The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: EGF103009

Title: A Phase II Study to Evaluate the Efficacy, Safety and Pharmacodynamics of Lapatinib in Patients with Relapsed or Refractory Inflammatory Breast Cancer

Phase: II

Study Period: The first subject enrolled in this study on 03 March 2005. The last subject last visit (LSLV) date (Day 84 visit for the last subject enrolled) of the data cut off for efficacy analyses was 17 September 2007. Thus, the best objective overall response rate (ORR) at the Day 84 visit would confirm initial responses from earlier assessment visits (Day 28 and Day 56 for skin disease assessments and Response Evaluation Criteria in Solid Tumors [RECIST], respectively). The survival data cut-off date for the report was 03 October 2008. The cut-off date (last subject last visit) for this report is 31 May 2010 and provides a final accountability of safety for subjects remaining on study following the efficacy cut-off date from the previous report.

Study Design: This was a single-arm, 2-cohort, Phase II, open label, multicenter study

Centres: This study was carried out at 27 centers in 8 countries (Belgium, Canada, France, Israel, Spain, Tunisia, United Kingdom, and the United States). Twenty five of these centers enrolled subjects, the remaining 2 centers, 1 in Spain and 1 in Israel, received investigational product but did not enroll subjects.

Indication: Inflammatory breast cancer

Treatment: A daily dose of lapatinib 1500 mg (6 x 250 mg tablets) was taken orally at the same time each day (at least 1 hour before or 1 hour after a meal). The dose of lapatinib could be reduced to 1000 mg or dosing could be temporarily suspended to allow resolution of drug related toxicities.

Objectives: The primary objective of this study was to evaluate the Overall Response Rate (ORR defined as complete response [CR] or partial response [PR]), of treatment with daily lapatinib in subjects with relapsed or refractory inflammatory breast cancer (IBC) whose tumors overexpress human epidermal growth factor receptor-2 (HER2; ErbB2) .

Primary Outcome/Efficacy Variable: The primary endpoint of the study comprised of ORR (CR + PR).
A clinical evaluation of disease response was made for disease confined to the skin of the breast and/or trunk of the body.

- CR was defined as the disappearance of all clinical evidence of active tumor by clinical evaluation. The subject was to be free of all symptoms.
- PR was defined as a 50% or greater decrease in clinical evidence of active tumor, taking as reference the baseline disease status.
- PD was defined as at least a 25% increase in clinical evidence of active tumor, taking as reference the baseline disease status.
- SD was defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD, taking as reference the baseline disease status.

In the presence of measurable disease, the objective status and best response to treatment was also determined for each subject according to definitions established by RECIST.

- CR was defined as the disappearance of all evidence of active tumor. The subject must have been free of all symptoms.
- PR was defined as a decrease of >30% in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
- Progressive disease (PD) was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
- SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

If a CR or PR was documented, either by RECIST or clinical evaluation, a confirmatory disease assessment was performed 4 weeks after the criteria for response were first met.
For subjects who had both measurable and clinically evaluable skin disease, the response of the subject was defined

by the best response, provided there was no evidence of disease progression. Note: A best overall response of CR was documented only if the response for both measurable and clinically evaluable skin disease was a CR, as shown in the following table:

RECIST-Based Overall Response	Clinically Evaluable Skin Disease Response	Combined "Best" Response
CR	CR	CR
CR or PR	PR or SD	PR
PR or SD	CR or PR	PR
PD	Any	PD
Any	PD	PD
NE	CR or PR	PR
NE	SD	SD

NE=Not evaluable.

Independent review based on digital photographs was retrospectively performed for response assessments of cutaneous disease. This evaluation was not pre-specified in the protocol and did not include all investigator observations such as warmth, tenderness, induration and edema (if subtle) which required physical examination of the subject.

Secondary Outcome/Efficacy Variable(s): The secondary efficacy parameters were clinical benefit, PFS, time to response, and response duration.

1. Clinical benefit was defined as CR or PR for at least 4 weeks, or SD for at least 6 months.
2. PFS was defined as the time between the first dose of investigational product and the first documented sign of disease progression or death.
3. Overall Survival was defined as the time from the first dose of investigational product until death due to any cause.
4. Time to response was defined as the time between the first dose of investigational product and the first documented CR or PR.
5. Response duration was defined as the time from initial documented CR or PR to the first documented sign of disease progression or death due to breast cancer.
6. QOL measurements included changes in EORTC-QLQ-C30 and pain scale responses from baseline.

Statistical Methods: A total of 120 subjects were to be enrolled in the study. The sample size was determined by logistic feasibility and was not driven by statistical considerations.

The primary analysis population was the Intent-to-Treat (ITT) population, defined as all subjects who received at least 1 dose of lapatinib who were assigned to Cohort A or Cohort B. Cohort A subject tumor's overexpressed HER2 (IHC 2+/3+ or FISH amplified) and Cohort B subject tumor's expressed EGFR without HER2 overexpression. A per protocol (PP) population and HER2+ population were also analyzed. The PP population included all subjects assigned to a cohort in the ITT population with confirmed HER2 and EGFR central laboratory results and no major protocol violations. The HER2+ population included all subjects in the ITT population whose tumors overexpressed HER2 (IHC 3+ or FISH amplified by either local or central laboratory results). These analyses were performed to account for the change in determination of HER2 status introduced following Protocol EGF103009 Amendment 3.

The primary efficacy endpoint was ORR which was based on investigator assessment of best response using RECIST, clinically evaluable skin disease criteria, and combined RECIST and/or clinically evaluable skin disease criteria, and also the independent assessment of best response using clinically evaluable skin disease criteria. Response rates were summarized, together with exact 95% confidence intervals (CI).

The rate of clinical benefit was calculated as the percentage of subjects achieving a CR or PR for at least 4 weeks, or disease stabilization for $\geq$6 months. This rate was presented with unadjusted exact 95% CIs. For ORR and the clinical benefit response rate, subjects in each cohort with an unknown or missing response were treated as non-responders. The percentage of surviving subjects who were progression-free 3 months (12 weeks) after the start of treatment was summarized using a Kaplan-Meier survival curve. Overall survival was defined as the time from the first dose of investigational product until death due to any cause. For subjects who did not die, time to death was censored at the time of last contact. The median overall survival, first and third quartiles were presented with 95% CIs and summarized using Kaplan-Meier survival curves.

Time to response was defined as the time from the start of treatment until first documented evidence of CR or PR. Duration of response was calculated for subjects whose tumors showed a CR or PR, and was defined as the time from first documented evidence of response until the first documented sign of disease progression or death due to breast cancer. Time to response and duration of response data were summarized using a cumulative incidence curve. Safety data (AEs, clinical laboratory evaluations, vital signs, electrocardiogram (ECG), ECHO/MUGA scans, and ECOG performance status) were presented using summary statistics.

Study Population: Subjects were non-pregnant females using adequate contraception who were ≥18 years with a life expectancy of ≥12 weeks. Subjects had histologically confirmed IBC based on the presence of inflammatory changes in the involved breast, including diffuse erythema, edema, and peau d'orange, with or without an underlying palpable mass, involving the majority of the skin of the breast. Pathologic evidence of dermal lymphatic invasion was noted but was not required for diagnosis. Documented disease progression or relapse following treatment was required, which must have included an anthracycline and taxane-containing regimen in the adjuvant or metastatic setting (30 subjects were required). Where trastuzumab was available, prior treatment must also have included trastuzumab in the treatment regimen (90 subjects were required). Documented HER2 overexpression defined as 2+ or 3+ by IHC or FISH amplified (this was changed by Protocol EGF103009 Amendment 3 to IHC 3+ or FISH amplified to be consistent with the current product indication for lapatinib and the product label for trastuzumab) was also required. All subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, measurable disease according to RECIST or clinically evaluable skin disease. Subjects who received prior chemotherapy, immunotherapy, biologic therapy or hormonal therapy within the past 14 days (with the exception of mitomycin C [within the past 6 weeks]) were not eligible.

	All Subjects (N=153)
Completion status, n (%)	
Discontinued study and study medication[a]	153 (100) [b]
Continuing in the study[b]	0
Reason for discontinuation from the study, n (%)	
Adverse event	10 (7) [c]
Lost to follow-up	1 (<1)
Death	6 (4)
Investigator decision	2 (1)
Subject decided to withdraw from study	5 (3)
Disease progression	127 (83)
Other	1 (<1)[d]
Data not available	1 (<1)

a. Subjects received lapatinib until disease progression, consent withdrawal or unacceptable toxicity.
b. Includes 1 subject (Subject 10394005) who was incorrectly listed as completing the study.
c. Twenty-three subjects actually had AEs that led to discontinuation from the study; for these subjects the end of study record (Listing 6.3 - Attachment 2) lists the reason for discontinuation as death for 3 subjects, AE for 10 subjects and disease progression for 10 subjects.
d. Subject 10394001 was hospitalized in another hospital. The CRF states that there was disease progression but no photos of clinically evaluable skin disease were taken.

	All Cohort A Subjects[a] (N=141)	Cohort A HER2+ Population[b] (N=126)	Cohort B Subjects[a] (N=12)
Mean Age (standard deviation)	53.9 (10.87)	53.8 (11.14)	49.4 (13.18)
Race			
African American/African Heritage	5 (4)	5 (4)	2 (17)
American Indian or Alaska Native	1 (<1)	1 (<1)	0
Asian			
East Asian Heritage	1 (<1)	1 (<1)	0
South East Asian Heritage	1 (<1)	1 (<1)	0
White			
Arabic/North African Heritage	20 (14)	15 (12)	1 (8)
Caucasian/European Heritage	113 (80)	103 (82)	9 (75)
ECOG PS			
N	141	126	12
0	103 (73)	91 (72)	8 (67)
1	26 (18)	23 (18)	2 (17)
2	12 (9)	12 (10)	2 (17)
Primary Efficacy Results:			
	All Cohort A Subjects[a] (N=141)	Cohort A HER2+ Population[b] (N=126)	Cohort B Subjects[a] (N=12)
Investigator-evaluation			
Combined response (clinically evaluable skin disease criteria and/or RECIST)			
Response Rate (CR or PR), % (95%CI)[c]	36.2 (28.3, 44.7)	38.9 (30.3, 48.0)	8.3 (0.2, 38.5)
Clinically evaluable skin disease criteria			
Response Rate (CR or PR), % (95%CI)[c]	36.9 (28.9, 45.4)	39.7 (31.1, 48.8)	8.3 (0.2, 38.5)
RECIST			
Response Rate (CR or PR), % (95%CI)[c]	10.6 (6.1, 16.9)	11.1 (6.2, 17.9)	8.3 (0.2, 38.5)
RECIST for subjects with evaluable disease at Baseline[d]			
Response Rate (CR or PR), % (95%CI)[c]	14.6 (8.4, 22.9)	15.2 (8.6, 24.2)	10.0 (0.3, 44.5)
Independent-evaluation (clinically evaluable skin disease criteria)			
n	102	90	10
Response Rate (CR or PR), % (95%CI)[c]	16.7 (10.0, 25.3)	17.8 (10.5, 27.3)	0 (0, 30.8)
a. ITT population. b. The HER2+ population was a subpopulation of the Cohort A ITT population and was of special interest for efficacy in this study. c. Subjects with unknown or missing responses were treated as non-responders. d. This was an ad-hoc analysis.			
Secondary Outcome Variable(s):			
	All Cohort A Subjects[a] (N=141)	Cohort A HER2+ Population[b] (N=126)	Cohort B Subjects[a] (N=12)
Clinical benefit response rate (combined response [Clinically evaluable skin disease criteria and/or RECIST])			
Response Rate (CR or PR), % (95%CI)[c]	36.2 (28.3, 44.7)	38.9 (30.3, 48.0)	8.3 (0.2, 38.5)
Kaplan-Meier estimate of progression-free survival (weeks)			
Progressed or died, n (%)	127 (90)	112 (89)	12 (100)
1st quartile (95% CI)	7.4 (6.9, 8.1)	7.9 (7.1, 10.3)	3.2 (2.1, 4.0)
Median (95% CI)	12.4 (11.9, 15.1)	14.6 (12.1, 16.0)	4.0 (3.3, 4.3)
3rd quartile (95% CI)	24.0 (18.3, 26.0)	24.4 (20.1, 29.9)	5.6 (4.0, 7.4)

Overall survival (months)[d], n (%)			
Died due to any cause (event)	92 (65)	80 (63)	10 (83)
Censored	49 (35)	46 (37)	2 (17)
Kaplan-Meier estimate of overall survival [d] (months)			
1st quartile (95% CI)	5.3 (3.8, 7.4)	5.4 (4.0, 7.7)	1.7 (0.9, 2.1)
Median (95% CI)	11.2 (9.1, 13.5)	11.2 (9.1, 13.5)	2.1 (1.7, 7.0)
3rd quartile (95% CI)	22.4 (16.5, 27.4)	25.4 (16.5, 26.4)	7.0 (2.0, 21.9)
Time to response (weeks)			
Subjects with a complete or partial response, n (%)	51 (36)	49 (39)	1 (8)
CR or PR by week 4	14 (27)	13 (27)	1 (100)
CR or PR by week 8	27 (53)	27 (55)	0
CR or PR by week 12	7 (14)	6 (12)	0
CR or PR by week 16	3 (6)	3 (6)	0
Duration of response (weeks) (cumulative incidence estimate)			
n	51	49	1
1st quartile	12.3	12.7	8.3
Median	20.1	20.9	8.3
3rd quartile	31.1	32.1	8.3

a. ITT population.
b. The HER2+ population was a subpopulation of the Cohort A ITT population.
c. Subjects with unknown or missing responses were treated as non-responders.
d. Survival data were from the 03 October 2008 data cut.

On-therapy was defined as the time from first dose of lapatinib to 28 days post last dose of lapatinib therapy.

	Cohort A (N=141)	Cohort B (N=12)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
At least 1 AE	130 (92)	12(100)
Diarrhea	83 (59)	7 (58)
Fatigue	28 (20)	4 (33)
Nausea	28 (20)	3 (25)
Rash	25 (18)	1 (8)
Anorexia	22 (16)	2 (17)
Dyspnea	20 (14)	3 (25)
Vomiting	18 (13)	5 (42)
Back pain	16 (11)	3 (25)
Serious Adverse Events - On-Therapy		
	Cohort A (N=141)	Cohort B (N=12)
Subjects with non-fatal SAEs		
Any non-fatal SAE	35 (25) [9]	3 (25) [0]
Dyspnea	4 (3) [1]	0
Pleural effusion	5 (4)	0
Pyrexia	2 (1)	0
Diarrhea	2 (1) [2]	0
Anaemia	2 (1) [2]	0
Abdominal pain	2 (1) [1]	0
Vomiting	2 (1) [1]	0
Fatigue	2 (1) [1]	0
Ejection fraction decreased	2 (1) [1]	0
Pneumothorax	2 (1)	0
Dehydration	2 (1)	0

Pain in extremity	2 (1)	0
Pericardial effusion	0	1 (8)
Ileus	1 (<1) [1]	0
Nausea	1 (<1) [1]	0
Cholecystitis	1 (<1) [1]	0
Hyperbilirubinaemia	1 (<1) [1]	0
Thrombocytopenia	1 (<1) [1]	0
Erythema nodosum	1 (<1) [1]	0
Breast infection	1 (<1)	0
Cellulitis	1 (<1)	0
Extradural abscess	1 (<1)	0
Psoas abscess	1 (<1)	0
Skin infection	1 (<1)	0
Staphylococcal infection	1 (<1)	0
Wound infection	1 (<1)	0
Abdominal pain upper	1 (<1)	0
Dysphagia	1 (<1)	0
Asthenia	1 (<1)	0
Edema peripheral	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Hepatic function abnormal	1 (<1)	0
Hypercalcaemia	1 (<1)	0
Hyperkalaemia	1 (<1)	0
Back pain	1 (<1)	0
Bone pain	1 (<1)	0
Febrile neutropenia	1 (<1)	0
AST increased	1 (<1)	0
Bladder neoplasm	1 (<1)	0
Metastatic pain	1 (<1)	0
Neuralgia	1 (<1)	0
Somnolence	1 (<1)	0
Lymphoedemea	1 (<1)	0
Concussion	1 (<1)	0
Upper limb fracture	1 (<1)	0
Wrist fracture	1 (<1)	0
Confusional state	1 (<1)	0
Renal failure	1 (<1)	0
Pneumonia	0	1 (8)
Brachial plexopathy	0	1 (8)

Subjects with fatal SAEs		
Dyspnea	5 (4) [1]	0
Hepatitis acute	1 (<1) [1]	0
Abdominal sepsis	1 (<1) [1]	0
Intestinal obstruction	1 (<1) [0]	
Pulmonary embolism	1 (<1) [0]	0
Pericardial effusion	1 (<1) [0]	0
Pulmonary edema	1 (<1) [1]	0
Superior mesenteric artery syndrome	1 (<1) [1]	0
Cyanosis	1 (<1) [1]	0
Pyrexia	1 (<1) [1]	0
Jaundice	1 (<1) [1]	0
Cardiac failure	1 (<1) [0]	0
Hypoxia	1 (<1) [0]	0
Pleural effusion	1 (<1) [0]	0
Respiratory failure	1 (<1) [0]	0
Ventricle rupture	0	1 (>1) [0]

Conclusion: In the HER2+ population an investigator-evaluated ORR of 39.7% (95% CI: 31.1, 48.8) was observed using clinically evaluable skin disease criteria. An investigator-evaluated ORR of 38.9% (95% CI: 30.3, 48.0) was also observed in HER2+ population with the combination of skin disease criteria and/or RECIST. The AEs reported were consistent with the safety profile observed in the lapatinib program as a whole. Following the data cut-off for the primary analysis (18 Dec 2007), safety data for five ongoing subjects were collected until all subjects withdrew from study (all of whom withdrew due to disease progression). These additional data did not affect the conclusions presented in the aforementioned publication.