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.: EGF102580
Title: A Phase II study to evaluate the efficacy, safety, and pharmacodynamics of lapatinib in combination with paclitaxel as neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer
Rationale: GW572016 (lapatinib) is a reversible tyrosine kinase inhibitor that potently inhibits both EGFR (ErbB1) and HER2 (ErbB2) receptors which are frequently over-expressed or altered in human cancers. This study was designed to evaluate the efficacy and safety of lapatinib in two cohorts of subjects with treatment-naïve inflammatory breast cancer (IBC), whose tumors either over-express HER2 (Cohort A) or did not over-express HER2 but express EGFR (Cohort B).
Phase: II
Study Period: 11 April 2005 - 01 November 2006
Study Design: Phase II, open-label, two-stage, multicenter, single-arm, international study
Centres: 13 centers in 8 countries
Indication: Inflammatory breast cancer
Treatment: Each cohort received 1500 mg oral lapatinib alone for the first 14 days (monotherapy phase), followed by daily lapatinib (1500 mg) and weekly paclitaxel (80 mg/m^2) for 12 weeks (combination therapy phase). Patients achieving clinical complete response (CR) after 12 weeks of combination therapy underwent surgical resection as clinically indicated. Pathologic response to treatment was evaluated at the time of surgical resection. Subjects achieving only a clinical partial response (PR) had the option to receive up to 12 additional weeks of combination therapy with daily lapatinib and weekly paclitaxel.
Objectives: To evaluate the pathologic response rate following 14 days of neoadjuvant daily lapatinib as monotherapy followed by 12 weeks of daily lapatinib in combination with weekly paclitaxel, in patients with treatment-naïve IBC whose tumors over-express human epidermal growth factor receptor 2 (HER2) ± epidermal growth factor receptor (EGFR; Cohort A) and in patients whose tumors express EGFR but do not over-express HER2 (Cohort B).
Primary Outcome/Efficacy Variable: Pathological complete response rate (pCR)
Secondary Outcome/Efficacy Variable(s): 1) Clinical response at end of study evaluated by Response Evaluation Criteria in Solid Tumors (RECIST). 2) Clinical response at end of study evaluated by skin disease criteria. 3) Clinical response at end of 14-day lapatinib monotherapy phase evaluated by skin disease criteria. 4) Changes from baseline in intratumoral expression of EGFR, HER2, IGF-1R, Bcl-2, TGFα, and other marker by direct and genome-wide methods following treatment (this will be reported separately at a later date). 5) Changes from baseline in serum levels of EGFR and HER2 extracellular domains following treatment (this will be reported separately at a later date). 6) Pharmacogenetic (PGx) studies, in the event of unusual clinical activity or safety findings (Samples were collected for PGx studies, but no analyses were performed).
Statistical Methods: The primary analysis population was the Intent-to-Treat (ITT) Population, defined as all subjects who received at least one dose of lapatinib. Demographic and disease characteristics were summarized using descriptive statistics. Response rates (percent of subjects achieving a CR or PR) were summarized, together with exact 95% confidence intervals (CIs). Qualitative and quantitative results were summarized for AEs and serious AEs (SAEs) overall, by age, relationship to lapatinib, and events leading to withdrawal. Qualitative assessments were summarized for clinical laboratory tests, vital signs, Eastern Cooperative Oncology Group (ECOG) Performance Status, and ECHO/MUGA scans. Qualitative and quantitative results were summarized for biomarkers obtained from archived tissue samples and

blood serum.

Study Population: Female or male subjects 18 years or older with histological confirmation of breast carcinoma and a clinical diagnosis of IBC based on the presence of inflammatory changes in the involved breast, including diffuse erythema and edema (peau d'or ange), with or without an underlying palpable mass, involving the majority of the skin of the breast were eligible, provided that surgical resection of the primary tumor was planned following completion of neoadjuvant treatment. Pathologic evidence of dermal lymphatic invasion was noted, but was not required for diagnosis.

Tumors over-expressing HER2 (+2 or +3 by IHC or FISH+), with or without expression of EGFR (Cohort A), or tumors expressing EGFR (+ by IHC), without over-expression of HER2 (Cohort B). Subjects in Cohort A who had tumors over-expressing HER2 (+3 by IHC or FISH+) were designated HER2+ subjects; these subjects were of special interest for efficacy analysis. Documentation of EGFR and HER2 expression status was required prior to dosing.

In addition, subjects were required to have: (i) accessible tumors to facilitate multiple biopsies; (ii) ECOG performance status of 0 to 2; (iii) adequate bone marrow, renal, and hepatic function; (iv) left ventricular ejection fraction (LVEF) ≥ 50% based on ECHO or MUGA; and (v) agreed to provide written informed consent.

Number of Subjects	**Cohort A**	**Cohort B**
Planned, N	30	30
Randomised, N	42	7
Completed, n (%)	30 (71)	5 (71)
Total Number Subjects Withdrawn, n (%)	12 (29)	2 (29)
Withdrawn due to Adverse Events, n (%)	7 (17)	2 (29)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for other reasons, n (%)	5 (12)	0

	Cohort A		**Cohort B**
Demographics	**All**	**HER2+***	
N (ITT)	42	32	7
Females: Males	42:0	32:0	7:0
Mean Age, years (SD)	52.2 (9.29)	52.9 (10.23)	60.9 (13.06)
White, n (%)	41 (98)	31 (97)	5 (81)

*HER2+ subjects were a subset of Cohort A, with tumors over-expressing HER2 (3+ by IHC or FISH+).

Primary Efficacy Results:

pCR rate in ITT population	**Cohort A**		**Cohort B**
	All N=42	**HER2+ N=32**	**N=7**
Response rate, n (%)	4 (9.5)	3 (9.4)	0 (0)
95% C.I.	(2.7, 22.6)	(2.0, 25.0)	(0.0, 41.0)
pCR rate in subjects who underwent surgical resection (n)	23	18	4
Response rate, n (%)	4 (17.4)	3 (16.7)	0 (0)
95% C.I.	(5.0, 38.8)	(3.6, 41.4)	(0, 60.2)

Secondary Outcome Variable(s):

Clinical response, RECIST (End of Study)	**Cohort A**		**Cohort B**
	All N=42	**HER2+ N=32**	**N=7**
Complete Response (CR)	1 (2)	1 (3)	0
Partial Response (PR)	17 (40)	14 (44)	3 (43)
Stable Disease (SD)	17 (40)	11 (34)	2 (29)
Progressive Disease (PD)	1 (2)	1 (3)	0
Unknown	6 (14)	5 (16)	2 (29)
Response Rate (CR or PR)			

Response Rate (%)	42.9	46.9	42.9
95% C.I.	(27.7, 59.0)	(29.1, 65.3)	(9.9, 81.6)
Clinical response, Skin Disease Criteria (End of Study)	**Cohort A**		**Cohort B N=7**
	All N=42	**HER2+ N=32**	
Complete Response (CR)	3 (7)	3 (9)	0
Partial Response (PR)	30 (71)	22 (69)	5 (71)
Stable Disease (SD)	3 (7)	2 (6)	0
Progressive Disease (PD)	1 (2)	1 (3)	1 (14)
Unknown	5 (12)	4 (13)	1 (14)
Response Rate (CR or PR)			
Response Rate (%)	78.6	78.1	71.4
95% C.I.	(63.2, 89.7)	(60.0, 90.7)	(29.0, 96.3)
Combined Clinical Response (RECIST + Skin Disease Criteria; End of Study)	**Cohort A**		**Cohort B N=7**
	All N=42	**HER2+ N=32**	
Complete Response (CR)	0	0	0
Partial Response (PR)	33 (79)	25 (78)	5 (71)
Stable Disease (SD)	3 (7)	2 (6)	0
Progressive Disease (PD)	1 (2)	1 (3)	1 (14)
Unknown	5 (12)	4 (13)	1 (14)
Response Rate (CR or PR)			
Response Rate (%)	78.6	78.1	71.4
95% C.I.	(63.2, 89.7)	(60.0, 90.7)	(29.0, 96.3)
Clinical response, Skin Disease Criteria (End of Monotherapy Phase; 14 days)	**Cohort A**		**Cohort B N=7**
	All N=42	**HER2+ N=32**	
Complete Response (CR)	1 (2)	1 (3)	0
Partial Response (PR)	9 (21)	9 (28)	0
Stable Disease (SD)	26 (62)	17 (53)	4 (57)
Progressive Disease (PD)	0	0	0
Unknown	6 (14)	5 (16)	3 (43)
Overall Response (CR or PR)	10 (24)	10 (31)	0

Safety Results:

	Cohort A N=42	**Cohort B N=7**
Ten Most Frequent AEs[1] On-Therapy (Entire Study)	**n (%)**	**n (%)**
Subjects with any AEs	41 (98)	7(100)
Diarrhea	40 (95)	6 (86)
Rash	30 (71)	4 (57)
Vomiting	26 (62)	2 (29)
Alopecia	24 (57)	6 (86)
Nausea	23 (55)	4 (57)
Asthenia	21 (50)	1 (14)
Headache	12 (29)	1 (14)
Abdominal pain upper	11 (26)	1 (14)
Anorexia	11 (26)	2 (29)
Abdominal pain	10 (24)	1 (14)
Epistaxis	10 (24)	2 (29)
Paraesthesia	9 (21)	3 (43)

[1]Due to the low number of subjects in Cohort B, the 10 most frequent AEs have been ranked based on those experienced by Cohort A subjects

Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**		
	Cohort A **N=42**	**Cohort B** **N=7**
Subjects with any SAEs (includes both non-fatal and fatal events), n (%)	9 (21)	1 (14)
	n (%) [related]	**n (%) [related]**
Diarrhea	4 (10) [4]	0
Vomiting	4 (10) [3]	0
Nausea	2 (5) [1]	0
Cellulitis	1 (2) [0]	0
Cystitis	1 (2) [0]	0
Pneumonia	1 (2) [0]	0
Skin infection	1 (2) [0]	0
Urinary tract infection	1 (2) [0]	0
Pyrexia	3 (7) [0]	0
Hyperthermia	1 (2) [0]	0
Anorexia	1 (2) [0]	0
Diabetes mellitus	1 (2) [0]	0
Renal failure	1 (2) [0]	0
Renal failure acute	1 (2) [1]	0
Hypotension	1 (2) [0]	1 (14) [0]
Neutropenia	1 (2) [1]	0
Jaundice	1 (2) [0]	0
Ejection fraction decreased	0	1 (14) [1]
Bone pain	1 (2) [0]	0
Ataxia	0	1 (14) [1]
Mental status changes	0	1 (14) [1]
Pulmonary embolism	1 (2) [0]	0
	Cohort A **N=42**	**Cohort B** **N=7**
Subjects with fatal SAEs, n (%)	1 (2)	0 (0)

Conclusion: In the ITT population, the pCR rate was 9.5% for all Cohort A subjects and 9.4% for the subset of HER2+ subjects within Cohort A; no subjects in Cohort B had a pCR. Among all Cohort A subjects who underwent surgery at the end of the study, the pCR rate was 17.4%; among the subset of HER2+ subjects in Cohort A who underwent surgery, the pCR rate was 16.7%. The combined clinical response rate (based on RECIST and evaluable skin disease criteria) at the end of the study was 78.6% in all Cohort A subjects, 78.1% in HER2+ subjects, and 71.4% in Cohort B subjects. A total of 48 subjects experienced AEs; diarrhea, rash, alopecia, and nausea were among the most frequent AEs reported. Ten of the subjects experienced SAEs; diarrhea and vomiting were most frequent. One subject in Cohort A died during the course of the study; the two listed causes of death (diabetes mellitus, renal failure), were not considered related to study treatment.

Publications: No publications.

Date updated: 18-Jan-2008