was reported as ongoing at the time of death.

Follow up information received on [REDACTED] (b) (6)

The investigator reported that the scan did not show definite evidence of disease progression in the subject's liver or bile ducts i.e causing the jaundice. The disease progression was in the subject's lungs. The investigator reported that the obstructive picture of the subject's liver function would make disease progression more likely but the investigator could not fully exclude lapatinib from the cause of jaundice. The investigator reported that the event progressed after the subject came off the drug (due to disease progression in her lungs).

Follow up information received on [REDACTED] (b) (6)

The investigator reported that "the subject had disease progression in lung but not in liver. The picture presented was typical for obstruction but the cause of obstruction was not found. Stenting failed so it was likely to be due to disease but lapatinib could not be excluded completely". The investigator reported that there was a possibility that the jaundice and confusion could have been caused by lapatinib.

Follow-up information received [REDACTED] (b) (6)

Relevant CT scan results taken on [REDACTED] (b) (6) were - pulmonary angiogram: Complete collapse of right upper lobe and right nodular lobe. Possibility of tumour. Large right pleural effusion. Suspicion of intratracheal component of tumour in the posterior aspect at the level of the aortic arch. Left parasternal soft tissue mass appeared to have increased in size and measured 3.7 x 2cm (was previously 3.3 x 1.7 cm). Further metastatic deposits were also noted at T1 vertebra. Scan of abdomen: Gall bladder hugely distended. Metastatic deposits seen in the posterior aspect of the right lobe measuring 2.9cm (more defined than on previous scans). No definite metastatic bony deposits were seen in the abdomen.

The Investigator reported that appearance of these CT scans were suspicious for progressive disease.

Relevant laboratory results taken [REDACTED] (b) (6) (units and normal range unknown) included - Alanine aminotransferase 49, Albumin 21, Alkaline phosphatase 624, Bilirubin total 321 and Prothrombin time 0.95.

Protocol Id: LAPANP
 Investigator Number:
 Subject Number:
 Treatment Number:
 Case Id: (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Diarrhoea, Hepatic failure

This female subject was a named patient enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received lapatinib at 1250mg daily from an unspecified date and capecitabine from an unspecified date.

At an unknown time after the start of lapatinib, the subject developed grade 3 diarrhea. The event was clinically significant (or requiring intervention). The subject was treated with loperamide hydrochloride. Treatment with lapatinib was interrupted for 5 days. The event lasted 5 days and resolved on an unspecified date. Investigator causality was unknown at the time of reporting.

Follow up information received on (b) (6)

The investigator reported that the subject died due to liver insufficiency after 4 weeks of treatment with lapatinib and xeloda. The subject presented a breast metastatic cancer. With the 1st line treatment (unspecified) she presented a liver insufficiency. With the 2nd line treatment no liver abnormalities were reported. Before starting 3rd line treatment (lapatinib and Xeloda) she presented a 6cm metastasis on the liver. She had a very good response but a liver insufficiency was detected and the treatment was withdrawn and about a week and a half ago the subject died.

Narrative for subject who remains blinded

Protocol Id: EGF104535
 Investigator Number: (b) (6)
 Subject Number: (b) (6)
 Treatment Number: (b) (6)
 Case Id: (b) (6)
 Suspect Drugs: Blinded trial medication, Paclitaxel
 Serious Events: Hepatobiliary disease

This 44-year-old female subject was enrolled in a blinded study for the treatment of metastatic breast cancer. The subject received oral investigational product at 1500 mg per day from (b) (6) and intravenous paclitaxel at 80 mg/m² weekly for three weeks of each four week cycle from (b) (6)

On (b) (6) 272 days after the start of investigational product and paclitaxel, the subject developed grade 3 or severe hepatobiliary disorder. The event was clinically significant (or requiring intervention) per protocol definition. She also experienced abdominal discomfort. Diagnostic test results on (b) (6) included: bilirubin 189.5 umol/L and gamma-glutamyltransferase (GGT) 154 umol/L (reference range 0 - 40). The subject was treated with ascorbic acid and Glucuro lactone. Treatment with paclitaxel had been discontinued per investigator decision on (b) (6) Treatment with

investigational product was discontinued due to the event and the subject was withdrawn from the study. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the hepatobiliary disorder may have been caused by investigational product and paclitaxel.

Follow-up information received on [REDACTED] (b) (6) Additional diagnostic test results from [REDACTED] (b) (6) included: Aspartate aminotransferase (AST) 429 IU/L (reference range 0 - 45); alanine aminotransferase (ALT) 154 IU/L (reference range 0 - 40).

Follow-up information received on [REDACTED] (b) (6)

The event have fatal outcome as the subject died on [REDACTED] (b) (6) It was unknown if an autopsy was performed.

APPENDIX 5 NARRATIVE FOR HEPATIC FAILURE EVENT RECEIVED FROM [REDACTED] (b) (6)

Protocol Id: LAPANP
 Investigator Number:
 Subject Number:
 Treatment Number:
 Case Id: [REDACTED] (b) (6)
 Suspect Drugs: Capecitabine, Lapatinib
 Serious Events: Diarrhoea, Hepatic failure

This female subject was a named patient enrolled in an open-label study for the treatment of metastatic breast cancer. The subject received lapatinib at 1250mg daily from an unspecified date and capecitabine from an unspecified date.

At an unknown time after the start of lapatinib, the subject developed grade 3 diarrhea. The event was clinically significant (or requiring intervention). The subject was treated with loperamide hydrochloride. Treatment with lapatinib was interrupted for 5 days. The event lasted 5 days and resolved on an unspecified date. Investigator causality was unknown at the time of reporting.

Follow up information received on [REDACTED] (b) (6)

The investigator reported that the subject died due to liver insufficiency after 4 weeks of treatment with lapatinib and xeloda. The subject presented a breast metastatic cancer. With the 1st line treatment (unspecified) she presented a liver insufficiency. With the 2nd line treatment no liver abnormalities were reported. Before starting 3rd line treatment (lapatinib and Xeloda) she presented a 6cm metastasis on the liver. She had a very good response but a liver insufficiency was detected and the treatment was withdrawn and about a week and a half ago the subject died.

APPENDIX 6 DISPROPORTIONALITY ANALYSIS

Spontaneously reported adverse event data are difficult to assess quantitatively because they are derived from voluntary reports and lack a reliable denominator. Statistical methods based on disproportionality of adverse event reporting are applied to spontaneous reporting databases to assess the relative reporting of a drug-event combination against the background of the entire database.

Data Mining Algorithm: MGPS

MGPS (Multi-Item Gamma Poisson Shrinker)^{1,2} is an empirical Bayes data mining algorithm and GSK's preferred method for disproportionality analysis (DPA) of post-marketing adverse event data in spontaneous reporting databases. MGPS uses information for all drugs and all events in a given database to compute the Empiric Bayes Geometric Mean (EBGM) for each observed drug-event combination in that database. EBGM values are adjusted estimates of relative reporting ratios (i.e., observed reporting rate / expected reporting rate) after Bayesian "shrinkage." An EBGM value of 5 is interpreted to mean that a drug-event combination has been reported at least 5 times as frequently as would be expected if reports involving the drug and reports of the event were independent (i.e., no reporting association). MGPS also computes the 2-sided 90% confidence interval (EB05, EB95) for each EBGM value.

The computations within MGPS are internally stratified, using a Mantel-Haenszel approach,³ by age, gender, and year of report. Stratification minimizes the detection of apparent drug-event associations that may be due to independent relationships between a drug and a stratum variable and an event and the same stratum variable. (An example is the reporting association between a drug used commonly in the elderly and an event commonly reported in the elderly.) Stratification by year of report reduces the chance of detecting signals that might arise due to "trendiness" in the reporting of specific drugs and/or events.

MGPS can compute EBGM values in two ways on the basis of how the reporter classified the drug at the time of reporting - as "suspect" or "concomitant." The "Suspect Only" computation includes drugs identified by the reporter as suspect. The "Suspect and Concomitant" computation includes all drugs in the adverse event report.

Adverse Event Reporting Databases: OCEANS and AERS

¹ DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system (with discussion). *Am Stat* 1999; 53 (3): 177-202.

² DuMouchel W, Pregibon D. Empirical Bayes screening for multi-item associations. *Proc KDD 2001*, San Diego, CA, ACM Press.

³ Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-48.

OCEANS is GlaxoSmithKline's worldwide safety database. OCEANS contains spontaneous adverse event reports from worldwide sources for GSK's marketed products, as well as serious adverse event reports from clinical trials of GSK compounds in development. Disproportionality analyses of OCEANS data are applied only to spontaneous adverse event reports for marketed non-vaccine products; clinical trials reports are not considered in the analyses.

AERS (Adverse Event Reporting System) is the safety database of the U.S. Food and Drug Administration (FDA). AERS is a passive surveillance system that relies on voluntary reporting of adverse events to FDA by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufacturers. AERS includes all spontaneous reports from US sources; serious and unlabeled spontaneous reports from non-US sources; and serious, unlabeled, and attributable post-marketing clinical trial reports from all sources. At GSK, DPA is run against quarterly public-release versions of AERS, as provided by a third-party vendor. The public-release versions of AERS may not contain all reports received by the FDA due to delays in data entry and prioritization of data entry.

Interpretation and Limitations of Disproportionality Analysis

DPA provides information about the relative reporting of adverse events in the post-marketing setting. DPA does **not** provide estimates of the incidence of adverse events.

A high relative reporting ratio (high EBGM value) indicates that there is an *association* between a drug and an event in a given database. A causal relationship between the drug and the event is only one of the possible explanations for the association; DPA alone cannot identify the nature of the association. High relative reporting ratios may be seen when events are actually related to medical conditions or co-prescribed drugs, or when adverse event reporting has been stimulated in some way (e.g., publicity, Dear Doctor letters, litigation). For these reasons, high relative reporting ratios are interpreted as hypotheses regarding potential causal associations between drugs and events. The U.S. FDA has used $EB05 \geq 2$ as a threshold for signal detection.⁴

A low relative reporting ratio indicates that a drug-event pair has not been reported more frequently than expected. It does not guarantee the absence of a causal relationship between a drug and an event.

Comparisons of relative reporting ratios between drugs should be made cautiously and should be interpreted as hypothesis-generating rather than confirmatory. A number of factors other than causality may affect the reporting frequencies of adverse events for a drug of interest or drugs in the same class, including the length of time on the market, labelling changes, and publicity. Awareness of potential reporting biases is critical when making comparisons.

⁴ Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* 2002; 25 (6): 381-92.

APPENDIX 7 PREVALENCE OF ELEVATED LFT VALUES AMONG CANCER PATIENTS AT BASELINE USING POOLED GSK ONCOLOGY CLINICAL TRIAL DATA FROM INET

Hepatic lab test	Threshold value	BASELINE PREVLANCE (%) [†]					
		Without Liver Metastases (N=2852)			With Liver Metastases (N=1146)		
		n/N	%	95% CI	n/N	%	95% CI
ALT	≥ 3xULN	37/2257	1.6	1.2, 2.3	30/996	3.1	2.1, 4.4
	≥ 5xULN	7/2257	0.3	0.1, 0.6	7/966	0.7	0.3, 1.5
	≥ 8xULN	3/2257	0.1	0.03, 0.4	0/966	0	--
	≥ 10xULN	2/2257	0.1	0.01, 0.3	0/966	0	--
	> 20xULN	0/2257	0	--	0/966	0	--
BILI	≥ 2xULN	8/2589	0.3	0.1, 0.6	6/1076	0.6	0.2, 1.2
	≥ 3xULN	4/2589	0.2	0.04, 0.4	2/1076	0.2	0.02, 0.7
	≥ 5xULN	1/2589	0.04	0, 0.2	0/1076	0	--
	≥ 10xULN	0/2589	0	--	0/1076	0	--
ALT+ BILI	≥3xULN & ≥1.5xULN	4/2243	0.2	0.05, 0.5	2/962	0.2	0.03, 0.8
	≥3xULN & ≥2xULN	3/2243	0.1	0.03, 0.4	1/962	0.1	0, 0.6
	Normal & ≥1.5xULN	5/2243	0.2	0.07, 0.5	6/962	0.6	0.2, 1.4
ALT+ BILI+ ALP	≥3xULN & ≥1.5xULN & Normal	0/2042	0	--	0/939	0	--
	≥3xULN & 2xULN & Normal	0/2042	0	--	0/939	0	--
	≥3xULN & ≥1.5xULN & >2xULN	2/2042	0.1	0.01, 0.4	2/939	0.2	0.03, 0.8
AST+ALT+BILI	>3XULN or >3XULN & >1.5X	7/2567	0.3	0.1, 0.6	3/989	0.3	0.06, 0.9
	>3XULN or >3XULN & >2X	5/2567	0.2	0.06, 0.5	2/989	0.2	0.02, 0.7

[†]Prevalence defined based on the pre-screening laboratory value. Subjects for which these values were missing were excluded from the denominator population.

Thus, prevalence = The number (n) of subjects meeting the threshold level / total number (N) of subjects in study for which lab values exist for that pre-screening visit. Ns were different for different LFT due to missing values of the lab tests.

APPENDIX 8 CUMULATIVE INCIDENCE OF NEW LFT ELEVATIONS USING POOLED GSK ONCOLOGY CLINICAL TRIAL DATA FROM INET†

		CUMULATIVE INCIDENCE (%)					
Hepatic lab test	Threshold value	Without Liver Metastases (N=2852)			With Liver Metastases (N=1146)		
		n/N	CumInc	95% CI	n/N	CumInc	95% CI
ALT	≥ 3xULN	49/1900	2.58	1.91, 2.8	7/663	1.06	0.43, 1.34
	≥ 5xULN	15/1900	0.79	0.44, 0.9	1/663	0.15	0, 0.34
	≥ 8xULN	6/1900	0.32	0.12, 0.39	1/663	0.15	0, 0.34
	≥ 10xULN	1/1900	0.05	0, 0.11	1/663	0.15	0, 0.34
	> 20xULN	0/1900	0	--	0/663	0	--
BILI	≥ 2xULN	37/2528	1.46	1.03, 1.59	33/1027	3.21	2.22, 3.6
	≥ 3xULN	15/2528	0.59	0.33, 0.67	18/1027	1.75	1.04, 2.01
	≥ 5xULN	8/2528	0.32	0.14, 0.38	8/1027	0.78	0.34, 0.95
	> 10xULN	3/2528	0.12	0.02, 0.17	2/1027	0.19	0.02, 0.32
ALT+ BILI	≥3xULN & ≥1.5xULN	2/1856	0.11	0.01, 0.17	1/648	0.15	0, 0.34
	≥3xULN & ≥2xULN	1/1856	0.05	0, 0.11	1/648	0.15	0, 0.34
	Normal & ≥1.5xULN	40/1856	2.16	1.54, 2.35	24/648	3.7	2.39, 4.28
ALT+ BILI+ ALP	≥3xULN & ≥1.5xULN & Normal	2/1090	0.18	0.02, 0.3	1/270	0.37	0.01, 0.87
	≥3xULN & 2xULN & Normal	1/1090	0.09	0, 0.2	1/270	0.37	0.01, 0.87
	≥3xULN & ≥1.5xULN & ≥2xULN	1/1090	0.09	0, 0.2	0/270	0	--
AST+ALT+ BILI	>3XULN or >3XULN & >1.5X	4/2441	0.16	0.04, 0.22	0/713	0	--
	>3XULN or >3XULN & >2X	2/2411	0.08	0.01, 0.13	0/713	0	--

†Subjects with missing laboratory values at pre-screening were excluded. Thus, cumulative incidence (CumInc) = The number (n) of subjects meeting the threshold level during the study period / Number (N) of patients at baseline who did not have missing values and had normal LFTs; CI = confidence interval. Ns were different for different LFT due to missing values of the lab tests.

APPENDIX 9 INCIDENCE RATE OF NEW LFT ELEVATIONS USING POOLED GSK ONCOLOGY CLINICAL TRIAL DATA FROM INET†

Hepatic lab test	Threshold value	INCIDENCE RATES (in 1000 PERSON MONTHS)					
		Without Liver Metastases (N=2852)			With Liver Metastases (N=1146)		
		n/person-month	IR	95% CI	n/person-month	IR	95% CI
ALT	≥ 3xULN	49/8330	5.9	4.4, 7.8	7/3337	2.1	0.8, 4.3
	≥ 5xULN	15/8429	1.8	1.0, 2.9	1/3349	0.3	0.01, 1.7
	≥ 8xULN	6/8453	0.7	0.3, 1.5	1/3349	0.3	0.01, 1.7
	≥ 10xULN	1/8465	0.1	0.003, 0.7	1/3349	0.3	0.01, 1.7
	> 20xULN	0/8469	0	--	0/3353	0	--
BILI	≥ 2xULN	37/11574	3.2	2.3, 4.4	33/4819	6.9	4.7, 9.6
	≥ 3xULN	15/11659	1.3	0.7, 2.1	18/4854	3.7	2.2, 5.9
	≥ 5xULN	8/11682	0.7	0.3, 1.3	8/4861	1.6	0.7, 3.2
	> 10xULN	3/11692	0.3	0.05, 0.7	2/4862	0.4	0.05, 1.5
ALT+ BILI	≥3xULN & ≥1.5xULN	2/8323	0.2	0.03, 0.9	1/3306	0.3	0.01, 1.7
	≥3xULN & ≥2xULN	1/8326	0.1	0.003, 0.7	1/3306	0.3	0.01, 1.7
	Normal & ≥1.5xULN	40/8216	4.9	3.5, 6.6	24/3227	7.4	4.8, 11.1
ALT+ BILI+ ALP	≥3xULN & ≥1.5xULN & Normal	2/5617	0.4	0.04, 1.3	1/1519	0.7	0.02, 3.7
	≥3xULN & 2xULN & Normal	1/5620	0.2	0.005, 1.0	1/1519	0.7	0.02, 3.7
	≥3xULN & ≥1.5xULN & >2xULN	1/5620	0.2	0.005, 1.0	0/1519	0	--
AST+ALT+BILI	>3XULN or >3XULN & >1.5X	4/11195	0.4	0.1, 0.9	0/3574	0	--
	>3XULN or >3XULN & >2X	2/11198	0.2	0.02, 0.6	0/3574	0	--

† Subjects with missing laboratory values at pre-screening were excluded. Thus, incidence rate (IR) = The number (n) of new events meeting outcomes criteria during the study period / Follow-up period (in person time); CI = confidence incidence. Ns were different for different LFT due to missing values of the lab tests.

APPENDIX 10 CLINICAL TRIAL LITERATURE REVIEW: LIVER FUNCTION TEST (LFT) EVENTS (GRADE 3 OR 4 ONLY) AMONG ONCOLOGY PATIENTS RECEIVING TKI DRUGS AS CANCER TREATMENT

	Report G3/4 events by test		Trial indication	Grade 3/4 LFT toxicity, %		
	Study (N) ^a	% ^b		ALT	AST	BILI
Class I: Small molecule TKIs						
Gleevec (Imatinib)	17	28	Leukemia, breast, glioma, HCC, lung, glioblastoma, prostate, myeloma, ovarian	0-8% (G3); <1% (G4)	0-19% (G3); 0% (G4)	0-19% (G3/4)
Iressa (Gefitinib)	29	35	Lung, breast, colorectal, glioma, glioblastoma, HCC, prostate, ovarian, H&N, RCC, mesothelioma	0-14% (G3/4)		Not listed in most trials; 0-11% (G3), 0% (G4)
Tarceva (Erlotinib)	11	26	Lung, pancreatic, biliary, gastric, colorectal, glioma, HCC, prostate, H&N	0-11% (G3/4)		0-5% (G3); 0% (G4)
Nexavar (Sorafenib)	12	48	RCC, lung, H&N, prostate	0-10% (G3/4)	0-5% (G3/4)	0-7% (G3/4)
Sprycel (Dasatinib)	1	33	Leukemia	2% (G3/4)	2% (G3/4)	0%
Sutent (Sunitinib)	1	10	RCC	2-3% (G3)		0-1%
Tykerb (Lapatinib)	1	13	Breast, Salivary Glands	ALT/AST= 4% (G3/4)		--
Tasigna (Nilotinib)	2	100	Leukemia	1-3% (G3/4)		3%-9% (G3/4)
Class II: Humanized monoclonal antibodies directed against receptor target tyrosine kinases and their ligands						
Herceptin (Trastuzumab)	9	17	Breast, urothelial	0-5% (G3); 0-4% (G4)		0-9% (G3/4)
Avastin (Bevacizumab)	7	15	Colorectal, HCC, ovarian, RCC, pancreatic, carcinoid, sarcoma	G3 only: 0-15% (ALT); 0-33% (AST); 6% (BILI)		
Erbix (Cetuximab)	10	26	H&N, rectal, ovarian, gastric, breast, HCC, lung, Nasopharyngeal	0-10% (G3/4)		0-2% (G3/4)
Vectibix (Panitumumab)	0	0 ^c	--	--	--	--

- a. Number of studies reporting Grade 3 or 4 events of individual LFT elevations for each TKI of interests. References are included in APPENDIX 11.
- b. Proportion (%) = number of studies reported Grade 3 or 4 events of individual LFT elevations / Total number of studies which reported some hepatotoxicity events.
- c. Six studies, which reported some hepatotoxicity events, were reviewed but none included Grade 3-4 events of individual LFT elevations

APPENDIX 11 REFERENCES FOR CLINICAL TRIAL LITERATURE REVIEW

Gleevec (imatinib) (17 studies)

Al-Batran S-E, et al. Imatinib Mesylate for Targeting the Platelet-derived Growth Factor b Receptor in Combination With Fluorouracil and Leucovorin in Patients With Refractory Pancreatic, Bile Duct, Colorectal, or Gastric Cancer: A Dose-escalation Phase I Trial. *Cancer* (2007) 109:1897-904.

Alberts DS, et al. Phase II trial of imatinib mesylate in recurrent, biomarker positive, ovarian cancer (Southwest Oncology Group Protocol S0211). *Int J Gynecol Cancer* (2007) 17:784-788.

Bajaj GK, et al. Phase II Study of Imatinib Mesylate in Patients with Prostate Cancer with Evidence of Biochemical Relapse After Definitive Radical Retropubic Prostatectomy or Radiotherapy. *Urology* (2007) 69:526-531.

Carpenter PA, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome–positive leukemia. *Blood* (2007) 109:2791-2793.

Eckel F, et al. Pharmacokinetic and Clinical Phase II Trial of Imatinib in Patients with Impaired Liver Function and Advanced Hepatocellular Carcinoma. *Oncology* (2005) 69:363-371.

Fischer T, et al. Safety and efficacy of STI-571 (imatinib mesylate) in patients with bcr/abl-positive chronic myelogenous leukemia (CML) after autologous peripheral blood stem cell transplantation (PBSCT). *Leukemia* (2002) 16:1220-1228.

Gibbons J, et al. Phase I and Pharmacokinetic Study of Imatinib Mesylate in Patients With Advanced Malignancies and Varying Degrees of Renal Dysfunction: A Study by the National Cancer Institute Organ Dysfunction Working Group. *J Clin Oncol* (2008) 28:570-576.

Krug LM, et al. Imatinib Mesylate Lacks Activity in Small Cell Lung Carcinoma Expressing c-kit Protein: A Phase II Clinical Trial. *Cancer* (2005) 103:2128-31.

Lin AM, et al. A phase II trial of imatinib mesylate in patients with biochemical relapse of prostate cancer after definitive local therapy. *BJU* (2006) 98:783-789.

* Modi S, et al. A phase I study of cetuximab/paclitaxel in patients with advanced-stage breast cancer. *Clin Breast Cancer* (2006) 7:270-277.

O'Brien SG, et al. Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. *N Engl J Med* (2003) 348:994-1004.

Ottmann OG, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome–positive acute lymphoid leukemias. *Blood* (2002) 100:1965-1971.

Rao K, et al. A phase II trial of imatinib mesylate in patients with prostate-specific antigen progression after local therapy for prostate cancer. *Prostate* (2005) 62:115-122.

Reardon DA, et al. Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme. *J Clin Oncol* (2005) 23:9359-9368.

Sawyers CL, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* (2002) 99:3530-3539.

Talpaz M, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* (2002) 99:1928-1937.

Wen PY, et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consortium Study 99-08. *Clin Cancer Res* (2006) 12:4899-4907.

Iressa (gefitinib) (29 studies)

Asahina H, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer* (2006) 95:998-1004.

Chau I, et al. Gefitinib and irinotecan in patients with fluoropyrimidine-refractory, irinotecan-naïve advanced colorectal cancer: a phase I–II study. *Ann Oncol* (2007) 18:730-737.

Chen C, et al. Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer. *J Clin Oncol* (2007) 25:4880-4886.

* Ciardiello F, et al. Phase II study of gefitinib in combination with docetaxel as first-line therapy in metastatic breast cancer. *Br J Cancer* (2006) 94:1604-1609.

Cohen EE, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* (2003) 21:1980-1987.

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- Xu JM, et al. Phase II trial of sequential gefitinib after minor response or partial response to chemotherapy in Chinese patients with advanced non-small-cell lung cancer. *BMC Cancer* (2006) 6:288.

Tarceva (erlotinib) (11 studies)

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- Dragovich T, et al. Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial. *Cancer Chemother Pharmacol* (2007) 60:295-303.
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Awada A, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumors. *Br J Cancer* (2005) 92:1855-1861.

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Duran I, et al. Phase I Targeted Combination Trial of Sorafenib and Erlotinib in Patients with Advanced Solid Tumors. *Clin Cancer Res* (2007) 13:4849-4857.

Elser C, et al. Phase II Trial of Sorafenib in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck or Nasopharyngeal Carcinoma. *J Clin Oncol* (2007) 25:3766-3773.

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Ratain MJ, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* (2006) 24:2505-2512.

Ryan CW, et al. Sorafenib with Interferon Alfa-2b As First-Line Treatment of Advanced Renal Carcinoma: A Phase II Study of the Southwest Oncology Group. *J Clin Oncol* (2007) 25:3296-3301.

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Sutent (sunitinib) (1 study)

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Tykerb (lapatinib) (1 study)

* Johnston S, et al. Phase II Study of Predictive Biomarker Profiles for Response Targeting Human Epidermal Growth Factor Receptor 2 (HER-2) in Advanced Inflammatory Breast Cancer With Lapatinib Monotherapy. *J Clin Oncol* (2008) 26:1066-1072.

Tasingna (nilotinib) (2 studies)

le Coutre P et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. *Blood* (2008) 111(4):1834-9.

Kantarjian H, et al. Nilotinib in Imatinib-Resistant CML and Philadelphia Chromosome-Positive ALL. *N Engl J Med* (2006) 354:2542-51.

Herceptin (trastuzumab) (9 studies)

* Adamo V, et al. Safety and activity of trastuzumab-containing therapies for the treatment of metastatic breast cancer: our long-term clinical experience (GOIM study). *Ann Oncol* (2007) 18(Suppl 6):11-15.

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* Schaller G, et al. Phase II Study of Capecitabine Plus Trastuzumab in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancer Pretreated With Anthracyclines or Taxanes. *J Clin Oncol* (2007) 25:3246-50.

Avastin (bevacizumab) (7 studies)

Chen HX, et al. Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: An NCI treatment referral center trial TRC-0301. *J Clin Oncol* (2006) 24:3354-3360.

Garcia AA, et al. Phase II Clinical Trial of Bevacizumab and Low-Dose Metronomic Oral Cyclophosphamide in Recurrent Ovarian Cancer: A Trial of the California, Chicago, and Princess Margaret Hospital Phase II Consortia. *J Clin Oncol* (2008) 26:76-82.

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Yang JC, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* (2003) 349:427-34.

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Zhu AX, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* (2006) 24:1898-1903.

Erbix (cetuximab) (10 studies)

Chan ATC, et al. Multicenter, Phase II Study of Cetuximab in Combination With Carboplatin in Patients With Recurrent or Metastatic Nasopharyngeal Carcinoma. *J Clin Oncol* (2005) 23:3568-3576.

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Hofheinz R-D, et al. Phase I Trial Of Cetuximab In Combination With Capecitabine, Weekly Irinotecan, And Radiotherapy As Neoadjuvant Therapy For Rectal Cancer. *Int J Rad Oncol Biol Phys* (2006) 66:1384-1390.

* Modi S, et al. A phase I study of cetuximab/paclitaxel in patients with advanced-stage breast cancer. *Clin Breast Cancer* (2006) 7:270-277.

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Robert F, et al. Phase I Study of Anti–Epidermal Growth Factor Receptor Antibody Cetuximab in Combination With Radiation Therapy in Patients With Advanced Head and Neck Cancer. *J Clin Oncol* (2001) 19:3234-3243.

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Rodel C, et al. Phase I-II Trial Of Cetuximab, Capecitabine, Oxaliplatin, And Radiotherapy As Preoperative Treatment In Rectal Cancer. *Int J Rad Oncol Biol Phys* (2008) 70:1081-1086.

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Zhu AX, et al. Phase 2 Study of Cetuximab in Patients With Advanced Hepatocellular Carcinoma. *Cancer* (2007) 110:581-9.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22059	----- SUPPL 7	----- SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	----- TYKERB TABLETS

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/s/

KIM J ROBERTSON

09/02/2009

02September09 OSE Consult; John Senior; Tykerb Hepatotoxicity

From: Robertson, Kim
Sent: Monday, August 31, 2009 12:13 PM
To: Rich.Swenson@gsk.com
Subject: sNDA 22-059; Tykerb-Clinical Request for Information

Importance: High
Hello Richard:

Please see the following Clinical Request for Information below, as it pertains to GSK's sNDA for Tykerb:

- Please submit all the CRFs for the patients who had a PFS event (disease progression or death of any cause).

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON

08/31/2009

31August09 Clinical Information Request re: sNDA 22-059 Tykerb

From: Robertson, Kim
Sent: Thursday, August 27, 2009 6:24 PM
To: Rich.Swenson@gsk.com
Subject: sNDA 22-059 Tykerb

Importance: High
Hello Richard:

The clinical reviewer has the following question as it pertains to your sNDA for Tykerb®

1. The protocol was amended to include patients with stage IV disease only (exclude stage III) in Amendment 1. Please provide the subject IDs and list which subjects had received treatment for neoadjuvant disease as a bridge to surgery for their primary breast cancer.

Thank you,
Kim

*Kim J. Robertson
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Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON

08/31/2009

27August09 Clinical Request for Information re: sNDA 22-059



NDA 22-059/S-007

FILING COMMUNICATION

GlaxoSmithKline
2301 Renaissance Boulevard
RN0210 P.O. Box 61540
King of Prussia, PA 19406-2772, USA

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

Please refer to your March 31, 2009, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tykerb® (lapatinib ditosylate) Tablets, 250mg.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, this supplemental application is considered filed 60 days after the date we received your supplemental application in accordance with 21 CFR 314.101(a). The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is January 31, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
08/07/2009

From: Robertson, Kim
Sent: Tuesday, August 04, 2009 10:37 AM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole--Request for Information

Importance: High
Hello Richard:

The DSI Reviewer of your sNDA 22-059/SLR-007, for Tykerb/Letrozole has the following requests for information:

- Please provide the contact information (i.e., phone, fax # or e-mail) for Drs. Pivot, Lichinitser and Gomez
- Please provide primary endpoint patient data organized by these Clinical Investigators (namely, Dr. Lichinitser ID#001433, Dr. Pivot ID#049858, and Dr. Gomez ID#053310) and further stratified by randomization group (letrozole with placebo VS. letrozole with lapatinib). Please tabulate individual patient "progressive free survival" time in days or weeks (as preferred), as well as the corresponding calendar dates (in month, day and year format). As defined in the protocol, "progressive free survival" is time from randomization until the earliest date of disease progression or death due to any cause, if sooner.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim

Sent: Monday, August 17, 2009 4:23 PM

To: 'Rich.Swenson@gsk.com'

Subject: RE: Tykerb & Letrozole--ODAC

Thanks Richard. I will say that I was a little surprised about the decision as well. The clinical team leader is away on vacation now, but I will **certainly** ask Dr. Justice if he can give me an explanation.

Please let me confer with them, and I will most definitely provide you with further details.

Regards,
Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Monday, August 17, 2009 4:00 PM

To: Robertson, Kim

Subject: Re: Tykerb & Letrozole--ODAC

Dear Kim:

No, we have not been told previously that the lapatinib/letrozole sNDA will be going to ODAC.

To be honest, we are somewhat surprised by this decision given this is a supplement and the original application did not go to ODAC.

Can you provide any insight into why FDA feels we need to take this application to ODAC and if there is an opportunity for GSK to provide a rationale why this applications should not go to ODAC?

Thanks and Regards,

rich

Richard Swenson, Ph.D.

Senior Director

Global Regulatory Affairs - Oncology

From: Robertson, Kim
Sent: Monday, August 17, 2009 5:15 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: Tykerb & Letrozole--ODAC
Richard:

I was informed that the clinicians and statisticians have issues with the population and the risk/benefit ratio for this application.

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Monday, August 17, 2009 4:00 PM
To: Robertson, Kim
Subject: Re: Tykerb & Letrozole--ODAC

Dear Kim:

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Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs - Oncology

From: Robertson, Kim
Sent: Wednesday, August 26, 2009 2:45 PM
To: 'Rich.Swenson@gsk.com'
Cc: Cross Jr, Frank H
Subject: RE: Tykerb sNDA and ODAC

Importance: High
Hello Richard:

Yes, Bob was correct in what I conveyed to him on Monday, but I did emphasize that it was a **“MIGHT not be going”**. I just spoke with Dr. Patricia Cortazar today (the Clinical Team Leader of your sNDA), and she has asked me to have you/GSK to please put your rationale for not having this supplement go before ODAC **in writing**. She and the primary clinical reviewer would like to review the rationale, prior to considering a t-con to discuss this.

Please provide us with a robust rationale, and perhaps everyone can have an end-result that is preferable for all involved.

Thanks Richard,
Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Wednesday, August 26, 2009 9:23 AM
To: Robertson, Kim
Cc: Cross Jr, Frank H
Subject: Tykerb sNDA and ODAC

Dear Kim:

On Monday, Bob Watson called me to say that after a discussion with you it may no longer be likely that our recent efficacy supplement for Tykerb/aromatase-inhibitor would be required to go before ODAC.

As you know, preparing for an ODAC is an expensive, time-consuming activity. Can you confirm that we are no longer slated to appear before ODAC.

Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director

From: Robertson, Kim
Sent: Thursday, August 27, 2009 6:24 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb

Importance: High
Hello Richard:

The clinical reviewer has the following question as it pertains to your sNDA for Tykerb®

1. The protocol was amended to include patients with stage IV disease only (exclude stage III) in Amendment 1. Please provide the subject IDs and list which subjects had received treatment for neoadjuvant disease as a bridge to surgery for their primary breast cancer.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Thursday, August 27, 2009 3:00 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb/Letrozole

Importance: High
Hello Richard:

Dr. Cortazar told me that GSK should have their written rationale to us within 2 weeks. We will look for it no later than September 11, 2009. Please provide the robust rationale of GSK's reasons why this sNDA should not go to ODAC.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Monday, August 31, 2009 12:13 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059; Tykerb-Clinical Request for Information

Importance: High
Hello Richard:

Please see the following Clinical Request for Information below, as it pertains to GSK's sNDA for Tykerb:

- Please submit all the CRFs for the patients who had a PFS event (disease progression or death of any cause).

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

August '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Richard Swenson, Ph.D.

From: Kim J. Robertson

Fax:

Fax: 301-796-9845

Phone:

(b) (6)

Phone: 301-796-1441

Pages, including cover sheet: 1

Date: 19 June 2009

Re: **sNDA#22-059; Lapatinib and Letrozole-Clinical Request for Information**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Dear Dr. Swenson:

The clinical reviewer of your sNDA for Lapatinib & Letrozole has the following request for information:

Clinical:

1. Did the independent review committee follow an independent review charter to assess PFS? If so, please provide the link and charter.

Regards,

Kim J. Robertson
Consumer Safety Officer

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/s/

Kim Robertson
6/19/2009 07:12:01 PM
CSO
19June09 Clinical Request for Information

From: Robertson, Kim
Sent: Tuesday, June 16, 2009 2:34 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 SLR-007 Tykerb

Importance: High
Hello Richard:

The clinical reviewer of your sNDA for Tykerb has the following questions/comment:

- In the pfsinv.xpt dataset, what does abbreviation "ACT " represent?
- Under the "Reason" column, "ACT prior to event - censor at last scan prior to ACT" is noted, but no abbreviation for ACT is given.
- We cannot find the explanation in the dataset definition file.

Would you please provide us with assistance on these matters Richard?

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22059	SUPPL-7	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	TYKERB TABLETS

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/s/

KIM J ROBERTSON

01/20/2010

June '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole



NDA 22-059/S-007

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
UP4110
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Richard Swenson, Ph.D.
Senior Director, US
Regulatory Affairs

Dear Dr. Swenson:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tykerb® (lapatinib) Tablets, 250 mg

NDA Number: 22-059

Supplement number: 007

Review Priority Classification: Standard

Date of supplement: March 31, 2009

Date of receipt: March 31, 2009

This supplemental application proposes the following change(s): Tykerb in combination with (b) (4)

[Redacted area]

(b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 31, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kim Robertson

5/28/2009 01:24:49 PM

60-Day PAS Acknowledgement Letter NDA 22-059 SLR-007 '09

From: Robertson, Kim
Sent: Wednesday, May 27, 2009 4:13 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Lapatinib & Letrozole

Attachments: 27May09 Clinical Request for Information.pdf
Hello Richard:

Please see the attached .pdf document, as it contains a clinical request for information.

Regards,
Kim



27May09
Clinical Request fo

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Fax



DIVISION OF DRUG ONCOLOGY PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Richard Swenson, Ph.D.

From: Kim J. Robertson

Fax:

Fax: 301-796-9845

Phone: (b) (6)

Phone: 301-796-1441

Pages, including cover sheet: 1

Date: 27 May 2009

Re: **sNDA#22-059; Lapatinib and Letrozole-Clinical Request for Information**

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● Dear Dr. Swenson:

The clinical reviewer of your sNDA for Lapatinib & Letrozole has the following request:

Clinical:

1. In the CRFs for SAEs and non-SAEs, it is noted that the maximum toxicity grading is marked with an "X" as "not applicable" as opposed to grade 1 to 5 for adverse events. Please explain this assessment.

Regards,

Kim J. Robertson
Consumer Safety Officer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

KIM J ROBERTSON

01/20/2010

May '09 IRs for GSK; sNDA 022059/S-007; Tykerb + Letrozole



NDA 22-059/S-007

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
UP4110
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Richard Swenson, Ph.D.
Senior Director, US
Regulatory Affairs

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5901-B Ammendale Road
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Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kim Robertson

5/28/2009 01:24:49 PM

60-Day PAS Acknowledgement Letter NDA 22-059 SLR-007 '09

From: Robertson, Kim

Sent: Friday, April 10, 2009 1:12 PM

To: 'Rich.Swenson@gsk.com'

Cc: Ryan, Qin; Ibrahim, Amna; Alaknanda.J.Preston@gsk.com; Julie.Byrne@gsk.com; steven.h.stein@gsk.com; Stephanie.F.Guerrera@gsk.com; Chattopadhyay, Somesh

Subject: RE: NDA 22-059 Tykerb--Survival Updates

Importance: High

Richard:

In addition to the dataset, please submit the following:

1. Data definition file
2. A SAS transport file containing any user defined formats if they are use.

Thank you,

Kim

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]

Sent: Thursday, April 09, 2009 4:19 PM

To: Robertson, Kim

Cc: Ryan, Qin; Ibrahim, Amna; Alaknanda.J.Preston@gsk.com; Julie.Byrne@gsk.com; steven.h.stein@gsk.com; Stephanie.F.Guerrera@gsk.com

Subject: Re: NDA 22-059 Tykerb--Survival Updates

Dear Kim:

In response to your email of 31 March 2009 and Dr. Ryan's telephone call of 2 April 2009, GlaxoSmithKline would like to explain what we can deliver to meet your request for additional information on the following Tykerb (lapatinib) submissions:

- **(1) The most recent US Periodic (quarterly) Update**

The next US Periodic (USP) Report will be submitted 10 April 2009 for the timeframe 13 December 2008 to 12 March 2009. When the USP is submitted, all of the cases included in the report are electronically transferred into the FDA's AERS database.

GSK will submit: GlaxoSmithKline (GSK) can provide an SGML file of these data or a PDF of the 3500 Forms. (Note: the USP only contains cases that have not previously been reported electronically into AERs as alerts.

- **(2) The most recent quarterly update of hepatotoxicity cases associated with the use of**

**Tykerb (lapatinib) dated 31 March 09 and covering a period of 18-Oct-2008 to 16-Jan-2009.
(Submitted to NDA 22-059 on 9 April 2009 [Sequence 031]).**

GSK evaluated lapatinib hepatobiliary cases by running a standard MedDRA query ("Possible drug-related hepatic disorders", comprehensive SMQ, MedDRA v11.1) to identify cases from the GSK "OCEANS" safety database. These identified cases are then manually reviewed and evaluated.

Part of the report submitted to FDA on 9 April 2009 consisted of summary tables of laboratory values produced programmatically from approximately 24 ongoing studies.

GSK will submit: We propose to provide a PDF file of the CIOMS forms for the 42 key cases identified from the OCEANS safety database during the review period for the current report (18-Oct-2008 to 16-Jan-2009).

The dataset and series of programs needed to generate the summary tables of laboratory values included in the quarterly hepatotoxicity report will be delivered to FDA as follows from the GSK Clinical Trials Database:

- 24 Lab data sets (as .XPT files)
- 24 Data Definitions Tables (DDTs) for the lab data sets (.PDF)
- 1 aggregated ABN data set () containing all abnormalities for the 24 studies as reported in the last quarterly update.
- 1 DDT for the ABN data set (.PDF)
- 5 SAS programs (.SAS) which generate quarterly summaries for 24 studies.

- **(3) The update of overall survival (OS) from the 19 May 2008 submission (NDA 22-059, Sequence # 0012).**

The following items will be provided from the GSK Clinical Trials Database for the submitted OS update for Study EGF100151:

- 4 SAS transport File
- 1 DDT containing metadata for the 4 datasets

GSK will prepare these documents as soon as possible. If these items are NOT what FDA believes most appropriate, please let us know quickly.

Thanks and Regards,

rich

Richard Swenson, Ph.D.
Senior Director
Global Regulatory Affairs - Oncology

From: Robertson, Kim
Sent: Wednesday, April 22, 2009 2:23 PM
To: 'Rich.Swenson@gsk.com'
Subject: sNDA 22-059 Tykerb + Letrozole

Importance: High

Attachments: Table by site, PI, address, etc.xls
Hello Richard:

Please see the attached excel table. Our clinicians are asking GSK to please fill it in (site #, PI, address, etc.).

Thank you,
Kim



Table by site,
I, address, et.

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
01/20/2010
April '09 IRs for GSK; sNDA 022059; Tykerb + Letroole

From: Robertson, Kim
Sent: Tuesday, March 31, 2009 4:27 PM
To: 'Rich.Swenson@gsk.com'
Subject: NDA 22-059 Tykerb--Survival Updates

Hello again Richard:

Drs'. Ryan and Ibrahim have asked me to ask you the following as it pertains to Tykerb:

Do you have any **safety updates** parallel to your OS follow-up time frame? If so, please provide datasets to support the information.

Thanks,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

KIM J ROBERTSON
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March '09 IRs for GSK; sNDA 022059; Tykerb + Letrozole