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Human Medicines Development and Evaluation

Withdrawal Assessment Report for Tyverb

International Nonproprietary Name: lapatinib

EMEA/H/C/000795/II/0017

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Questions and Answers" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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1. Introduction

1.1. Scope of the variation

Based primarily on data from the pivotal study EGF104535 and the supportive study EGF30001, the MAH wishes to extend the indication of Tyverb to encompass first-line metastatic breast cancer in combination with paclitaxel.

Changes (**in bold**) proposed for SPC section 4.1 are:

> "Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2):

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1).
- **in combination with paclitaxel for the treatment of patients with metastatic disease. The patients in the registration study were not previously treated with trastuzumab in either the adjuvant or metastatic setting (see section 5.1).**
- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor (See section 5.1)."

Related changes are proposed for SmPC sections 4.2, 4.4, 4.5, 4.8, 5.1 and 6.5. Minor changes, unrelated to the extension of indication, in line with the QRD template are proposed for 4.6. The package leaflet is proposed to be updated accordingly.

2. Scientific Discussion

2.1. Non-clinical aspects

2.1.1. General background

Pharmacodynamic, pharmacokinetic and toxicological studies with lapatinib have been conducted and were submitted in the original MAA for use in combination with capecitabine. For the current proposed combination e.g. lapatinib and paclitaxel, only a small number of studies, with direct relevance to the new indication were discussed in the overview presented by the MAH. Hence, two primary pharmacology studies (lapatinib, paclitaxel and docetaxel alone and in different combinations) and three in-vitro drug interaction studies were conducted.

In the primary assessment of Tyverb in 2007, lapatinib exhibited low acute toxicity with no lethality at oral doses up to 200mg/kg. Repeat dose toxicity studies were performed in rats and dogs and main findings in these studies were attributed to exaggerated pharmacology such as epithelial effects in the skin and gastrointestinal tract. The recommended dose of lapatinib is 1500 mg (i.e. six tablets) once daily, continuously, when taken in combination with paclitaxel administered 80 mg/m^2 weekly, or 175 mg/m^2 every 3 weeks.

2.1.2. Pharmacology

The MAH has conducted two studies to support the current variation application for the use of lapatinib tablets for oral administration with paclitaxel for the treatment of patients with HER2 (Erb2)-positive metastatic breast cancer. A summary of these studies is given below:

Lapatinib and paclitaxel (Report RH2005/00059/01)

The combination of lapatinib and paclitaxel was examined in mice bearing three different human tumour xenografts, BT474, HN5 and NCI-H322, which express various levels of ErbB1 and ErbB2 receptors. The inhibitory effect on tumour growth was studied for lapatinib and paclitaxel either alone or in different combinations. The results are given in table 1. A crude evaluation of the toxicity of each agent was also assessed by body weight loss.

Table 1: Effects of Combination Treatment of lapatinib with Paclitaxel in BT474, HN5 and NCI-H322 Mouse Tumour Xenograft Models

Study ID	**Treatment regimen/Dose (mg/kg)**		**Tumour growth inhibition (% of control)**		
			BT474 (n= 8 CB-17 SCID mice)	**NCI-H322** (n= 8 CB-17 SCID mice)	**HN5** (n= 8 nude mice)
Report RH2005/00059/01	**Lapatinib** (as suspension in aqueous 0.5% HPMC, 0.1% tween 80)	**Paclitaxel** (as 6mg/ml solution in cremophor:ethanol formulation)			
	30 oral 2x/day for 21 days	**0**	**60, 75**	**89, 56**	**71, 29**
	100 oral 2x/day for 21 days	**0**	**101, 112**	**128, 116**	**97, 95**
	0	**6 iv On days 1 and 5**	**13, 0**	**33, 0**	**23, 34**
	0	**12 iv On days 1 and 5**	**58, 42**	**88, 83**	**72, 60**
	30 oral 2x/day for 21 days	**6 On days 1 and 5**	**53, 77**	**94, 58**	**60, 61**
	30 oral 2x/day for 21 days	**12 On days 1 and 5**	**79, 98**	**132, 114**	**72, 92**
	100 oral 2x/day for 21 days	**12 On days 1 and 5**	**105, 121**	**137, 143**	**toxic**

1. The percent tumour inhibition values are reported from two separate studies on Day after last dose.
2. Tumour volume significant versus lapatinib alone.
3. Tumour volume significant versus taxol alone.
4. Tumour volume significant versus lapatinib and taxol.

As seen in the table 1, the combination of lapatinib and paclitaxel (30 or 100mg/kg lapatinib with 12mg/kg paclitaxel) resulted in inhibition of tumour growth that was better than inhibition of either agent alone. However, the combination of higher doses of lapatinib (100mg/kg) and paclitaxel (12mg/kg) resulted in increased toxicity (indicted by increased body weight loss) in SCID mice with BT474 and NCI-H322 tumour xenografts and was lethal in HN5 bearing nude mice. Therefore, it was concluded by the MAH that different strain of mice show different sensitivities toward toxicity of combining lapatinib and paclitaxel. The clinical relevance of this finding is not clear.

Lapatinib and docetaxel (Report UH2006/00052/01)

The effects of combination of oral doses of lapatinib ditosylate monohydrate with intraperitoneal doses of docetaxel were examined in 8 female CB-17 SCID mice bearing BT474 tumour xenografts (data not shown).

2.1.3. Pharmacokinetics

Three *in-vitro* studies have been conducted to investigate the potential pharmacokinetic interactions between lapatinib and paclitaxel. In addition, a clinical study was conducted with lapatinib and paclitaxel in patients with solid tumours. In this section, only the results from non-clinical studies are summarized. For a detailed report on human pharmacokinetic please see the clinical assessment of this report.

In *in-vitro* studies have shown that lapatinib is an inhibitor of CYP2C8 (Ki = 0.6 μM) and CYP3A4 (Ki = 4 μM), enzymes. These enzymes are the major metabolising enzyme for paclitaxel, converting it to p-3'-hydroxpaclitaxel (by CYP3A4) and 6-alpha-hydroxypaclitaxel (by CYP2C8). Therefore a number of *in vitro* studies were also performed to determine the potential for interaction between paclitaxel and lapatinib. The related taxane, docetaxel, was also investigated.

Potential for inhibition of paclitaxel and docetaxel metabolism by lapatinib (Report RD2001/01665/00)

The inhibitory effect of lapatinib on the metabolism of paclitaxel, docetaxel and vinorelbine by CYP3A4 was examined using pooled human liver microsomes. Inhibition of metabolism was only shown for combination of lapatinib and paclitaxel. Lapatinib inhibited the formation of p-3' hydroxypaclitaxel and 6 alphahydroxypaclitaxel by IC50 values of 1.9 μM and 2.5 μM, respectively.

Potential for inhibition of lapatinib metabolism by paclitaxel (Report RD2002/00921/00)

Studies have shown that lapatinib is eliminated mainly through metabolism by CYP3A4/5 with a minor contribution from CYP2C19 and CYP2C8. Inhibition of the metabolism of lapatinib to its phenol metabolite, GW690006, by paclitaxel, docetaxel and vinorelbine was assessed *in vitro* in pooled human liver microsomes. IC50 values for inhibition of lapatinib were 30-70 μM, 1.3 μM and 13.2 μM for paclitaxel, docetaxel and vinorelbine respectively. Hence, Docetaxel was shown to be the most potent inhibitor with a mean IC50 of 1.3 μM.

P-glycoprotein inhibitors and paclitaxel

Studies have shown that lapatinib is substrate as well as in inhibitor for P-glycoprotein (Pgp) transporter. Similarly, paclitaxel is a known substrate for this transporter. Studies with these inhibitors or in Pgp knockout animals [Bardelmeijer, 2000; Van Asperen, 1998] have shown to alter the oral bioavailability and exposure of paclitaxel. Studies in Pgp knockout mice showed that paclitaxel AUC is increased 2-fold compared to wild-type mice [Sparreboom, 1997].

2.1.4. Toxicology

In the primary assessment of Tyverb in 2007, lapatinib exhibited low acute toxicity with no lethality at oral doses up to 200mg/kg. Repeat dose toxicity studies were performed in rats and dogs and main findings in these studies were attributed to exaggerated pharmacology such as epithelial effects in the skin and gastrointestinal tract. The principal findings in repeat dose toxicity studies with paclitaxel have shown to include hypoplasia of the bone marrow and lymphoid depletion. Hence, the MAH believed that these nonclinical findings do not indicate any potential for additive or synergistic toxicity when combining lapatinib and paclitaxel that could not be monitored clinically. No combination toxicology studies were conducted to support the safety of lapatinib and paclitaxel for the treatment of patients with hormone receptor positive metastatic breast cancer.

2.1.5. Ecotoxicity/environmental risk assessment

No further environment risk assessment has been submitted.

2.1.6. Discussion and conclusion on non-clinical aspects

To support the current indication, the MAH has conducted two combination studies with lapatinib added to paclitaxel and docetaxel. The results showed that combination of high doses of lapatinib and paclitaxel could cause increased body weight loss and that sensitivities of different strains of mice to toxicity of the combination was different. While lapatinib and paclitaxel caused reduced body weight gain in SCID mice bearing BT474 and NCI-H322 tumour xenografts, this combination was lethal in HN5 bearing nude mice. Combination of Lapatinib and docetaxel, on the other hand, had no significant effect on the body weight gain of mice over the effect of docetaxel alone in all treatment groups.

As mentioned above, the endpoint for toxicity in these studies was chosen to be the body weight reduction. Although, these studies have shown some synergistic effect on tumour growth inhibition for the proposed combination lapatinib and paclitaxel, the models used are xenograft models of human cancer in mice, the predictable power of which has been debated for the past years. The need for developing more useful animal models reflecting the process underlying cancer development in man is obvious. Another challenge in preclinical modelling is the selection of appropriate endpoints that simulate those used in human clinical trials e.g. overall survival (OS) and progression free survival (PFS), time to progression and overall response rate. It is difficult to draw statistical parallels between these clinical endpoints and those commonly used in standard xenograft models such as tumour growth delay or optimal median treated-tumour mass/median control-tumour mass. Hence, these studies are not considered predictable for the clinical situation.

In-vitro studies indicated that lapatinib is an inhibitor of CYP3A4, CYP2C8 and also the efflux transporters Pgp and BCRP. Additionally, metabolism of paclitaxel to its two main metabolites e.g. 6-α-hydroxylase and paclitaxel para-3-hydroxylase is dependent on CYP2C8 and CYP3A4 activities respectively. Hence, the *in-vitro* data have demonstrated a potential for lapatinib to affect the pharmacokinetics of paclitaxel. Therefore, the potential pharmacokinetic interaction between paclitaxel and lapatinib has been evaluated clinically. For a detailed report of these studies please refer to the clinical part of this assessment report.

Due to the extensive clinical experience with combination of lapatinib and paclitaxel, which showed a more pronounced of already known side effects of each compound when combining lapatinib and paclitaxel, the MAH concluded that nonclinical findings did not indicate any potential for additive or synergistic toxicity when combining lapatinib and paclitaxel that could not be monitored clinically. This conclusion is endorsed by the CHMP. Additionally, in regard to relevant guidelines, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not warranted.

In the 2009 a full environmental risk assessment has been undertaken for lapatinib. The CHMP has concluded that lapatinib is unlikely to represent a risk to the aquatic or terrestrial environment. According to the CHMP guideline "Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00) For type II variations, the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase.

The MAH did not analyze the impact of this new indication on extend of human use, and therefore on the environmental exposure. This is very important mainly because the CHMP concluded that lapatinib is unlikely to represent a risk to the aquatic or terrestrial environment provided that the market forecasts applied in the calculation of PEC/PNEC ratios are not exceeded. Therefore the MAH is asked

to provide an ERA considering the indication applied for, in accordance with the guideline EMEA/CHMP/SWP/4447/00, taking into consideration a possible increase of environmental exposure to the drug substance following this new indication. A complete analysis needs to be performed before any conclusion on the environmental risk assessment could be made (see other concerns).

2.2. Clinical aspects

The studies used to support the proposed indication are shown in Table 3.

Table 3. Pivotal and supporting studies for the proposed indication

Protocol Code Phase (Status)	Treatment/s	Design/Population	Primary Endpoint	Number of Subjects	Data Cut off Date[a]
Pivotal Study for Efficacy and Safety					
EGF104535 Phase III (fully enrolled)	Paclitaxel 80 mg/m^2 weekly + lapatinib 1500 mg OD *or/* Paclitaxel + placebo	MC, 2A, PG, PC R, DB; HER2-amplification MBC	OS	ITT pop: Lap+Pac: 222 Pla+Pac: 222 Safety pop: Lap+Pac: 222 Pla+Pac: 221	Clinical cut off 18 Jun 2010
Supporting Studies for Efficacy and Safety					
EGF30001 Phase III (reported)	Paclitaxel 175 mg/m^2 Q3W + lapatinib 1500 mg OD *or/* Paclitaxel + placebo	MC, 2A, PG, R, DB, PC; MBC (HER2 untested or –ve)	TTP	ITT pop Lap+Pac: 291 Pla+Pac: 288 Safety pop Lap+Pac:293 Pla+Pac:286 HER2+ pop Lap+Pac: 52 Pla+Pac: 39	Clinical cut off 29 Mar 2007 OS & Safety Update Cut off 25 Aug 2010
Supporting Studies for Safety					
EGF105764 Phase II (reported)	Lapatinib 1500 mg OD + paclitaxel 80 mg/m^2 weekly	OL, SA, MC; patients with treatment naive HER2-overexpressing MBC	ORR	57	12 Mar 2008 Safety Update Cut off: 18 Jun 2010
EGF102580 Phase II (completed)	Lapatinib 1500 mg OD + paclitaxel 80 mg/m^2 weekly for 12 weeks	OL, SA, MC; I BC Cohort A: HER2 overexpressing;± EGFR Cohort B;EGFR+ , no HER2 over- expression	pCR	ITT pop 49 HER2+ cohort 42	01 Nov 2006 Safety Update Cut off: 24 Jul 2007
EGF10009 Phase I (completed)	Lapatinib up to 1500 mg OD + paclitaxel (up to 225 mg/m^2 Q3W or up to 100 mg/m^2 weekly)	OL, DE, PK interaction; patients with solid tumours	Safety	56	23 Feb 2005

2A – 2 arm; DB – double-blind; DE – dose escalating; EGFR – epidermal growth factor receptor; HER2 – human epidermal growth factor receptor 2; IBC – inflammatory breast cancer; ITT – intent-to-treat; MBC – metastatic breast cancer; MC – multicentre; NI – non-inferiority; OD – once daily; OL – open label; ORR – overall response rate OS – overall survival; PC – placebo controlled; pCR – pathological complete response; PD – progressive disease; PFS – progression-free survival; PG – parallel group; PK – pharmacokinetic; pop – population; Q3W – every 3 weeks;; S – superiority; SA – single arm; R – randomised; TTP – time to (tumour) progression.
Cut off date for SAE reporting was 12 Sep 2010.

GCP

The MAH stated that all studies were undertaken in accordance with the principles of Good Clinical Practice and conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the

version of the Declaration of Helsinki that applied at the time the studies were conducted. Where regulatory approval was required, this was obtained from the relevant health authority.

A routine GCP inspection request for the pivotal study EGF104535 was adopted by the CHMP on 19 May 2011. The request was subsequently amended to correct the clinical trial information that quoted an incorrect study protocol. Three sites are to be inspected: Bangkok in Thailand; Guangzhou and Shanghai in China. General triggers were used in the choice of this dossier and the sites involved, in line with the GCP Inspection Policy for Centralised Procedure (Revised November 2006). Thus, the choice of routine inspection was based on a) the indication (treatment of breast cancer) and b) the fact that the pivotal trial was conducted completely in third Country (China, Brazil, Russia, Hong Kong, Pakistan, Thailand, Peru, Ukraine), primarily in China.

The outcome of the GCP inspection and satisfactory responses to its findings should form an integral part of the responses to this RSI.

2.2.1. Clinical pharmacology

For the current variation application the MAH discussed three clinical pharmacology studies. Study EGF10009 (previously submitted) and EGF104578 (new data) concern the pharmacokinetic interaction between lapatinib and paclitaxel. Study 10020 (synopsis previously submitted, original report written in Japanese) was a Phase I dose-escalating study conducted to assess activity, pharmacokinetics and safety of lapatinib monotherapy in Japanese subjects.

Pharmacokinetic interaction between lapatinib and paclitaxel

The potential pharmacokinetic interaction between paclitaxel and lapatinib has been evaluated in two different studies, one in Caucasian subjects with breast cancer and one in Japanese subjects with gastric cancer.

Study EGF 10009 was assessed during the original MAA and was also discussed during variation EMEA/H/C/795/II/12. This study was conducted to determine the optimally-tolerated regimen, safety, tolerability, and pharmacokinetics of the combination. A total of 17 subjects completed the pharmacokinetic cohort in which lapatinib 1500 mg/day was administered with paclitaxel 175 mg/m^2 every three weeks.

Compared with administration of each substance alone, lapatinib AUC increased on average 21% and paclitaxel AUC increased on average 23% when the two were given in combination (Table 4 and Table 5).

Table 4. Effect of paclitaxel on lapatinib pharmacokinetic parameters in Caucasian subjects

Lapatinib PK Parameter	Lapatinib Alone (Treatment B, n=17)[a]	Lapatinib + Paclitaxel (Treatment C, n=17)[a]	Treatment Comparison[b]
AUC(0-τ) (h.ng/mL)	54428 (39318 - 75346)	64538 (43309 - 96173)	1.21 (1.02 - 1.43)
Cmax (ng/mL)	3918 (2911 -5274)	5311 (3539 - 7972)	1.39 (1.15 - 1.67)
tmax (h)	3.00 (0.50 - 8.00)	4.07 (2.58 - 6.08)	0.80 (0.08 - 1.54)
tlag (h)	0.50 (0.00 - 1.00)	0.53 (0.00 - 0.62)	0.04 (0.00 - 0.10)

Table 5. Effect of lapatinib on paclitaxel pharmacokinetic parameters in Caucasian subjects

Paclitaxel PK Parameter	Paclitaxel Alone (Treatment A, n=17)[a]	Paclitaxel + Lapatinib (Treatment C, n=17)[a]	Treatment Comparison[b]
AUC(0-∞) (h.ng/mL)	15544 (13604 - 17761)	19126 (16137 - 22669)	1.23 (1.11 - 1.36)
t½ (h)	6.78 (6.20 - 7.42)	6.30 (5.81 - 6.83)	0.93 (0.84 - 1.02)
CL (mL/h/m^2)	11258 (9853 - 12864)	9150 (7720 - 10845)	0.81 (0.73 - 0.90)
Vss (mL/m^2)	48077 (38139 - 60605)	37574 (31119 - 45367)	0.78 (0.64 - 0.95)

Study EGF104578 is an ongoing phase III study in Japanese patients with gastric cancer (only data from subjects with intact stomach and pylorus are discussed here). The pilot part of the study, where pharmacokinetics were evaluated, is finalised. Lapatinib was administered as 1500 mg daily oral doses and paclitaxel as 80 mg/m^2 intravenously once weekly. Pharmacokinetic data are available from 6 subjects (Figure 1, Figure 2). These data indicate a similar interaction as in study 10009 at this lower paclitaxel dose, with a mean 27% increase in lapatinib AUC and a mean 30% increase in paclitaxel AUC (Table 6, Table 7).

Figure 1. Mean plasma lapatinib conc. vs. time profile with and without co-administration of paclitaxel in Japanese subjects, n=6 (Study EGF104578)

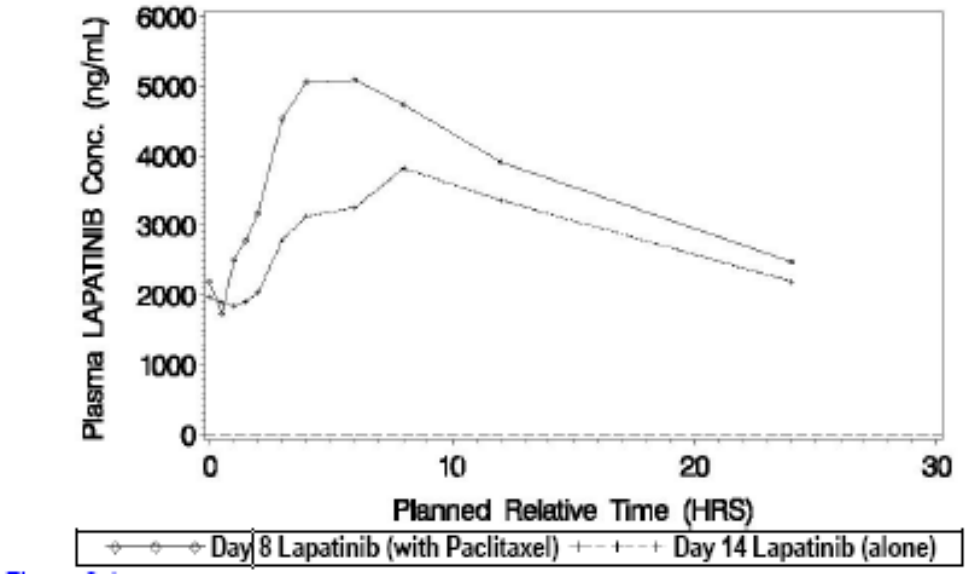


Table 6. Effect of paclitaxel on lapatinib pharmacokinetic parameters in Japanese subjects (n=6) as geometric LS mean ratio (90% CI) for AUC and Cmax and as median difference (90% CI) for Tmax

Lapatinib PK Parameter [a]	Subjects with intact stomach (Cohort 1)
	Lapatinib + Paclitaxel / Lapatinib Alone
$AUC_{(0-24)}$	1.27 (1.03, 1.56)
C_{max}	1.38 (1.06, 1.80)
t_{max} (h)	-2.98 (-4.98, -0.47)

Figure 2. Mean plasma paclitaxel conc. vs. time profile with and without co-administration of lapatinib in Japanese subjects, n=6 (Study EGF104578)

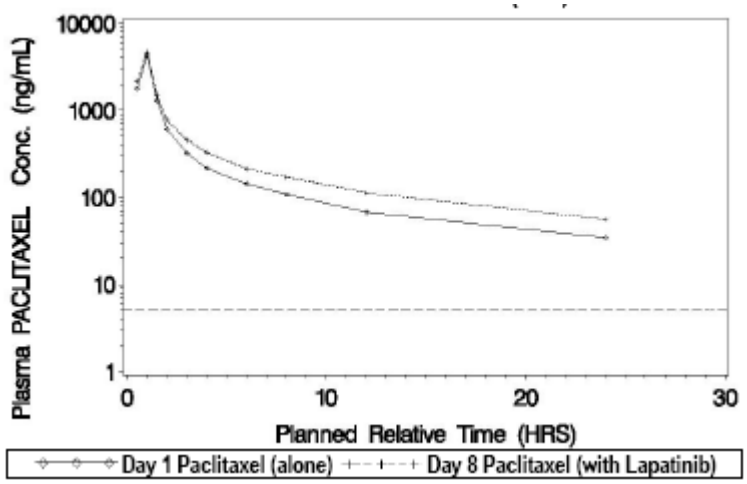


Table 7. Effect of lapatinib on paclitaxel pharmacokinetic parameters in Japanese subjects (n=6) as geometric LS mean ratio (90% CI) for AUC and Cmax and as median difference (90% CI) for Tmax

Paclitaxel PK Parameter [a]	Subjects with intact stomach (Cohort 1)
	Lapatinib + Paclitaxel / Paclitaxel Alone
$AUC_{(0-24)}$	1.30 (1.13, 1.49)
$AUC_{(0-inf)}$	1.33 (1.18, 1.50)
C_{max}	1.12 (1.00, 1.25)
t_{max} (h)	-0.02 (-0.16, 0.07)
$t_{1/2}$	1.02 (0.87, 1.20)
CL	0.75 (0.66, 0.85)
V_{ss}	0.94 (0.77, 1.14)

Effect of ethnicity on lapatinib and paclitaxel pharmacokinetics

Study EGF10020 was a repeated-dosing, dose escalation study of lapatinib monotherapy at doses of 900 to 1800 mg once daily, conducted in Japanese subjects with solid tumours. A total of 24 subjects were enrolled and received lapatinib once daily at dose levels of 900, 1200, 1600, and 1800 mg; six subjects were enrolled at each dose level. Blood samples for pharmacokinetic evaluation was collected during the dosing interval on Day 1 and Day 21, and predose on Day 7 and 14.

The MTD was determined as 1800 mg/day.

The pharmacokinetic results from the different dose cohorts are shown in Table 8. For comparison, previous results from Caucasian subjects are shown in Table 9 (extract from different studies in the original submission). The pharmacokinetic disposition of lapatinib in Japanese subjects appeared similar to those previously described in Western subjects. Systemic exposure to lapatinib increased with increasing dose in a less than proportional manner. No difference in tmax was observed, suggesting that there was no difference in absorption rate. Urinary excretion (< 0.1% of the dose), was confirmed as the minor role of this route of elimination.

Table 8. Summary of steady state lapatinib pharmacokinetic parameters in Japanese subjects in study EGF10020

Dose (mg)	N	AUC(0-τ) (h.mg/L)	Cmax (mg/L)	tmax (h)
900	6	29.3 (21.6, 39.6)	1.90 (1.32, 2.72)	3.99 (3.00, 5.97)
1200	6	25.7 (13.7, 48.0)	1.72 (0.97, 3.05)	3.59 (3.00, 7.93)
1600	6	51.1 (28.7, 91.1)	3.11 (1.94, 5.00)	5.05 (0.93, 8.02)
1800	5	39.5 (14.9, 104)	2.33 (0.93, 5.87)	3.92 (2.98, 7.32)

Table 9. Exposure (mean±SD) to lapatinib after escalating once daily multiple doses to cancer patients

Dose (mg)	***n***	**AUC_{inf} (mg*h/L)**	**AUCτ (ng*h/ml)**	
		Day 1	**Day 1**	**Day 14**
900	*4*	12.2 (7.7)	8.4 (5.9)	12.8 (1.9)
1200	*5-6*	10.8 (4.5)	9.6 (5.1)	20.0 (12.3)
1500		14.5	(single dose)	
1600	*4*	21.6 (12.0)	18.7 (7.3)	23.0 (4.1)
1800	*9*	24.4 (11.4)	19.5 (7.9)	29.6 (11.8)

During the original assessment, the MAH submitted a summary table over then available data for the effect of race on lapatinib pharmacokinetics (Table 10). It should be noted that the number of Asian subjects included in this analysis was only 4 (2 males, 2 females).

Table 10. Summary Statistics for Dose-Normalised Pharmacokinetic Parameters of lapatinib combined from different Phase I studies

Demographic	Cmax / Dose	AUCinf / Dose	Cmax-ss / Dose	AUCtau-ss / Dose
Asians (n)	*4*	*4*	*4*	*4*
Median (range)	1.36 (1.11 -1.47)	15.0 (11.3 - 21.6)	1.50 (1.03 - 2.45)	21.4 (16.0 - 25.9)
Geom. mean (95% CI)	1.31 (1.01 -1.70)	15.3 (8.81 - 26.4)	1.53 (0.71 - 3.28)	20.8 (13.9 - 31.3)
Blacks (n)	*59*	*56*	*11*	*11*
Median (range)	1.03 (0.14 -4.29)	13.6 (3.28 - 52.2)	1.80 (0.92 - 3.19)	20.7 (13.96 -55.0)
Geom. mean (95% CI)	1.02 (0.27 -3.76)	13.9 (4.03 - 48.0)	1.69 (0.81 - 3.51)	22.4 (9.01 - 55.7)
Hispanics (n)	*46*	*44*	*7*	*7*
Median (range)	0.82 (0.22 -3.25)	11.5 (3.84 - 34.7)	1.16 (0.70 - 4.93)	20.3 (7.88 - 94.7)
Geom. mean (95% CI)	0.79 (0.20 -3.18)	11.0 (3.32 - 36.1)	1.53 (0.35 - 6.70)	23.3 (4.31 – 126)
Whites (n)	*257*	*218*	*124*	*124*
Median (range)	0.99 (0.05 -3.81)	12.7 (0.36 - 57.0)	1.57 (0.26 - 7.86)	19.2 (1.43 - 122)
Geom. mean (95% CI)	1.00 (0.33 -2.98)	12.8 (4.24 - 38.4)	1.54 (0.48 - 4.97)	19.7 (5.22 - 74.0)

Dose finding study - Study EGF10009 (previously submitted)

This was an open-label, repeated-administration, dose escalation study of oral lapatinib and intravenous paclitaxel given in combination to subjects with advanced solid tumours. It was conducted to determine the safety, tolerability, and pharmacokinetics of lapatinib in combination with paclitaxel administered on a once every 3 weeks schedule. The study also evaluated the safety and tolerability of lapatinib 1500 mg once daily with paclitaxel given once every week for 3 weeks out of 4 (weekly schedule). A standard 3 + 3 design was used for dose escalation to determine the optimally tolerated regimen (OTR) for daily lapatinib in combination with paclitaxel.

A total of 56 subjects were enrolled of whom 50 were Caucasian. Forty-four subjects received lapatinib (1250 mg or 1500 mg, daily) + paclitaxel (135 to 225 mg/m^2) given once every 3 weeks. Twelve subjects received lapatinib (1500 mg, daily) + once weekly paclitaxel (80 mg/m^2) given every week for 3 weeks out of 4.

The OTRs were defined as follows: lapatinib 1500 mg once daily in combination with paclitaxel 175 mg/m^2 administered once every 3 weeks and lapatinib 1500 mg once daily in combination with paclitaxel 80 mg/m^2 administered on a weekly schedule for 3 weeks out of 4, based on DLTs of Grade 3 diarrhoea in both studies.

2.2.2. Discussion on clinical pharmacology

Metabolism and subsequent excretion in faeces appears to be the major elimination pathway for lapatinib. The major metabolising enzyme is CYP3A4 with smaller contribution of CYP2C8. Lapatinib is also a substrate for the Pgp/ABCB1 and BCRP/ABCG2 transporters. Ketokonazole, a CYP3A4 and Pgp inhibitor, increased lapatinib exposure by 3.6-fold.

The increase in lapatinib AUC observed in these studies may be due to decreased metabolism and/or increased absorption. Lapatinib is a CYP3A4 substrate and paclitaxel has been shown to inhibit CYP3A4 in vitro with Ki values that are within the range of plasma concentrations observed in this study. It is also possible that paclitaxel could competitively inhibit Pgp/ABCB1-mediated intestinal efflux of lapatinib and thereby increase its absorption.

Lapatinib has been shown to be an inhibitor of CYP3A4 and CYP2C8, of the efflux transporters Pgp and BCRP and the hepatic uptake transporter OATP 1B1 in vitro at clinically relevant concentrations.

The effect of lapatinib on paclitaxel may thus be consistent with inhibition of either CYP2C8 or Pgp. The low bioavailability of lapatinib might suggest a greater potential for interaction in the intestine, i.e. on Pgp, than in the liver where CYP2C8 is expressed. Paclitaxel is administered intravenously, but has been reported to be subject to enterohepatic re-circulation. Thus, lapatinib inhibition of Pgp-mediated biliary excretion and enhanced intestinal re-absorption due to inhibition of efflux would be consistent with "increased bioavailability" of an intravenous dose, since systemic exposure is also dependent on enterohepatic recycling.

The MAH suggested that the dual interaction and the similarity in the magnitude of the effect for each substance indicate a common mechanism of interaction involving inhibition of Pgp efflux in the gut. In addition, the plasma concentration time curves from study EGF104578 might indicate no effect on elimination, as the slope of the terminal phase is similar for single drug and for combination.

The MAH also suggested that given the overall high variability in lapatinib pharmacokinetics, the small increase in lapatinib AUC might not be clinically relevant, while for paclitaxel, with a narrow toxicity window, the increase might be meaningful. Indeed, an increased incidence of adverse events was seen for the combination. This is already reflected in the SmPC, where only the effect of lapatinib on paclitaxel is described, but not the effect of paclitaxel on lapatinib.

The MAH now proposed minor amendments, to reflect that lapatinib and paclitaxel is an indicated and studied combination:

"*Coadministration of lapatinib with intravenous paclitaxel increased the exposure of paclitaxel by 23%, due to lapatinib inhibition of CYP2C8 and/or Pgp. An increase in the incidence and severity of diarrhoea and neutropenia has been observed with this combination in clinical trials (see section 4.8). Caution is advised if when lapatinib is coadministered with paclitaxel*."

The CHMP noted that concomitant administration of lapatinib increased the paclitaxel AUC by on average 23% and 30% in Caucasian (n=17) and Japanese (n=6) subjects, respectively. Conversely, paclitaxel increased lapatinib AUC by 21% and 23%, respectively. Individual patients might have a larger or smaller effect. It is considered unlikely that such a small increase in paclitaxel exposure could explain an effect of the magnitude observed in study EGF104535. Thus, the improved efficacy seen in the lapatinib+paclitaxel arm compared with the paclitaxel alone arm is likely an add-on effect of lapatinib and not merely due to increased exposure to paclitaxel.

In view of the CHMP, the small difference between Caucasian and Japanese subjects in increase in paclitaxel AUC should be interpreted with caution. The number of subjects was smaller in the Japanese group and the 90% CIs were overlapping.

It is considered appropriate to refer to the data from the study in Caucasian subjects in section 4.5 the EU SmPC. The proposed amendments of section 4.5 are considered acceptable by the committee.

There might be genetic differences in e.g. CYP3A4 and Pgp expression between ethnic groups, but there are also many other factors that could affect expression and activity of metabolic enzymes, e.g. differences in diet, and the net effect is difficult to predict. Overall, available clinical data indicate that lapatinib AUC values in Japanese subjects are, on average, somewhat higher than AUC values from

mainly Caucasian subjects, although the variability is high. The clinical relevance of the ethnic difference observed for lapatinib remains to be established.

No clear differences in paclitaxel exposure have been observed between ethnic groups.

The doses of lapatinib and paclitaxel used in the pivotal and supportive studies for the sought indication (EGF1045335 and EGF30001) were based primarily on the DLT of grade 3 diarrhoea in the dose-finding study EGF10009. The doses used for each compound are the same as the standard doses in monotherapy, respectively.

2.3. Clinical efficacy

Two studies were used to evaluate the efficacy of lapatinib in combination with paclitaxel as first-line treatment for HER2 positive metastatic breast cancer, the pivotal study EGF104535 (n=444) and the supportive study EGF30001 (n= 91 HER2 positive, relevant for efficacy). (See Table 3)

The pivotal study EGF104535 was a Phase III, multicentre, randomised, double-blind, placebo-controlled study to evaluate and compare the efficacy and safety of lapatinib+paclitaxel with placebo+paclitaxel in patients with HER2 positive metastatic (Stage IV) breast cancer who have not received prior therapy for metastatic disease.

The study was conducted at 43 centres in 8 countries (in falling order of number of subjects recruited): China, Thailand, Russia, Brazil, Peru, Pakistan, Hong Kong, and Ukraine.

The supportive study EGF30001 was a Phase III, multicentre, randomised, double-blind, placebo-controlled, 2-treatment group, study to evaluate and compare the efficacy and tolerability of lapatinib administered in combination with paclitaxel versus placebo+paclitaxel in subjects with MBC who were untested or negative for overexpression of HER2.

The study was designed before lapatinib was established as a HER2 directed therapy, and the primary analyses evaluated subjects regardless of HER2 status (ITT population). In the present application, supportive efficacy data are based only on subjects with an established HER2 positive status (HER2 positive population), whereas safety data are based on all subjects who received lapatinib or placebo regardless of HER2 status (Safety population).

The study was conducted at 130 centres in 24 countries (in alphabetical order): Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Germany, Hungary, Italy, Korea, Latvia, Mexico, Netherlands, New Zealand, Pakistan, Peru, Poland, Russian Federation, Slovakia, South Africa, Spain, Turkey, United States.

Main study EGF104535

A Randomised, Multicentre, Double-Blind, Placebo-Controlled, Phase III Study of Lapatinib (GW572016) in Combination with Paclitaxel versus Paclitaxel plus Placebo in Subjects with HER2 Amplified Metastatic Breast Cancer (EGF104535)

Methods

Study Participants

Summary of eligibility criteria

The main inclusion criteria of the pivotal study EGF104535 were: histologically confirmed invasive metastatic breast cancer, HER2-positivity documented by immunohistochemistry or FISH, measurable disease according to RECIST criteria and ECOG performance status of 0 to 1. Patients were excluded

who had non-measurable disease only (e.g. bone-only disease), had received prior chemotherapy, immunotherapy, biologic therapy, or anti-epidermal growth factor receptor/HER2 therapy for metastatic breast cancer, as were patients with known CNS metastases, or peripheral neuropathy ≥ grade2. (For details, please see listing below.)

Inclusion Criteria

1. Signed informed consent.
2. Male or female ≥18 years.
3. Histologically confirmed invasive breast cancer with Stage IV disease. If the disease was restricted to a solitary lesion, its neoplastic nature was to have been confirmed by cytology or histology.
4. Documentation by central laboratory of HER2 status by IHC or amplification by FISH in primary or metastatic tumour tissue for randomisation into the study.
5. If a taxane was administered in the neoadjuvant or adjuvant setting, progression must have occurred >12 months after completion of this treatment and the subject recovered from all associated toxicities.
6. Measurable lesion(s) according to RECIST (Response Evaluation Criteria in Solid Tumours).
7. Radiotherapy as palliative treatment for painful metastatic disease was permitted but must have been stopped within 2 weeks prior to initiation of any investigational treatment. All subjects must have recovered from all radiotherapy related toxicities prior to initiation of any investigational treatment. The site of radiotherapy must not be used as a site of measurable disease.
8. Bisphosphonate therapy for bone metastases was allowed; however, treatment must have been initiated prior to the first dose of investigational treatment. Prophylactic use of bisphosphonates in subjects without bone disease was not permitted, except for the treatment of osteoporosis.
9. For those patients whose disease was ER+ and/or PgR+ one of the following criteria should have been met:
    - Subjects with visceral disease that required chemotherapy (e.g., subjects with liver or lung metastases).
    - Rapidly progressing or life threatening disease, as determined by the investigator.
    - Subjects who received hormonal therapy and were no longer benefiting from this therapy and the hormonal treatment must have been stopped before the first dose of investigational treatment.
10. Cardiac ejection fraction within institutional range of normal as measured by echocardiogram (ECHO). Multigated acquisition (MUGA) scans were accepted in cases where an echocardiogram could not be performed or was inconclusive.
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
12. Life expectancy of ≥12 weeks.
13. Able to swallow and retain oral medication.
14. Archived tumour tissue available for testing.
15. Women and men with potential to have children must have been willing to practice acceptable methods of birth control during the study.
16. Willing to complete all screening assessments as outlined in the protocol.
17. Adequate organ function as defined by baseline haematologic, hepatic, and renal laboratory values: ANC (absolute neutrophil count) ≥1.5 × 109/L, Haemoglobin ≥9 g/dL, Platelets ≥100 × 109/L, Albumin ≥2.5 g/dL, Serum bilirubin ≤ 2.0 x ULN, AST and ALT ≤3 × ULN without liver metastases, ≤5 × ULN if documented liver metastases, Serum Creatinine ≤2.0 mg/dL *OR* Calculated Creatinine Clearance ≥40 mL/min according to the Cockcroft and Gault Method.

Exclusion Criteria

1. Pregnant or lactating females at anytime during the study.
2. Subjects with only non-measurable metastatic sites of disease per RECIST, (e.g. bone metastases, pleural effusion, or ascites, etc.
3. Received prior chemotherapy, immunotherapy, biologic therapy, or anti-EGFR/HER2 therapy for metastatic disease.
4. Prior therapy with an EGFR and/or HER2 inhibitor, other than trastuzumab in the adjuvant setting. If trastuzumab was administered in the adjuvant setting, then >12 months must have elapsed since completion of trastuzumab therapy.
5. Planned concurrent anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy) while taking investigational treatment.
6. Unresolved or unstable, serious toxicity from prior administration of another investigational drug and/or of prior cancer treatment.
7. Peripheral neuropathy of Grade 2 or greater.
8. Malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, or resection of the stomach or small bowel. Subjects with ulcerative colitis were also excluded;
9. History of other malignancy. However, subjects who had been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma, were eligible.
10. 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.
11. Uncontrolled infection.
12. Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
13. Known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure.
14. Known history or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis.
15. Concurrent treatment with prohibited medications, including herbal remedies and Chinese traditional medicines.
16. Concurrent treatment with an investigational agent or participation in another clinical trial involving investigational agents.
17. Used an investigational drug within 30 days or 5 half-lives, whichever was longer, preceding the first dose of investigational treatment.
18. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to paclitaxel or lapatinib or their excipients.
19. Had current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).

- ***Treatments***

Subjects were randomised in a 1:1 ratio to receive either oral lapatinib (1500 mg once daily) plus paclitaxel (80 mg/m^2 intravenous [IV] weekly for 3 weeks every 4 weeks) or oral placebo (once daily) plus paclitaxel (80 mg/m^2 IV weekly for 3 weeks every 4 weeks).

- ***Objectives and endpoints***

Objectives, endpoints and their definitions

Primary

1. To evaluate and compare overall survival (OS) for subjects with HER2 amplified metastatic breast cancer when treated with lapatinib plus paclitaxel versus placebo plus paclitaxel. OS was defined as the time from randomisation to death due to any cause.

Secondary

To evaluate and compare the two treatment arms with respect to:

2. Progression-free survival (PFS), defined as the time from randomisation until the earliest date of disease progression or death due to any cause, if sooner.

3. Overall response rate (ORR), defined as the percentage of subjects having either a confirmed complete or partial tumour response, based on confirmed responses from the investigator assessment of best overall response during the randomised phase.

4. Clinical benefit rate (CBR), defined as complete response (CR) or partial response (PR) or stable disease (SD) ≥24 weeks).

5. Duration of response (DoR), defined as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause.

6. Time to response (TTR), defined as the time from randomisation until first documented evidence of partial or complete tumour response (whichever is recorded first).

7. To determine the qualitative and quantitative toxicities associated with the combination of paclitaxel and oral lapatinib.

8. To compare and correlate tumour response rates with relevant biomarkers and genetic changes in serum, plasma, and intra-tumoural samples (not reported).

Pharmacogenetic Objective

9. To investigate the relationship between genetic variants in candidate genes in the host and response (safety and efficacy) to the combination of lapatinib plus paclitaxel or placebo plus paclitaxel (reported separately).

Disease assessments

Disease assessments were performed at baseline and every 8 weeks, and at the time of withdrawal from study therapy. Response, per RECIST (Version 1.0), was evaluated at each follow-up disease assessment and at the time of withdrawal from study treatment.

To evaluate target lesions for partial or complete response the sum of the longest diameter was compared with the baseline measurement. To evaluate for progression, the sum of the longest diameter was compared with the nadir (smallest longest diameter measurement recorded across all time points).

A subject's best overall response was based on the confirmed overall responses. A PR and CR must have had a confirmation of PR or CR at a minimum of 4 weeks (28 days) between the scans. SD must have been present for a minimum of 7 weeks (49 days).

- ***Sample size***

The study was designed to provide evidence with respect to overall survival to support the null hypothesis H0: $\lambda \geq 1$ or reject it in favour of the alternative hypothesis HA, where $\lambda < 1$ is the hazard ratio (HR): lapatinib plus paclitaxel versus placebo plus paclitaxel. Assuming the OS times follow exponential distributions and are consistent with proportional hazards, the null hypothesis represents

equality of the median OSs in the two treatment arms, or a decreased median OS in the lapatinib plus paclitaxel arm, and the alternative hypothesis represents an increased median OS in the lapatinib plus paclitaxel arm.

A total of 255 deaths are required with 80% power and one-sided type I error of 0.025 to detect an HR of 0.70 corresponding to a 43% increase in median OS in subjects who receive lapatinib plus paclitaxel (28.6 months) compared with subjects who receive placebo plus paclitaxel (20 months).

- ***Randomisation***

Subjects were randomised to either lapatinib+paclitaxel or placebo+paclitaxel in a 1:1 ratio in accordance with the randomisation schedule. Subjects were stratified at randomisation according to hormonal status and metastatic disease sites. A unique subject number was assigned to each subject. Randomization was stratified according to the following 2 factors (with each factor containing 2 categories/strata):

1. Hormonal status of ER/PgR

- Positive (ER + and/or PgR +). Note: If ER and PR status is unknown, these subjects shall be classified as hormonal receptor positive.
- Negative (ER - and PgR +)

2. Metastatic disease sites

- Any visceral site
- Non-visceral only

- ***Blinding (masking)***

Treatment was blinded to subjects and all study and Sponsor personnel by use of matching placebo medication. Subjects were identified by a unique subject number that remained constant for the duration of the study. Investigators or designated staff telephoned the GSK interactive voice response system (IVRS) called Registration and Medication Ordering System (RAMOS) to register and record subject activity, followed by a confirmation by facsimile.

In a case of an emergency, when knowledge of treatment with lapatinib or placebo was essential for the clinical management or welfare of the subject, the investigator was permitted to unblind a subject's treatment assignment via the IVRS. In addition, a subject's lapatinib/placebo was permitted to be unblinded via IVRS at the time of disease progression, if the investigator and subject had the expectation that the subject would enrol into the extension phase if the subject was on placebo.

The unblinding of subjects to determine eligibility to enter the extension was performed via a third-party vendor (ClinPhone). Where the blind was broken for progression onto the open-label lapatinib monotherapy extension arm, only the investigator and subject were unblinded to the lapatinib or placebo received during the randomised therapy. GSK personnel associated with the conduct of the study remained blinded, and notifications of request and completion of unblinding did not include the treatment code.

- ***Statistical methods***

Standard statistical methods for oncology studies were used, and are therefore not discussed further. The method is specified in the results section for each analysis presented.

Results

- ***Participant flow***

A total of 444 subjects were randomised at 43 centres in 8 countries: China (20 centres with 296 (67%) subjects), Brazil (7 centres with 20 (5%) subjects), Russia (6 centres with 21 (5%) subjects), Hong Kong (3 centres with 12 (3%) subjects), Pakistan (3 centres with 17 (4%) subjects), Thailand (2 centres with 59 (13%) subjects), Peru (1 centre with 18 (4%) subjects) and Ukraine (1 centre with 1 (<1%) subject).

At the time of the analysis, 54% of subjects in the lapatinib+paclitaxel arm and 64% of subjects in the placebo+paclitaxel arm had died and by definition "completed" the study (Table 11). Thirty-eight percent of the subjects on the lapatinib+paclitaxel arm and 30% of subjects in the placebo+paclitaxel arm were ongoing (i.e. still on study treatment or being followed for survival at the clinical cut-off date of 18 June 2010). There were no subjects withdrawn from the study due to AEs as reported by the investigator. However, it should be noted that subjects could be withdrawn from IP due to AEs, but continue on study (see safety section).

Table 11. Subject disposition (ITT population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
Completed[a]	120 (54)	143 (64)
Withdrawn from study[b]	17 (8)	12 (5)
Ongoing	85 (38)	67 (30)
Primary reason for study withdrawal		
Lost to follow-up	12 (5)	8 (4)
Subject decided to withdraw from study	4 (2)	2 (<1)
Adverse event[c]	0	0
Protocol violation	0	0
Sponsor terminated study	0	0
Disease progression	0	0
Investigator decision	0	0
Other[c]	1 (<1)	2 (<1)

a. Completed was defined as subjects who had died.
b. Withdrawn from study was defined as subjects withdrawn from study but had not died.
c. Lapatinib+paclitaxel arm: 1 subject withdrew from the study to enter a new protocol; placebo+paclitaxel arm: 1 subject withdrew from the study to enter a new protocol, and 1 subject was a screen failure and was randomised in error.
d. IP discontinuation due to an AE is not captured in this table.

- ***Conduct of the study***

Protocol amendments

- The original protocol was dated 29 September 2005. There was one amendment made, Amendment#1, dated 27 June 2008, which occurred prior to the analysis of the study, when 146 subjects had been randomised and 7 deaths had occurred. The changes applied to all centres in all countries and are summarised below:

- The primary objective was changed from CBR to OS as this was considered a more reliable and precise endpoint. The number of subjects required for the original primary endpoint CBR was

424. The sample size was increased to 430 subjects to account for the number of deaths (events) required to meet the primary endpoint of OS.

- The secondary objective of time to treatment failure was also changed to time to response as this was considered a more clinically meaningful endpoint.
- An interim analysis was added at the recommendation of the IDMC in the event that superiority or futility for the combination could be demonstrated early during the conduct of the study.
- The assessment of overall response was revised to be more consistent with standard of care when evaluating patients for disease in the bone. The requirement to have a bone scan to rule out the presence of new bone lesions or progression of existing bone lesions was limited to only those subjects with bone disease at baseline.
- The extent of the biomarker studies were more broadly defined because data on serum EGFR and HER2 extracellular domain of protein receptors from other lapatinib studies had not provided any meaningful association with lapatinib treatment and response. The collection of samples was reduced because serial samples for the entire study were no longer required.
- Guidance was added on the management of liver toxicity because of increased liver chemistry values observed in the lapatinib program.
- The key inclusion criteria #4 was changed from requiring documented amplification of ErbB2 by fluorescence in situ hybridization (FISH) in primary or metastatic tumour tissue by the central laboratory, to allowing also documentation by central laboratory of ErbB2 status by Immunohistochemistry (IHC). The rationale was that both assays are validated and approved by regulatory agencies for documentation of positive ErbB2 status of tumours, and that sometimes specimen processing makes FISH impossible while IHC is still possible. Additionally, the study enrolment had been expanded to include countries where IHC is a common assay for testing ErbB2 status.

Protocol violations

A total of 7 subjects (2%) were recorded as having one or more inclusion/exclusion criteria deviation at the start of the study. Protocol deviations were determined programmatically based on the inclusion/exclusion criteria panel in the eCRF and central laboratory FISH status.

Two subjects were not centrally confirmed as HER2 positive: 1 subject was not tested for HER2 status by FISH (Subject 1311, who was immediately withdrawn following randomisation did not receive any randomised treatment) and 1 subject had negative IHC (Subject 605).

Table 12. Major protocol deviations (ITT population), Pivotal study EGF104535

	Number of Subjects (%)		
	Lapatinib +paclitaxel (N=222)	Placebo +paclitaxel (N=222)	Total (N=444)
Major protocol deviations	3 (1)	4 (2)	7 (2)
Non-positive FISH HER2 result	0	2 (<1)	2 (<1)
Received prior chemotherapy, hormone therapy if not ER/PgR positive, immunotherapy, biologic therapy, or anti-EGFR/HER2 therapy for advanced or metastatic disease	1 (<1)	0	1 (<1)
Received other anti-cancer medications, surgery or radiation therapy while on investigational treatment	2 (<1)	1 (<1)	3 (<1)
Did not take any investigational treatment	0	1 (<1)	1 (<1)
Had additional lesion after baseline	0	1 (<1)	1 (<1)

- ***Baseline data***

Baseline and demographic data for the two treatment arms and the total study population are shown in the tables below (Table 13– demographics, Table 14 – race, Table 15 – prognostic factors, Table 16 – prior therapy).

Table 13. Summary of demographic characteristics (ITT population), Pivotal study EGF104535

	Lapatinib +paclitaxel (N=222)	Placebo + paclitaxel (N=222)	Total (N=444)
Age (yrs)	n=222	n=222	n=444
Mean (SD)	49.1 (10.74)	49.3 (9.75)	49.2 (10.25)
Median (min-max)	50.0 (25-74)	50.5 (26-73)	50.0 (25-74)
Age groups; n (%)	n=222	n=222	n=444
≥65 years of age	16 (7)	13 (6)	29 (7)
<65 years of age	206 (93)	209 (94)	415 (93)
<75 years of age	222 (100)	222 (100)	444 (100)
Sex; n (%)	n=222	n=222	n=444
Female	222 (100)	217 (98)	439 (99)
Male	0	5 (2)	5 (1)
Child-bearing potential; n (%)	n=222	n=217	n=439
Post-menopausal	138 (62)	132 (61)	270 (62)
Potentially able to bear children	67 (30)	65 (30)	132 (30)
Sterile	17 (8)	20 (9)	37 (8)
Pre-menarcheal	0	0	0
Height (cm)	n=218	n=217	n=435
Mean (SD)	157.4 (6.19)	158.2 (6.23)	157.8 (6.21)
Median (min-max)	158.0 (140-171)	159.0 (140-182)	158.0 (140-182)
Weight (kg)	n=222	n=221	n=443
Mean (SD)	61.8 (11.04)	61.4 (10.60)	61.6 (10.81)
Median (min-max)	60.0 (40-110)	60.0 (33-90)	60.0 (33-110)

Table 14. Summary of race and racial combinations (ITT population), Pivotal study EGF104535

	Number of Subjects (%)		
	Lapatinib + paclitaxel (N=222)	Placebo +paclitaxel (N=222)	Total (N=444)
Ethnicity; n (%)	n=222	n=222	n=444
Hispanic or latino	21 (9)	16 (7)	37 (8)
Not hispanic or latino	201 (91)	206 (93)	407 (92)
Race category	n=222	n=222	n=444
White	9 (4)	13 (6)	22 (5)
Asian	192 (86)	192 (86)	384 (86)
Hispanic	21 (9)	16 (7)	37 (8)
Other	0	1 (<1)[a]	1 (<1)
Racial Combination	n=222	n=222	n=444
African american/african heritage	2 (<1)	3 (1)	5 (1)
American indian or alaska native	13 (6)	5 (2)	18 (4)
Asian - central/south asian heritage	9 (4)	4 (2)	13 (3)
Asian - east asian heritage	149 (67)	154 (69)	303 (68)
Asian - south east asian heritage	34 (15)	33 (15)	67 (15)
Asian - mixed race	0	1 (<1)	1 (<1)
White - white/caucasian/european heritage	14 (6)	22 (10)	36 (8)
Mixed race	1 (<1)	0	1 (<1)

a. This subject (Subject 1225 from a site in Peru) was non-hispanic, and of American Indian or Alaskan Native heritage.

Table 15. Baseline prognostic factors identified for efficacy analyses (ITT population), Pivotal study EGF104535

	Lapatinib +paclitaxel (N=222)	Placebo +paclitaxel (N=222)	Total (N=444)
Data Available for All Covariates; n (%)			
Yes	212 (95)	211 (95)	423 (95)
No	10 (5)	11 (5)	21 (5)
Metastatic disease site, n (%)			
Visceral	187 (84)	186 (84)	373 (84)
Non-visceral	35 (16)	36 (16)	71 (16)
Hormone Status; n (%)			
ER+ and/or PgR+ or unknown	111 (50)	113 (51)	224 (50)
ER- and PgR-	111 (50)	109 (49)	220 (50)
Stage of Disease at Initial Diagnosis; n (%)			
Stage I – II	107 (48)	119 (54)	226 (51)
Stage III	75 (34)	68 (31)	143 (32)
Stage IV	30 (14)	24 (11)	54 (12)
Unknown	10 (5)	11 (5)	21 (5)
ECOG Performance Status; n (%)			
0	103 (46)	113 (51)	216 (49)
1	119 (54)	109 (49)	228 (51)
Number of Metastatic Sites; n (%)			
≥3	131 (59)	115 (52)	246 (55)
<3	91 (41)	107 (48)	198 (45)
Age groups; n (%)			
≥65 years of age	16 (7)	13 (6)	29 (7)
<65 years of age	206 (93)	209 (94)	415 (93)
Disease-Free Interval (months)			
Mean (SD)	27.51 (27.481)	29.04 (34.522)	28.27 (31.174)
Median (Min-Max)	23.43 (0-242.7)	21.60 (0-322.1)	21.85 (0-322.1)

Table 16. Prior anti-cancer therapy by type and intent (ITT Population), Pivotal study EGF104535

	Number of Subjects (%)		
	Lapatinib +paclitaxel (N=222)	Placebo +paclitaxel (N=222)	Total (N=444)
Any therapy	171 (77)	182 (82)	353 (80)
Chemotherapy	160 (72)	173 (78)	333 (75)
Hormonal therapy	53 (24)	44 (20)	97 (22)
Immunotherapy	0	0	0
Biologic therapy	0	4 (2)	4 (<1)
Surgery	190 (86)	196 (88)	386 (87)
Radiotherapy	94 (42)	85 (38)	179 (40)
Any neo-adjuvant therapy	36 (16)	34 (15)	70 (16)
Chemotherapy	35 (16)	30 (14)	65 (15)
Hormonal therapy	0	1 (<1)	1 (<1)
Radiotherapy	2 (<1)	4 (2)	6 (1)
Any adjuvant therapy	166 (75)	172 (77)	338 (76)
Chemotherapy	146 (66)	161 (73)	307 (69)
Hormonal therapy	48 (22)	37 (17)	85 (19)
Biologic therapy	0	4 (2)	4 (<1)
Radiotherapy	80 (36)	68 (31)	148 (33)
Any advanced/metastatic therapy	12 (5)	12 (5)	24 (5)
Chemotherapy	1 (<1)	1 (<1)	2 (<1)
Hormonal therapy	6 (3)	7 (3)	13 (3)
Radiotherapy	5 (2)	6 (3)	11 (2)
Any local therapy	8 (4)	7 (3)	15 (3)
Chemotherapy	2 (<1)	1 (<1)	3 (<1)
Hormonal therapy	1 (<1)	0	1 (<1)
Radiotherapy	6 (3)	6 (3)	12 (3)
Any prophylactic therapy	2 (<1)	2 (<1)	4 (<1)
Radiotherapy	2 (<1)	2 (<1)	4 (<1)
Any palliative therapy	6 (3)	2 (<1)	8 (2)
Radiotherapy	6 (3)	2 (<1)	8 (2)
Any maintenance therapy	1 (<1)	5 (2)	6 (1)
Chemotherapy	0	1 (<1)	1 (<1)
Hormonal therapy	1 (<1)	4 (2)	5 (1)

Table 17. Summary of most common prior adjuvant and neo-adjuvant therapy (10% or more in any treatment arm) by type (ITT population), Pivotal study EGF104535

	Number of Subjects (%)		
	Lapatinib +paclitaxel (N=222)	Placebo +paclitaxel (N=222)	Total (N=444)
Neo-adjuvant therapy			
Any Chemotherapy	35 (16)	30 (14)	65 (15)
Cyclophosphamide	29 (13)	22 (10)	51 (11)
Adjuvant therapy			
Any Chemotherapy	146 (66)	160 (72)[a]	306 (69)
Cyclophosphamide	122 (55)	129 (58)	251 (57)
Fluorouracil	91 (41)	103 (46)	194 (44)
Epirubicin	51 (23)	51 (23)	102 (23)
Methotrexate	28 (13)	32 (14)	60 (14)
Doxirubicin	21 (9)	24 (11)	45 (10)
Docetaxel	15 (7)	23 (10)	38 (9)
Pirarubicin	16 (7)	22 (10)	38 (9)
Any hormonal	48 (22)	37 (17)	85 (19)
Tamoxifen	36 (16)	28 (13)	64 (14)
Any biologic	0	4 (2)	4 (<1)
Trastuzumab	0	4 (2)	4 (<1)

a. Subject 317 had only the class and intent of prior therapy recorded. Since no information on the name of the drug was available, the subject was not included in this analysis, but was included in Table 15 in this AR.

Post-study therapy

Post-study therapy has the potential to influence the long term results of the study, i.e. overall survival.

Table 18. Anti-cancer therapy (10% or more in any treatment arm) post study by type (ITT population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
Any therapy	149 (67)	136 (61)
Chemotherapy	123 (55)	118 (53)
Radiotherapy	55 (25)	52 (23)
Hormonal therapy	52 (23)	27 (12)
Biologic therapy	27 (12)	38 (17)

According to the data source of the original table, 16 patients (7%) in the lapatinib+paclitaxel arm and 9 (4%) in the placebo+paclitaxel arm were given "traditional Chinese medicine". Surgery was performed on 7 and 5%. Less than 1% in both arms were unknown. For numbers receiving relevant systemic therapies, see table below.

Table 19. Most common (at least 10% in any treatment arm) anti-cancer therapy – biologic, chemotherapy, immunological and hormonal post treatment (ITT population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
Any post-treatment therapy	142 (64)	129 (58)
Capecitabine	62 (28)	70 (32)
Vinorelbine	41 (18)	54 (24)
Cyclophosphamide	29 (13)	27 (12)
Docetaxel	26 (12)	32 (14)
Cisplatin	24 (11)	32 (14)
Trastuzumab	22 (10)	35 (16)
Gemcitabine	21 (9)	27 (12)
Fluorouracil	19 (9)	24 (11)

NB This table includes therapies received following the randomised and extension phase.

- ***Numbers analysed***

Table20. Study population's analysed, Pivotal study EGF104535

	Number of Subjects (%)		
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)	Total (N=444)
ITT Population	222 (100)	222 (100)	444 (100)
PP Population	219 (99)	218 (98)	437 (98)
Safety Population	222 (100)	221 (>99)	443 (>99)
ME Population	0	149 (67)	149 (34)

The PP population is very similar to the ITT population

- ***Outcomes and estimation***

The main efficacy results of the pivotal study are summarised in Table 21.

Table21. Study EGF104535 Summary of Efficacy Results (ITT Population)

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
Primary Endpoint		
Cox Proportional Hazards Model of OS		
Adjusted HR (95% CI)	0.64 (0.49, 0.82)	
One-sided p-value	0.0002	
Two-sided p-value	0.0005	
Analyses Supporting the Primary Endpoint		
Kaplan Meier estimates of OS		
Median (95% CI) (months)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
Stratified hazard ratio estimates (95% CI)	0.74 (0.58, 0.94)	
Stratified log-rank test one-sided p-value	0.0062	
Stratified log-rank test two-sided p-value	0.0124	
Secondary Endpoints		
Kaplan Meier estimates of PFS		
Median (95% CI) (months)	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
Stratified hazard ratio estimate (95% CI)	0.52 (0.42, 0.64)	
Stratified log-rank test p-value	<0.0001	
ORR (CR or PR)		
Percent response rate (95% CI)	69 (62.9, 75.4)	50 (42.8, 56.3)
Estimate of odds ratio for response (95% CI)	2.30 (1.54, 3.47)	
p-value	<0.0001	
Estimated Relative Risk (95% CI)	1.40 (1.19, 1.64)	
CBR (CR or PR or SD for ≥24 weeks)		
Percent response rate (95% CI)	75 (68.5, 80.3)	56 (49.1, 62.5)
Estimate for odds ratio for response (95% CI)	2.34 (1.54, 3.58)	
p-value	<0.0001	
Estimated Relative Risk (95% CI)	1.34 (1.16, 1.54)	
Lapatinib Monotherapy Extension Phase		
	(N=149)	
Kaplan Meier estimates of PFS		
Median (95% CI) (months)	3.7 (3.6, 4.4)	
ORR (CR or PR)		
Percent response rate (95% CI)	17 (11.2, 23.8)	
OS from start of lapatinib monotherapy (post-hoc analysis)		
Median OS (months) (95% CI)	15.3 (13.2, 19.1)	

Primary endpoint – Overall survival

The primary analysis of the primary objective was according to a Cox proportional hazards regression model for overall survival adjusted for prognostic factors in the ITT population.

This analysis was adjusted for the two stratification factors, hormonal status (positive/negative) and metastatic disease sites (visceral/non-visceral); and five pre-specified prognostic factors: Stage of disease at initial diagnosis (I-II/III/IV), ECOG performance status at baseline (0/1), number of metastatic sites (<3/≥3), age (in years) (<65/≥65), and disease-free interval defined as the time from initial diagnosis to metastases. Results for the primary analysis are summarised in Table 3, and the Cox proportional hazards ratio adjusted overall survival curves are shown in Figure 3.

The secondary analysis (sensitivity analysis) of the primary endpoint was according to Kaplan-Meier with point estimates based on the log rank test stratified for metastatic disease sites and hormonal status. Results for the secondary analysis are summarised in Table 29, and the Kaplan-Meier overall survival curves are shown in Figure 4.

Table 22. Summary of Overall Survival adjusted for prognostic factors (ITT Population) according to Cox proportional hazards regression model, pivotal study EGF104535

Covariate, N/n = 444/423	Hazard Ratio (95% CI)[a]	p-value[b]
Treatment		
Lapatinib+paclitaxel vs Placebo+paclitaxel	0.64 (0.49, 0.82)	0.0005
Hormonal Status		
Negative (ER- and PgR-) vs Positive (ER+ and/or PgR+) or Unknown	1.16 (0.90, 1.49)	0.2546
Metastatic Disease Sites		
Non-Visceral vs Visceral	0.75 (0.50, 1.13)	0.1654
Stage at Initial Diagnosis		
I, II vs IV III vs IV	1.11 (0.71, 1.74) 1.37 (0.90, 2.08)	0.6364 0.1454
ECOG Performance Status		
0 vs 1	0.66 (0.51, 0.86)	0.0020
Number of Metastatic Sites		
<3 vs ≥3	0.57 (0.43, 0.76)	0.0002
Age (years)		
<65 vs ≥65	0.80 (0.49, 1.32)	0.3855
Disease-Free Interval (months)		
Trend per 1 month increase	0.99 (0.98, 1.00)	0.0035

Data Source Table 7.0003

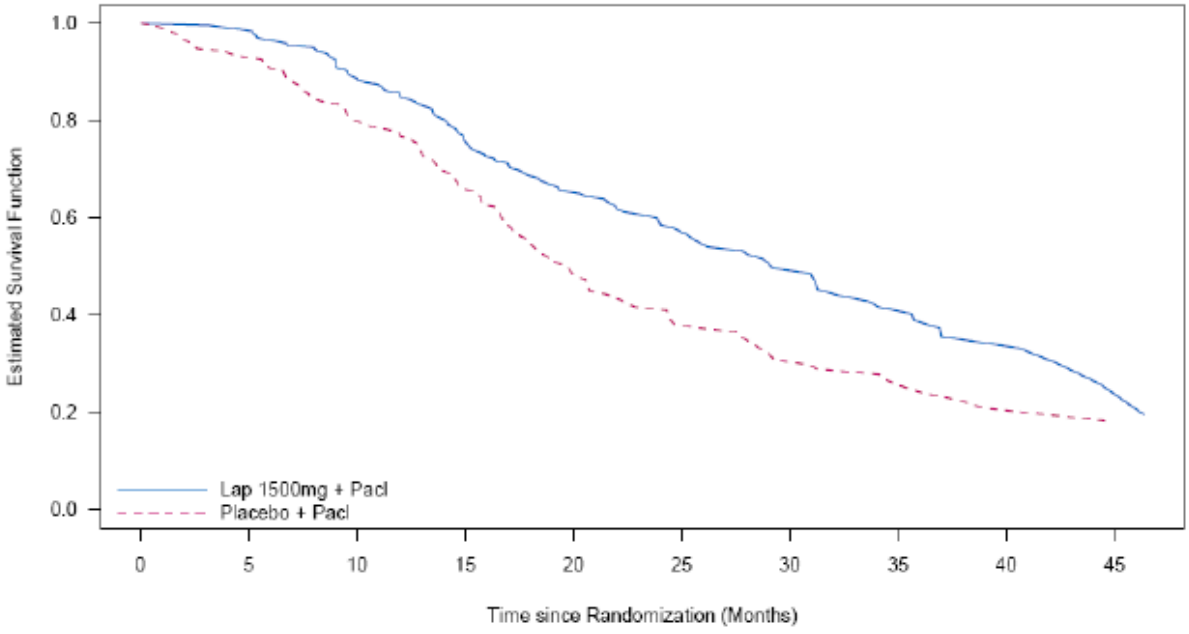
a. A hazard ratio <1 indicates a lower risk on the first effect tested compared with the other effects tested.
b. p-values are two-sided from Wald Chi-squared test.

Table 23. Summary of Overall Survival according to Kaplan-Meier analysis (ITT), pivotal study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
	n (%)	n (%)
Died due to any cause	120 (54)	143 (64)
Censored, follow-up ended	17 (8)	12 (5)
Censored, follow-up ongoing	85 (38)	67 (30)
Stratified hazard ratio[a] Estimate (95% CI)	0.74 (0.58, 0.94)	
Stratified log-rank (one-sided)[b] p-value	0.0062	
Estimates for OS (months)		
1st quartile (95% CI)	14.5 (13.1, 16.3)	12.5 (9.5, 14.3)
Median (95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
3rd quartile (95% CI)	46.4 (39.1, NE)	43.1 (34.1, NE)

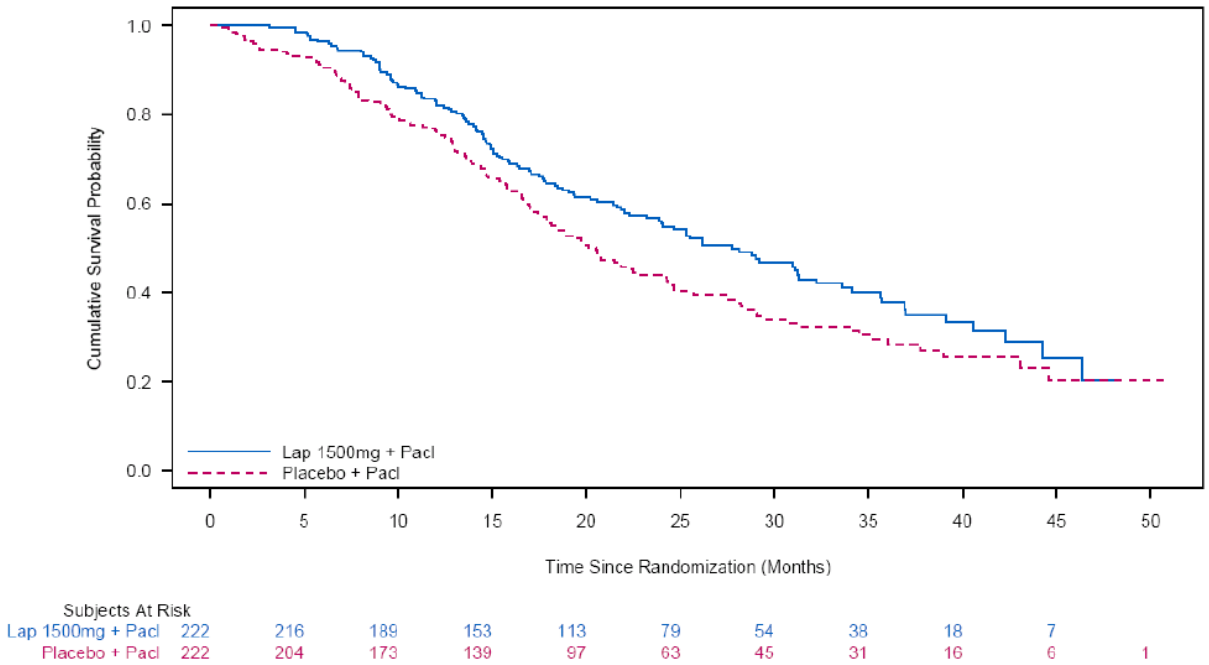
a. The Pike estimator of the treatment hazard ratio based on the log rank test stratifying for metastatic disease sites and hormonal status. A hazard ratio <1 indicates a lower risk with lapatinib+paclitaxel compared with placebo+paclitaxel.
b. One-sided p-value from stratified log-rank test, stratifying for metastatic disease sites and hormonal status. The two-sided p-value was 0.0124.

Figure 3. Overall Survival Curves according to Cox Proportional Hazards Ratio Adjusted Analysis (ITT), Pivotal Study EGF104535



Adjusted for the two stratification factors, hormonal status (positive/negative) and metastatic disease sites (visceral/non-visceral); and five pre-specified prognostic factors: Stage of disease at initial diagnosis (I-II/III/IV), ECOG performance status at baseline (0/1), number of metastatic sites (<3/≥3), age (in years) (<65/≥65), and disease-free interval defined as the time from initial diagnosis to metastases.

Figure 4. Overall Survival according to Kaplan-Meier (ITT Population), Pivotal Study EGF104535



Sensitivity analyses of the primary endpoint

The hazard ratios and confidence intervals of the primary analysis of the primary objective, Overall survival, and the three sensitivity analyses performed (including the "secondary" stratified KM analysis described above) are shown below.

Table 24. Overall survival: comparison of primary and sensitivity analyses (ITT population) Pivotal study EGF104535

Analysis #	**Description**	**HR (95% CI), p-value one-sided / two-sided**
	Primary analysis:	
	Cox Proportional Hazards Model adjusted for the two stratification factors and five pre-specified prognostic factors*	64 (0.49, 0.82) 0.0002/0.0005
	Sensitivity analyses:	
1.	Kaplan-Meier estimates and Pike estimator of Hazard Ratio	0.74 (0.58, 0.94) 0.0062 / 0.0124
2.	Cox Regression adjusting for Stratification Factors (hormonal status and sites of metastatic disease)	0.73 (0.57, 0.93) 0.0049 / 0.0099
3.	Stepwise Cox Regression (final model including treatment, ECOG PS, number of metastatic sites and disease-free interval)	0.63 (0.49, 0.81) 0.0002 / 0.0003

*Stage of disease at initial diagnosis, ECOG performance status at baseline, number of metastatic sites, age, and disease-free interval defined as the time from initial diagnosis to metastases.

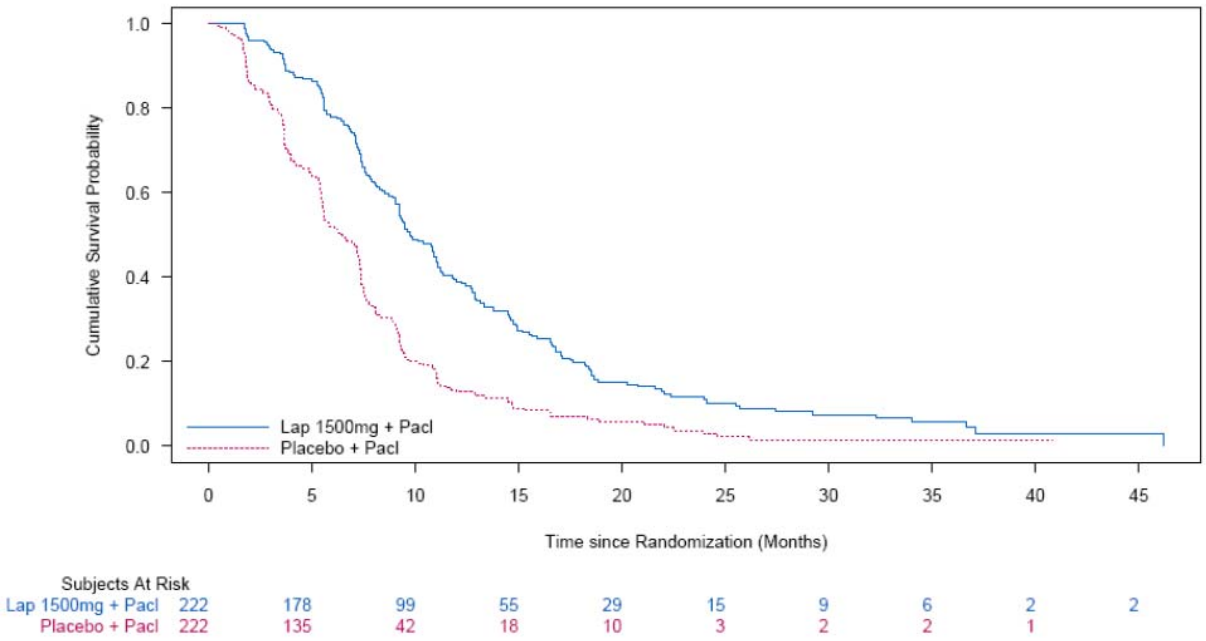
Secondary endpoint - Progression-free survival

Table25. Progression-Free Survival (ITT Population) Pivotal Study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
	n (%)	n (%)
Progressed or died due to any cause	188 (85)	204 (92)
Censored, follow-up ended	20 (9)	12 (5)
Censored, follow-up ongoing	14 (6)	6 (3)
Stratified hazard ratio[a] Estimate (95% CI)	0.52 (0.42, 0.64)	
Stratified log-rank (two-sided)[b] p-value	<0.0001	
Estimates for PFS (months)		
1st quartile (95% CI)	6.8 (5.6, 7.4)	3.6 (3.1, 3.9)
Median (95% CI)	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
3rd quartile (95% CI)	16.6 (14.5, 18.2)	9.2 (8.1, 10.1)

a. The Pike estimator of the treatment hazard ratio based on the log rank test stratifying for metastatic disease sites and hormonal status. A hazard ratio <1 indicates a lower risk with lapatinib+paclitaxel compared with placebo+paclitaxel. b. Two-sided p-value from stratified log-rank test, stratifying for metastatic disease sites and hormonal status

Figure 5. Progression-free Survival according to Kaplan-Meier (ITT Population), Pivotal Study EGF104535



Sensitivity analyses of progression-free survival

A number of sensitivity analyses for the secondary endpoint progression-free survival were also performed, see Table 26.

Table 26. Progression-free Survival sensitivity analyses (ITT Population), Pivotal Study EGF104535

Analysis Number	Description	HR (95% CI), p-value
1	Symptomatic progressions excluded	0.52 (0.42,0.63), <0.0001
2	Cox Regression adjusting for stratification factors (hormonal status and sites of metastatic disease)	0.50 (0.41,0.62), <0.0001
3	Adequate assessment #1 – Censored for PD or Death	0.51 (0.41,0.63), <0.0001
4	Adequate assessment #2 – Censored for PD	0.52 (0.42,0.64), <0.0001
5	Ignoring censoring for new anti-cancer therapy	0.52 (0.42,0.63), <0.0001
6	Ignoring censoring for new anti-cancer therapy with adequate assessment for PD or death	0.51 (0.42,0.63), <0.0001
7	New anti-cancer therapy considered as an event	0.54 (0.45,0.66), <0.0001

Notes on the PFS sensitivity analyses above:

Analysis #1 excluded 3 patients with symptomatic progression from the analysis; all others had radiological evidence of disease.

Analysis #3 and 4: The investigator-assessed PFS was analysed using adequate assessments to confirm that subjects who missed response assessments just prior to the PFS event (progression or death) would not impact the investigator-assessed PFS. Thus subjects with a gap of > 16 weeks in the tumour assessment just prior to the PFS event were censored at the time of the last adequate assessment. In analysis 4, the death date is used as date for PFS event.

Secondary endpoint - Overall Response Rate and Clinical Benefit Rate

Table 27. Best Overall Response Rate and Clinical Benefit Rate (ITT Population), Pivotal Study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
Best Response[a]; n (%)		
Complete response	16 (7)	7 (3)
Partial response	138 (62)	103 (46)
Stable disease	51 (23)	73 (33)
Progressive disease	8 (4)	29 (13)
Unknown[b]	9 (4)	10 (5)
ORR (CR or PR); n (%)	154 (69)	110 (50)
95% CI (%)	(62.9, 75.4)	(42.8, 56.3)
Difference in response rate (95% CI); %	20 (10.4, 29.0)	
p-value	<0.0001	
Odds ratio for response (95% CI)	2.30 (1.54, 3.47)	
p-value[c]	<0.0001	
Test for homogeneity of odds ratios across strata p-value	0.4133	
Estimated Relative Risk (95% CI)	1.40 (1.19, 1.64)	
CBR (CR or PR or SD for ≥24 weeks)		
Response rate; n (%)	166 (75)	124 (56)
95% CI (%)	(68.5, 80.3)	(49.1, 62.5)
Percent difference in response rate	19	
95% CI	(9.5, 28.1)	
p-value	0.0001	
Odds ratio for response (95% CI)	2.34 (1.54, 3.58)	
p-value [c]	<0.0001	
Test for homogeneity of odds ratios across strata p-value	0.1829	
Estimated Relative Risk (95% CI)	1.34 (1.16, 1.54)	

CBR = clinical benefit rate, CI = confidence interval, CR = complete response, ORR = overall response rate, PR = partial response, PD = progressive disease, SD = stable disease.
a. Subjects that had bone lesions at baseline also required confirmation using bone scans.
b. Subjects had only baseline disease assessments and no follow-up assessments or had no baseline disease assessment. c. p-value for the test of Odds Ratio being 1.

Table 28. ORR by stratification factors (ITT Population), Pivotal Study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=222)
	n/N (%)	n/N (%)
Overall ORR (CR+PR)	154/222 (69)	110/222 (50)
Hormonal Status		
Positive (ER+ and/or PgR+) or unknown	74/111 (67)	62/113 (55)
Negative (ER- and/or PgR-)	80/111 (72)	48/109 (44)
Metastatic disease site		
Visceral	128/187 (68)	89/186 (48)
Non-visceral	26/35 (74)	21/36 (58)

Secondary endpoint -Duration of Response

The median duration of response, defined as the time from first documented evidence of CR or PR until disease progression or death, was 9.3 months (95% CI: 7.7, 10.7) in the lapatinib+paclitaxel arm compared with 5.8 months (95% CI: 5.6, 7.4) in the placebo+paclitaxel arm. Only confirmed responses, i.e. by repeated imaging, were included. No formal comparisons between treatment arms were undertaken for this endpoint.

Secondary endpoint -Time to Response

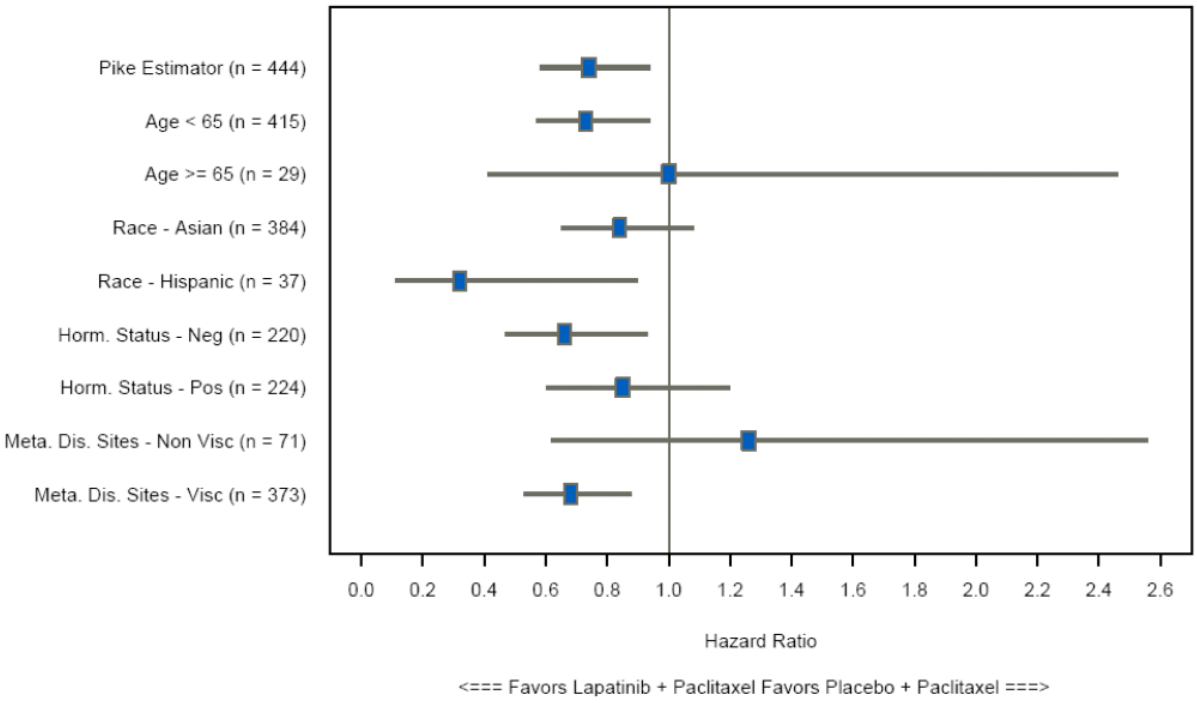
Time to response was defined as the time from randomisation until the first documented (and confirmed) evidence of CR or PR. By week 8, 42% of all subjects in the lapatinib+paclitaxel arm had responded to treatment compared with 27% of subjects in the placebo+paclitaxel arm. These represent 61 and 55%, respectively, of the total number of responders in each arm. By week 12, 60% of the lapatinib+paclitaxel treated patients had responded compared with 40% of the placebo+paclitaxel treated patients, representing 87% and 80% of the total number of responders in the two treatment arms, respectively. No formal comparisons between treatment arms were undertaken for this endpoint.

Sub-group analyses

- *Impact of baseline demographics and stratification factors*

The Pike estimator of the HR and 95% CI for OS and PFS by baseline demographic subgroups and the stratification factors subgroups are shown in Figure 6 and Figure 7.

Figure 6. Overall survival, Impact of baseline demographics and stratification factors, Pivotal study EGF104535



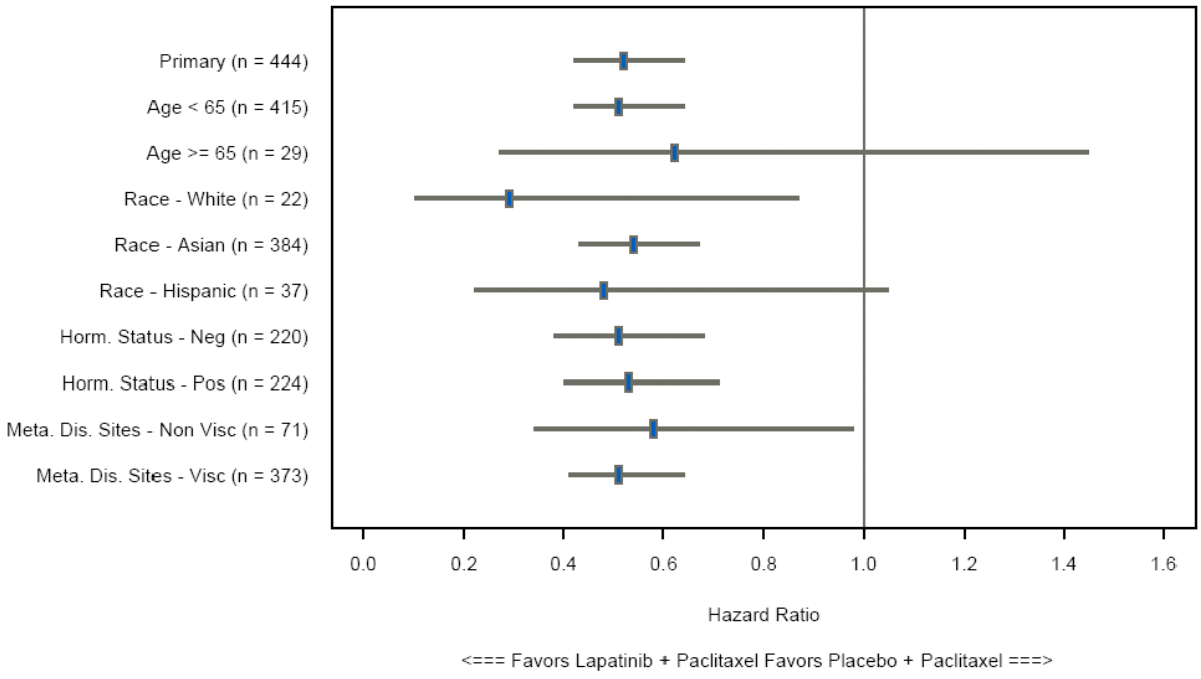
Notes on the baseline demographics analysis:
Race: The HR for OS in White subjects could not be estimated because there were no deaths in the lapatinib+paclitaxel arm compared with 6 deaths in the placebo+paclitaxel arm.

The assessment of the relative activity of lapatinib across race is further complicated by a large difference in the rate of cross-over, as 141 of the 192 (73%) Asian subjects randomized to the placebo+paclitaxel crossed-over to lapatinib monotherapy following progression while only 1 of the 16 (16%) Hispanic subjects randomized to placebo+paclitaxel crossed-over to lapatinib monotherapy.

The exact HRs for OS were as follows: Asian, 0.84 (95% CI 0.65,1.08), Hispanic, 0.32 (95% CI 0.11,0.90).

Age: While the HR for lapatinib+paclitaxel vs. placebo+paclitaxel was 1.00 in the age group over 65 years of age, the median OS was shorter in the lapatinib arm, 17.1 months compared with 21.9 months in the control arm (Data source: Study EGF104535 CSR, Table 7.0025). In the age group below 65 the median OS was however higher in the lapatinib+paclitaxel compared with the placebo+paclitaxel arm, and this was also the case for median PFS in both age groups.

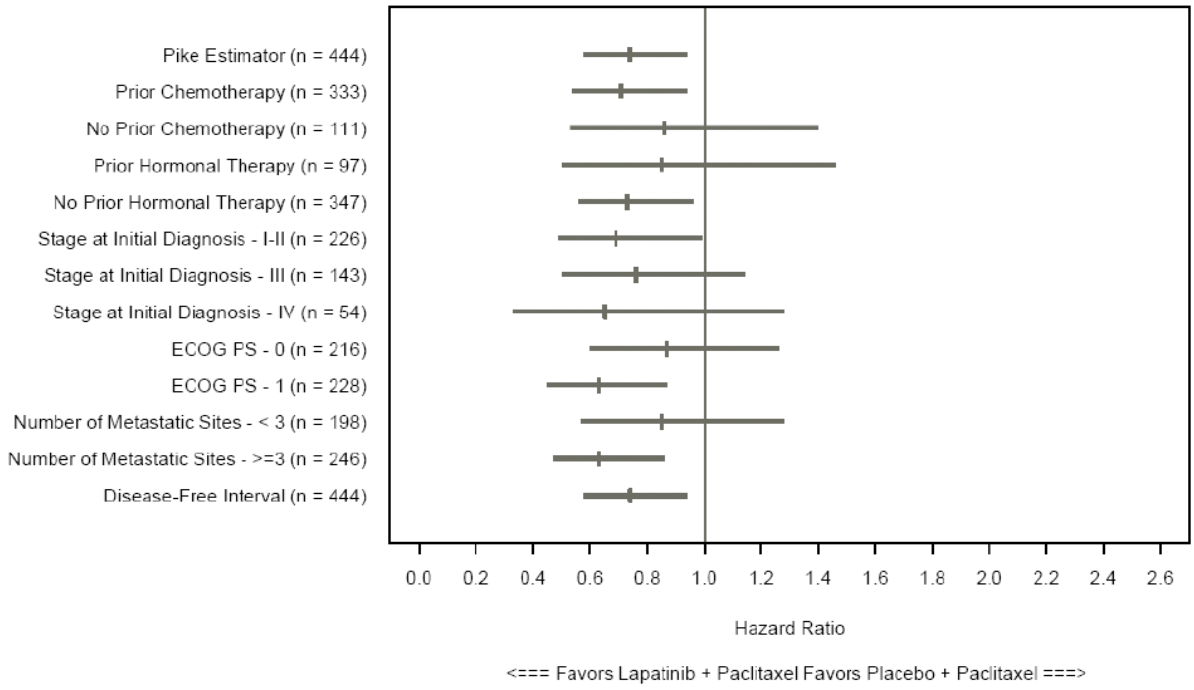
Figure 7. Progression-free survival, Impact of baseline demographic and stratification factors, Pivotal study EGF104535



- *Impact of prognostic factors*

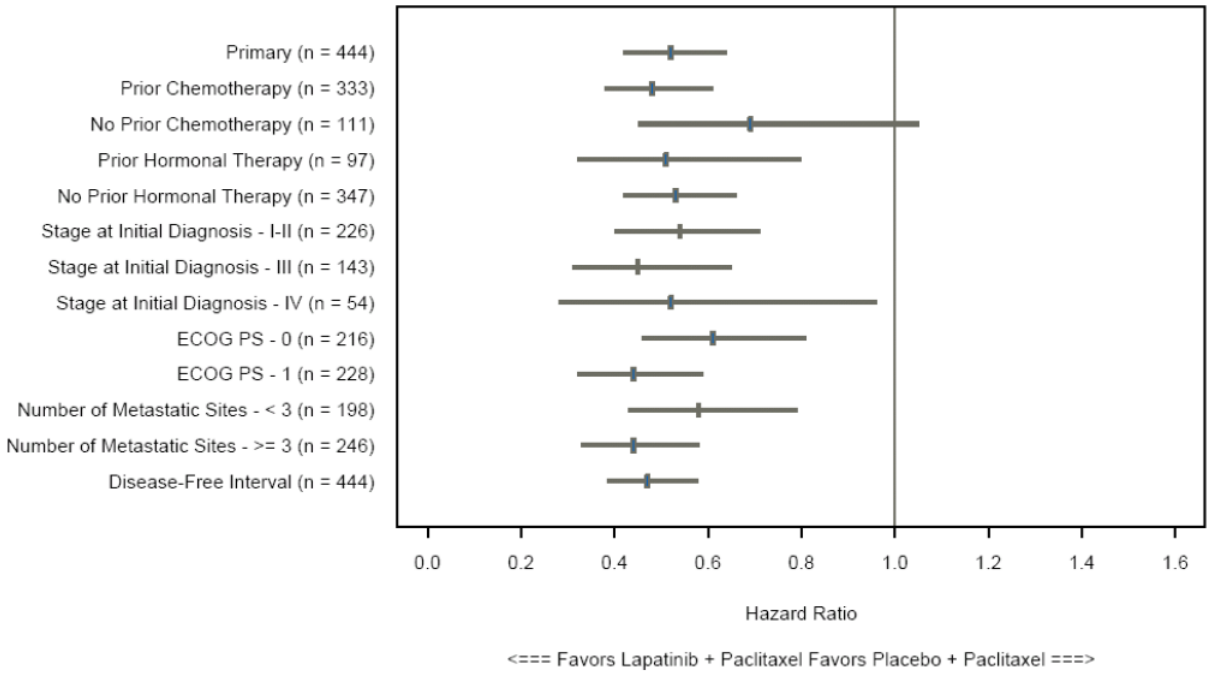
Pre-specified subgroup analyses for OS and PFS were performed by prior therapy use (chemotherapy and hormonal therapy, yes/no) and the prognostic factors of stage at initial diagnosis, ECOG performance status, number of metastatic sites and disease-free interval. No analyses were performed by prior trastuzumab exposure since only 4 subjects received such treatment and all were randomised to the placebo+paclitaxel arm. The Pike estimator of the treatment hazard ratio based on the log rank test and 95% CIs for OS and PFS by prognostic factor subgroups are shown in Figure 8 and Figure 9, respectively.

Figure 8. Overall survival, Impact of prognostic factors, Pivotal study EGF104535



A post-hoc analysis of OS by prior adjuvant anthracycline use showed similar HRs and 95% CIs compared with the overall population : HR 0.79 (95% CI 0.57,1.09) for subjects with no prior adjuvant anthracycline (n=244) , and HR 0.70 (95% CI 0.49,1.01) for subjects who had received adjuvant anthracycline therapy (n= 200).

Figure 9. Progression-free survival, Impact of prognostic factors, Pivotal study EGF104535



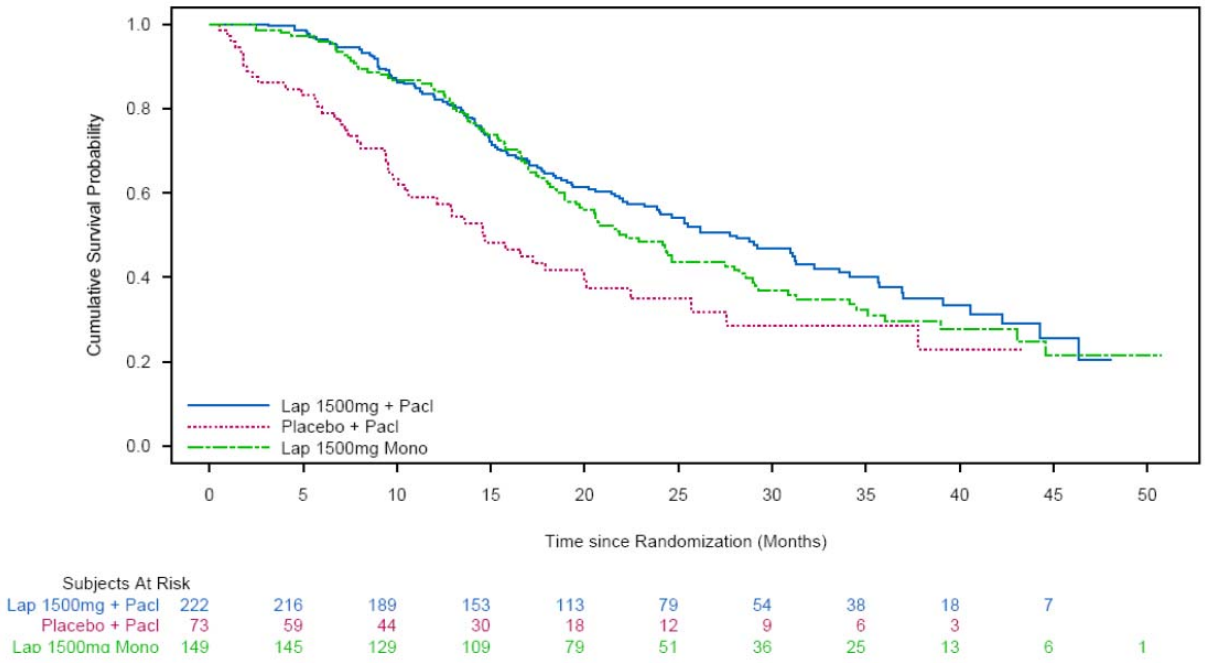
- *Impact of crossover*

The impact on the OS results of the 67% cross-over to lapatinib monotherapy from the placebo+paclitaxel arm following progression was investigated by a three treatment group-comparison (Figure 10) and three additional sensitivity analyses (not shown).

Subjects who crossed-over to lapatinib monotherapy were similar with respect to baseline demographic and prognostic factors, with the exception of hormonal receptor status, to those who did not crossover. Fifty-eight percent of the subjects in the crossover group (lapatinib monotherapy group) were ER+ and/or PgR+ compared with 37% in the group that did not cross-over (p-value=0.0043). There was also a slight difference in the baseline ECOG performance status 0 in favour of the lapatinib monotherapy group (53%), compared with the with the placebo+paclitaxel (without cross-over) group (47%, p = 0.4).

The four sensitivity analyses showed HRs for the OS comparison of lapatinib+paclitaxel vs. placebo+paclitaxel between 0.44 (first analysis, Figure 10) and 0.72. The first analysis, which excluded subjects who crossed over to lapatinib monotherapy, potentially favours the lapatinib+paclitaxel arm as it retains only subjects who were potentially too unwell to cross-over.

Figure 10. Sensitivity analysis: overall survival by three treatment groups (ITT population), Kaplan-Meier analysis, Pivotal study EGF104535



- *Incidence of CNS metastases*

Subjects with known CNS lesions at baseline were excluded from participating in the study. During the study, subjects were not screened for disease progression in the brain unless they were symptomatic. A post-hoc review of these symptomatic metastases showed that a similar number of subjects in each treatment arm (14 subjects in the lapatinib+paclitaxel arm and 16 subjects in the placebo+ paclitaxel arm) reported PD that included CNS as a new site of first progression.

2.3.1. Summary of main efficacy results

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29. Summary of main efficacy results, pivotal study EGF104535

Title: A Randomised, Multicentre, 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			
Study identifier	**EGF104535**		
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled study to evaluate and compare the efficacy and safety of lapatinib+paclitaxel versus placebo+paclitaxel. Subjects had HER2+ metastatic (Stage IV) breast cancer and had not received prior therapy for their metastatic breast cancer.		
	Duration of main phase:		16 January 2006–18 June 2010
	Duration of Extension phase:		From progression, Data cut-off: 18 June 2010
Hypothesis	Superiority		
Treatments groups	Lapatinib + paclitaxel		Lapatinib (1500 mg once daily) plus paclitaxel (80 mg/m^2 IV weekly for 3 weeks every 4 weeks). Number randomised: 222
	Placebo + paclitaxel		Oral placebo (once daily) plus paclitaxel (80 mg/m2 IV weekly for 3 weeks every 4 weeks). Number randomised: 222
Endpoints and definitions	Primary endpoint	Overall survival (OS)	OS was defined as the time from randomisation to death due to any cause.
	Secondary endpoint	Progression-free survival (PFS)	PFS was defined as the time from randomisation until the earliest date of disease progression or death due to any cause, if sooner.
	Secondary endpoint	Overall response rate (ORR)	ORR was defined as the percentage of subjects having either a confirmed complete or partial tumour response, based on confirmed responses (i.e. repeated imaging) from the investigator assessment of best overall response during the randomised phase.
	Secondary endpoint	Clinical benefit rate (CBR)	CBR was defined as complete response (CR) or partial response (PR) or stable disease (SD) ≥24 weeks).
Database lock	Clinical cut-off date: 18 June 2010		
Results and Analysis			
Analysis population and time point description		Intent to treat	
Descriptive statistics and estimate variability and Effect estimate per comparison	Treatment group	Lapatinib + paclitaxel	Placebo + paclitaxel
	Number of subject	222	222
	Primary analysis of primary endpoint: Cox Proportional Hazards Model of OS		
	Adjusted Hazard Ratio[a] (95% CI)	0.64 (0.49, 0.82)	
	p-value (two-sided)	0.0005	

	[a]: Adjusted for the two stratification factors, hormonal status (positive/negative) and metastatic disease sites (visceral/non-visceral); and five pre-specified prognostic factors: Stage of disease at initial diagnosis (I-II/III/IV), ECOG performance status at baseline (0/1), number of metastatic sites (<3/≥3), age (in years) (<65/≥65), and disease-free interval defined as the time from initial diagnosis to metastases.		
	Supporting analysis of primary endpoint: Kaplan Meier estimates of OS		
	OS Died due to any cause, n (%)	120 (54)	143 (64)
	Median survival in months(95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
	p-value (stratified log-rank, two-sided)[b]	0.0124	
	Stratified Hazard Ratio[c] (95% CI)	0.74 (0.58, 0.94)	
	[b]: Stratified by metastatic disease sites and hormonal status. [c]: The Pike estimator of the treatment hazard ratio based on the log rank test stratified for metastatic disease sites and hormonal status.		
	Secondary Endpoints		
	PFS - *Kaplan Meier estimates* Progressed or died (event); n (%)	188 (85)	204 (92)
	Median PFS in months (95% CI)	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
	p-value	<0.0001	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.52 (0.42, 0.64)	
	ORR No of patients with CR or PR (%)	154 (69)	111 (50)
	95% CI	(62.9, 75.4)	(42.8, 56.3)
	p-value	<0.0001	
	Odds ratio for response (95% CI) (Fisher's exact test)	2.30 (1.54, 3.47)	
	Estimated Relative Risk (95% CI)	1.40 (1.19, 1.64)	
	CBR No of patients with CR, PR or SD (%)	166 (75)	124 (56)
	95% CI	(68.5, 80.3)	(49.1, 62.5)
	p-value	0.0001	
	Odds ratio for response (95% CI) (Fisher's exact test)	2.34 (1.54, 3.58)	
	Estimated Relative Risk (95% CI)	1.34 (1.16, 1.54)	

Supportive study EGF30001

A Randomised, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Phase III Study of Oral GW572016 in Combination with Paclitaxel in Subjects Previously Untreated for Advanced or Metastatic Breast Cancer

Methods

▪ *Study Participants*

Summary of eligibility criteria

The main inclusion criteria of study EGF30001were female patients with histologically confirmed invasive breast cancer with incurable stage IIIb, stage IIIc with T4 lesion, or stage IV disease at primary diagnosis or at relapse after curative-intent surgery, with tumours that were untested or negative for overexpression of HER2. No prior systemic endocrine, cytotoxic or biologic therapy for metastatic disease or prior therapy with any ErbB1 and/or ErbB2 inhibitor in any setting was allowed. Patients with known CNS metastases, or peripheral neuropathy ≥ grade2 were also excluded.

▪ *Treatments*

Subjects were randomised 1:1 to receive either oral lapatinib (1500 mg once daily) with paclitaxel (175 mg/m^2 IV over 3 hours every 3 weeks), or oral placebo plus paclitaxel (175 mg/m^2 IV over 3 hours every 3 weeks). Each treatment group was stratified by sites of metastatic disease and stage of disease.

▪ *Objectives and endpoints*

Objectives, endpoints and their definitions

Primary

1. To evaluate and compare the two treatment groups with respect to time to progression (TTP) in subjects with metastatic breast cancer. TTP: the interval between the date of randomisation and the earliest date of disease progression or death due to breast cancer, if sooner. Disease progression was based on the assessments by the investigator including radiological and symptomatic progressions.

Secondary

The 13 secondary endpoints included standard oncology objectives: Tumour response rate (ORR), Clinical benefit (CBR) including SD for ≥6 months, Time to response (TTR), Duration of response (DoR), Six-month progression-free survival (6-m PFS), Overall survival (OS), evaluation of Toxicities, and Quality of life (QoL). Progression-free survival PFS, and Analysis of efficacy by HER2 over expression status were not specified in the protocol, but were prospectively defined in the Reporting and Analysis Plan (RAP) and added to the list of objectives prior to unblinding.

The following 3 secondary objectives were also present in study EGF30001:

- To collect and store serum specimens for comparing baseline and on-treatment serum concentrations of ErbB1 and HER2 ECDs, potentially perform proteomic analysis to detect other shed tumour proteins, identify changes in the protein profile and correlate to treatment response and adverse events (AEs).

- To further characterise the subject population by determination of intra-tumoural expression of ErbB1, HER2, and downstream biomarkers which may help elucidate the effects of lapatinib on the target and other proteins along relevant pathways in the tyrosine kinase pathway.
- *Pharmacogenetic Objective*
  To investigate the relationship between genetic variants in candidate genes in the host and the pharmacokinetics of lapatinib and/or the relationship between genetic variants in select candidate genes in the host and the efficacy, safety and tolerability of lapatinib.

▪ *Sample size*

Main study

The study was designed to provide evidence to support the primary null hypothesis H0: $\lambda >/= 1$ or to reject it in favour of the alternative hypothesis HA: $\lambda < 1$, where λ is the hazard ratio: lapatinib plus paclitaxel / lapatinib plus placebo. Assuming the TTP survival curves are consistent with proportional hazards, then the null hypothesis represents equality of the median TTPs in the two treatment arms, or a decrease median TTP in the lapatinib plus paclitaxel arm, and the alternative hypothesis represents an increased median TTP in the lapatinib plus paclitaxel arm. The same hypothesis was later added for the HER-2 positive subgroup (see below).

In order to achieve the desired statistical power 374 subjects with disease progression were required. To achieve this number, an estimated total of 570 subjects were to be enrolled, leading to an estimated maximum study duration of 22.5 months. The study was estimated to have approximately 90% power (2-sided alpha=0.05) to detect a 40% increase in median TTP in subjects who received lapatinib plus paclitaxel (8.4 months) compared with subjects who received paclitaxel alone (6 months).

HER-2 positive subgroup, used for the present application

During the course of this study, data became available that demonstrated lapatinib, in combination with capecitabine, improved clinical efficacy in women with advanced/metastatic HER2+ cancer as described in the introduction. Therefore the RAP for the study was written to include the investigation of the HER2+ subgroup as a secondary analysis and an assessment of sample size sensitivity for this subgroup was performed. In the HER2+ subgroup, the study was estimated to have 80% power to detect a 100% increase in median TTP in subjects who received lapatinib plus paclitaxel (12 months) compared with subjects who received paclitaxel alone (6 months). This assumed that 20% of subjects would fall into the HER2+ subgroup; the 68 events required for this analysis should have been achieved once the target number of events required for the main primary analysis (374) had been reached.

▪ *Randomisation*

Subjects were identified by a unique subject number that remained consistent for the duration of the study. Investigators were to telephone a GSK interactive voice response (IVR) system called Registration And Medication Ordering System (RAMOS) to register and record subject activity as well as order additional supplies for the study. Subject randomisation number/treatment group assignment was obtained based on the subject number and subject's sites of disease.

Randomisation was stratified according to the following:

1. Site of disease:

- Soft tissue/visceral disease (could also have metastases to bone).

- Bone-only disease.

2. Stage of disease:

- Stage IIIb/IIIc with T4 lesion.
- Stage IV.

Subjects who are classified as bone only disease are by definition Stage IV there were therefore only 3 possible strata groups:-

- Soft tissue/visceral disease that was Stage IIIb/IIIc with T4 lesion.
- Soft tissue/visceral disease that was Stage IV.
- Bone-only disease that was Stage IV (therefore the fourth group became redundant).

▪ *Blinding (masking)*

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

The investigator could unblind a subject's treatment assignment in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the subject. If the blind was broken for any reason, the investigator had to notify GSK immediately of the unblinding incident without revealing the subject's study treatment assignment and record the date and reason in the CRF. If a SAE was reported to GSK, Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind the treatment assignment for the individual subject.

▪ *Statistical methods*

Standard statistical methods for oncology studies were used, and are therefore not discussed further. The method is specified in the Results section for each analysis presented.

Results

▪ *Participant flow*

There is no disposition of subjects available for the HER2 positive subgroup relevant for the efficacy assessment. For primary reason for discontinuation from treatment for the entire patient population, please refer to Table 53 in the safety section.

The primary analysis was conducted when 448 events (investigator-assessed disease progressions) had occurred. At the time of the primary analysis (cut-off date of 02 October 2006), the majority of subjects in each treatment group had discontinued from the study. The percentage of subjects discontinued from the study and the reasons for discontinuation were similar between the treatment groups. Death due to disease progression was the primary reason for discontinuation from the study.

For the present application a clinical study report with updated OS and safety analyses was presented, with a data cut-off date of 25 August 2010. At this time, all subjects had completed the study, and there were none being followed for survival.

- ***Conduct of the study***

Protocol amendments

Table 30. Protocol amendments, Study EGF30001

Protocol and Amendment Number (GSK Document Number)	Protocol and Amendment Issue Date	No. Subjects Enrolled by Amendment Issue Date	Amended areas
Original Protocol	08-Aug-2003	0	
Amendment 1	17-Nov-2003	0	Country specific mandate (Spain) for the sponsor to supply all medications required to be administered during all clinical trials
Amendment 2	01-Apr-2004	14	Amendment for the pharmacogenetic research to be conducted on blood samples collected from consenting subjects. The amendment will apply only in Italy to comply with the "Italian Proposed Guideline for the Evaluation of Pharmacogenetic Research." Clarification regarding the supply of paclitaxel and pre-medications in Italy.
Amendment 3	02-Jul-2004	64	To provide further clarification to study design and conduct and update relevant sections to reflect current clinical practice.
Amendment 4	17-Dec-2004	315	Country Specific Amendment (Netherlands) removing Stage IIIb/c subjects from being eligible for this trial
Amendment 5	21-Jul-2005	577	To provide further clarification with regard to prohibited medications. To remove the interim analyses.
Amendment 6	30-May-2006	577	To provide clarification on subject completion, update prohibited medications, and update the contraception options.
Amendment 7	07-May-2008	577	Added liver toxicity stopping rules and follow-up guidance; extended safety assessment schedule for subjects on treatment greater than 2 years.

Protocol violations

There were 5 subjects (2%) in the lapatinib+paclitaxel arm who had inclusion or exclusion criteria deviations, and 4 subjects (1%) in the placebo+paclitaxel arm. One subject had a tumour untested or negative for HER2.

- ***Baseline data***

Baseline data in the supportive study's HER2 positive subgroup are shown in the tables below (Table 32, Table 33, Table 34), following the demographics of the entire study below (Table 31) which are relevant mainly for the safety assessment.

Table 31. Demographic characteristics (ITT population) (Cut-off date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=291)	Paclitaxel 175 mg/m² plus Placebo (N=288)	Total (N=579)
Age (years)[1]			
Mean (standard deviation)	51.3 (10.45)	52.4 (10.98)	51.8 (10.72)
Range	23 to 87	25 to 78	23 to 87
Age stratification, n (%)[2]			
<65 years of age	260 (89)	241 (84)	501 (87)
≥65 years of age	33 (11)	45 (16)	78 (13)
Race, n (%)			
White	190 (65)	182 (63)	372 (64)
American Hispanic	54 (19)	53 (18)	107 (18)
Asian	30 (10)	35 (12)	65 (11)
Black	10 (3)	10 (3)	20 (3)
Other	7 (2)	8 (3)	15 (3)

1. Age was calculated from the date of screening visit relative to date of birth, as recorded in the CRF.
2. Safety population.

Table 32. Demographic characteristics (HER2+ population) (Cut-off date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)	Total (N=91)
Age (years)[1]			
Mean (standard deviation)	50.9 (10.37)	51.4 (11.14)	51.1 (10.65)
Range	34 to 75	28 to 78	28 to 78
Race, n (%)			
White	34 (65)	18 (46)	52 (57)
American Hispanic	9 (17)	10 (26)	19 (21)
Asian	8 (15)	9 (23)	17 (19)
Black	0	0	0
Other	1 (2)	2 (5)	3 (3)

1. Age was calculated from the date of screening visit relative to date of birth, as recorded in the CRF.

Table 33. Disease Characteristics at Screening (HER2+ Population) (Cut-off date 02 October 2006), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)	Total (N=91)
Stage at screening			
IIIb/IIIc	6 (12)	8 (21)	14 (15)
IV	46 (88)	31 (79)	77 (85)
Number of metastatic sites			
≥3	26 (50)	24 (62)	50 (55)
2	18 (35)	12 (31)	30 (33)
1	8 (15)	2 (5)	10 (11)
0	0	1 (3)	1 (1)
Involved sites			
Soft tissue/Visceral only[1]	52 (100)	38 (97)	90 (99)
Unknown	0	1 (3)	1 (1)
Involved site group[2]			
Soft tissue	9 (17)	11 (28)	20 (22)
Visceral	36 (69)	20 (51)	56 (62)
Lymph nodes/breasts	39 (75)	32 (82)	71 (78)
Skin	5 (10)	12 (31)	17 (19)

Note: 'Soft tissue' included chest wall, bone marrow, peritoneum and pleura. 'Visceral' included abdomen/viscera, heart, liver, lung, pancreas, stomach and adrenals.
1. Included all other subjects who were not bone only.
2. Subjects could fall into more than 1 category.

Table 34. Hormone Receptor Expression Status at Baseline as per Investigator (HER2+ Population) (Cut-off date 02 October 2006), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)	Total (N=91)
Estrogen/Progesterone receptor status			
ER+/PR+	8 (15)	12 (31)	20 (22)
ER+/PR-	3 (6)	2 (5)	5 (5)
ER-/PR+	4 (8)	5 (13)	9 (10)
ER-/PR-	20 (38)	12 (31)	32 (35)
ER+/PR unknown	1 (2)	0	1 (1)
ER unknown/PR unknown	16 (31)	8 (21)	24 (26)

Prior and Subsequent therapy

Prior anti-cancer in this setting is confined to (neo-)adjuvant therapy, since no subjects received prior systemic anti-cancer therapy for metastatic disease.

Table 35. Prior anti-cancer systemic therapy (medication received by 10% or more subjects in either treatment group) (HER2+ Population) (Cut-off date 02 October 2006), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)	Total (N=91)
Antineoplastic and immunomodulating agents			
Any medication	26 (50)	18 (46)	44 (48)
Cyclophosphamide	24 (46)	18 (46)	42 (46)
Fluorouracil	20 (38)	13 (33)	33 (36)
Doxorubicin hydrochloride	12 (23)	7 (18)	19 (21)
Doxorubicin	8 (15)	6 (15)	14 (15)
Tamoxifen	5 (10)	6 (15)	11 (12)
Methotrexate	7 (13)	3 (8)	10 (11)
Epirubicin	2 (4)	4 (10)	6 (7)

Table 36. Post Progression Anti-Cancer Therapy (HER2+ Population) (Cut-off date 25 August 2010), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)	Total (N=91)
Any Anti-Cancer Therapy	35 (67)	25 (64)	60 (66)
Chemotherapy	31 (60)	24 (62)	55 (60)
Trastuzumab[1]	9 (17)	1 (3)	10 (11)
Hormonal therapy	8 (15)	9 (23)	17 (19)
Radiotherapy	7 (13)	8 (21)	15 (16)
Biologic therapy[2]	1 (2)	0	1 (1)
No recorded therapy	17 (33)	14 (36)	31 (34)

Note: Subjects can be counted in more than one therapy category.
Note: Therapy is unknown as subject entered a new study with blinded study medication.
1. Due to the significance of Trastuzumab therapy in Her-2 positive patients and potential impact on sequential treatment line, this biologic therapy was recorded separately. 2. Excludes trastuzumab.

- ***Numbers analysed***

Table 37. Populations analysed (Cut-off date 02 October 2006), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m²	Paclitaxel 175 mg/m² plus Placebo	Total
All subjects	292	288	580
ITT population	291 (>99)	288 (100)	579 (>99)
ITT population (sensitivity)[1]	292 (100)	288 (100)	580 (100)
HER2+ population[2,6]	52 (18)	39 (14)	91 (16)
HER2+ explorative population[3,6]	47 (16)	39 (14)	86 (15)
HER2- population[4,6]	199 (68)	202 (70)	401 (69)
PP population[5]	290 (99)	282 (98)	572 (99)
Safety population	293 (>100)	286 (99)	579 (>99)

1. Included all subjects who were randomised to study medication but did not take any study medication. Subject 027231/540 was randomised to the lapatinib plus paclitaxel group but did not receive investigational product.
2. Based on FISH and IHC data carried out by M. Press at USC.
3. Based on FISH and IHC data from Quest laboratory.
4. Based on FISH and IHC data carried out by M. Press at USC.
5. Eight subjects were excluded from the PP population (see Section 5.2)
6. 40 and 47 subjects in the lapatinib+paclitaxel and paclitaxel + placebo groups, respectively, were unevaluable for HER2 status according to the Press evaluation.

The HER2+ and HER2- populations were primarily defined in accordance with the evaluations performed by the Press laboratory. However, confirmatory analyses for the HER2+ population were also performed whereby this population was defined according to the Quest laboratory.

The HER2 positive populations (the primary by Press, and the exploratory population by Quest) comprised all randomised subjects who received at least one dose of randomised therapy (lapatinib or placebo) and who, at baseline, had documented amplification of HER2 by FISH or 3+ IHC in tumour tissue. These populations were defined prospectively in the RAP and prior to treatment unblinding.

- ***Outcomes and estimation***

The OS analysis was updated from data as of 25 August 2010, since the pre-specified number of deaths had not occurred at the time of the primary analysis (02 October 2006). No subjects were being followed for survival at the time of the updated analysis.

Table 38. Overall survival (HER2+ Population) (Cut-off Date 25 August 2010), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)
Number (%) of subjects		
Died (event)	37 (71)	29 (74)
Censored, follow-up ended	10 (19)	8 (21)
Censored, follow-up ongoing	5 (10)	2 (5)
Kaplan-Meier estimate of overall survival (months)		
1st Quartile (95% CI)	13.8 (10.8, 18.1)	8.1 (5.1, 14.1)
Median (95% CI)	24.3 (17.7,31.3)	19.2 (11.7, 29.7)
3rd Quartile (95% CI)	41.7 (31.0, NR)	32.7 (22.2, 62.1)
Hazard ratio		
Estimate[1] (95% CI)	0.77 (0.5, 1.3)	
Log-Rank test		
p-value[2]	0.281	

1. Estimate of the treatment hazard ratio based on the log-rank test, <1 indicates a lower risk with Lapatinib 1500 mg plus Paclitaxel 175 mg/m2 compared with Paclitaxel 175 mg/m2 plus Placebo.
2. P-value from unstratified log-rank test.

Figure 11. Kaplan-Meier Estimates of Overall Survival (HER2+ Population) (Cut-off Date 25 August 2010), Study EGF30001

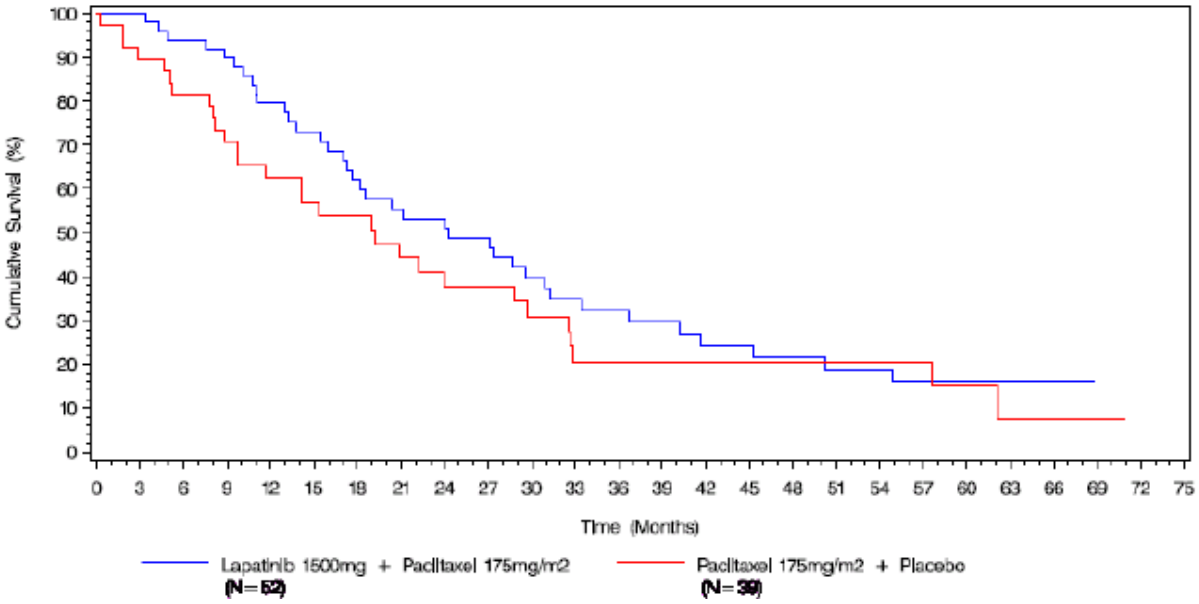
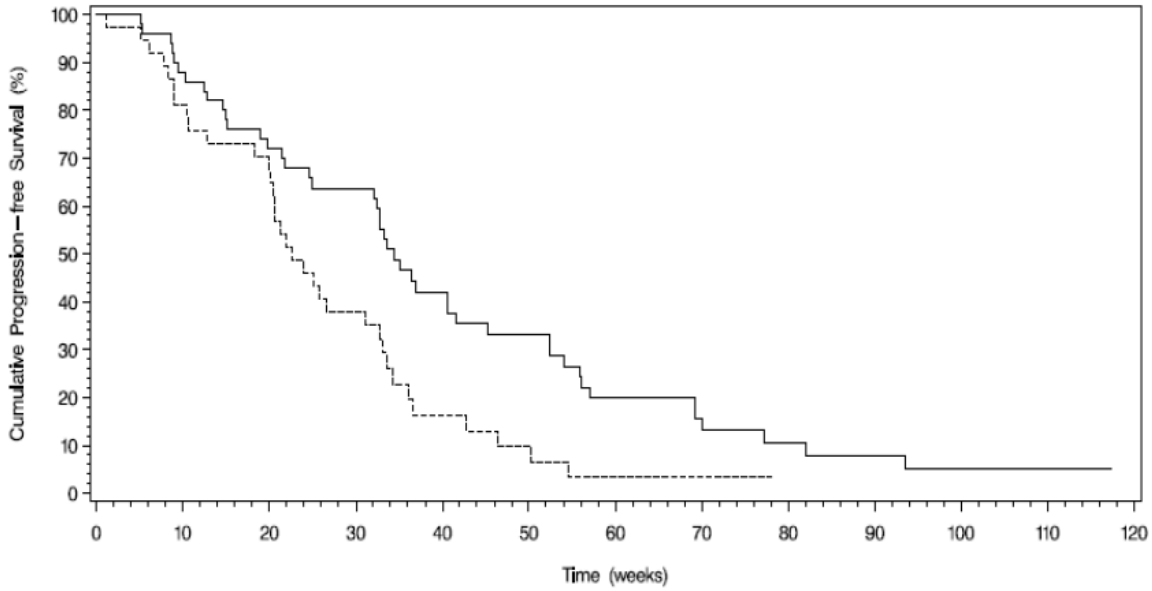


Table 39. Investigator-Evaluated Progression-Free Survival (HER2+ Population) (Cut-off Date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)
Number (%) of subjects		
Progressed or died (event)	44 (85)	34 (87)
Censored, follow-up ended	5 (10)	3 (8)
Censored, follow-up ongoing	3 (6)	2 (5)
Kaplan-Meier estimate of time to progression (weeks)		
1st Quartile (95% CI)	18.9 (12.4, 32.4)	12.9 (9.0, 20.6)
Median (95% CI)	34.4 (32.1, 41.6)	22.6 (20.1, 32.9)
3rd Quartile (95% CI)	55.9 (40.6, 70.0)	34.3 (25.7, 42.7)
Hazard ratio		
Estimate[1] (95% CI)	0.56 (0.34, 0.90)	
Log-Rank test		
p-value[2]	0.007	

1. Estimate of the treatment hazard ratio based on the log-rank test, <1 indicates a lower risk with Lapatinib 1500 mg plus Paclitaxel 175 mg/m2 compared with Paclitaxel 175 mg/m2 plus Placebo.
2. P-value from unstratified log-rank test.

Figure 12. Kaplan-Meier Estimates of Investigator-Evaluated Progression-Free Survival (HER2+ Population) (Cut-off Date 02 October 2006), Study EGF30001



_____ = Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)
---------- = Paclitaxel 175 mg/m² plus Placebo (N=39)

Table 40. Investigator-Evaluated Response Rate (HER2+ Population) (Cut-off Date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)
Investigator-evaluated response rate		
Best response, n (%)		
Complete response	5 (10)	1 (3)
Partial response	26 (50)	13 (33)
Stable disease	10 (19)	13 (33)
Progressive disease	9 (17)	8 (21)
Unknown	2 (4)	4 (10)
Response rate (CR or PR)[1]		
Percent response rate (95% CI)	59.6 (45.1, 73.0)	35.9 (21.2, 52.8)
Percent difference in response rate (95% CI)	23.7 (2.7, 43.2)	
Estimate of common odds ratio for tumor response		
Estimate (95% CI) p-value[2]	2.9 (1.1, 7.9) 0.027	
Estimated Relative Risk (95% CI)	1.66 (1.03, 2.67)	

1. Subjects with unknown or missing response were treated as non-responders.
2. P-value from exact test that common odds ratio equals 1.
Note: Tumour response was based on confirmed responses from the investigator-evaluated best response.

Table 41. Investigator-Evaluated Clinical Benefit Rate (HER2+ Population) (Cut-off Date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=52)	Paclitaxel 175 mg/m² plus Placebo (N=39)
Clinical benefit rate (CR or PR or SD ≥183 days)[1]		
Percent response rate (95% CI)	65.4 (50.9, 78.0)	38.5 (23.4, 55.4)
Percent difference in clinical benefit rate (95% CI)	26.9 (6.0, 46.2)	
Estimate of common odds ratio for clinical benefit		
Estimate (95% CI) p-value[2]	3.2 (1.2, 8.7) 0.014	
Estimated Relative Risk (95% CI)	1.70 (1.09, 2.65)	

1. Subjects with unknown or missing response were treated as non-responders.
2. P-value from exact test that common odds ratio equals 1.
Note: Clinical Benefit Rate is based on confirmed responses from the investigator-evaluated best response.

Table 42. Investigator-evaluated Time to Progression (HER2+ population) (Cut-off date 02 October 2006), Study EGF30001

	Lapatinib 1500 mg plus Paclitaxel 175 mg/m2 (N=52)	Paclitaxel 175 mg/m2 plus Placebo (N=39)
Number (%) of subjects		
Progressed or died due to breast cancer (event)	43 (83)	32 (82)
Died due to cause other than breast cancer (competing risk)	1 (2)	2 (5)
Censored, follow-up ended	5 (10)	3 (8)
Censored, follow-up ongoing	3 (6)	2 (5)
Cumulative incidence estimate of time to progression (weeks)		
1st Quartile	19.9	20.0
Median	35.1	25.1
3rd Quartile	56.1	36.1
Hazard ratio		
Estimate[1] (95% CI)	0.57 (0.34, 0.93)	
Log-Rank test		
p-value[2]	0.011	

1. Estimate of the treatment hazard ratio based on the log-rank test, <1 indicates a lower risk with Lapatinib 1500 mg plus Paclitaxel 175 mg/m2 compared with Paclitaxel 175 mg/m2 plus Placebo.
2. P-value from unstratified log-rank test.

CNS metastasis

No subjects in either treatment group in Study EGF30001 had symptomatic evidence of CNS metastases at baseline in the HER2+ population. As of the primary analysis (cut-off date of 02 October 2006), the percentage of subjects in the ITT population who had CNS metastases as a first site of relapse was similar in both treatment groups (4% in the lapatinib plus paclitaxel group and 3% in the paclitaxel plus placebo group). While there was a longer median time to first site of CNS relapse in HER2+ subjects in the lapatinib plus paclitaxel group compared with the paclitaxel plus placebo group (66.57 weeks vs. 26.0 weeks, respectively; the number of subjects reporting CNS relapse was too small to draw definitive conclusions.

2.4. Discussion and conclusion on clinical efficacy

The pivotal study was conducted outside the EU, North American, and Australian/New Zealand regions in so called third countries, with China as the major contributing country with 67% of the subjects; this may affect the validity of results for a European population.

The pivotal study EGF104535 was performed in the first-line metastatic setting, apart from the possibility of prior hormonal therapy for metastatic disease. The inclusion/exclusion criteria were acceptable, although the exclusion of patients with non-measurable disease will make the study population less representative of a normal first-line metastatic population.

The paclitaxel backbone regimens used in the pivotal as well as in the supportive study are established and in routine clinical use. The 3-weekly regimen used in the supportive study EGF30001 is less labour intensive, while the 1-weekly regimen (with 1 week's pause every 3 weeks) used in the pivotal study is considered to have less acute toxicity. In recent years studies with the 1-weekly regimen have shown better results including on OS thus explaining why this has become increasingly used. The chemotherapy backbone of the pivotal study is therefore a relevant regimen.

The RECIST criteria for evaluation of progression and response are standard for oncology studies. No independent review of images appeared to have been performed, implying a risk of investigator bias. However, only those responses that were confirmed by a second imaging were counted as responses, making the response data in that respect conservative.

The blinding procedures were considered acceptable. Considering the high frequency of certain adverse events (AEs), e.g. diarrhoea and neutropenia, it can however be questioned whether or not the investigator blinding could be maintained for all subjects.

Regarding the subject disposition in the pivotal study, the differences between treatment arms in the proportion of patients who died (54 vs. 64%) and patients with ongoing follow-up (38 vs. 30%), respectively, may be attributable to differences in the activity of the treatments. In other respects the attrition appears similar in the study arms. The demographic characteristics were well balanced between treatment arms, except that the five male patients (1% of all patients) were all randomised to the placebo+paclitaxel arm. Most subjects (86%) were Asian, reflecting the geographical regions in which the study was conducted.

Regarding the baseline prognostic factors identified for the efficacy analyses of the pivotal study the low proportion of patients with non-visceral disease only (16%) in this first-line metastatic setting is lower than expected in a European population (around 40% in the HERNATA study),, but could at least in part be explained by the exclusion of patients with only non-measurable metastatic sites, e.g. patients with bone-only disease. The exclusion of patients with non-measurable disease may decrease the representativity of a trial in relation to its target population. The frequency of hormone receptor positive tumours was 49% in line with several large trials of HER2-positive disease, where a hormone receptor positive percentage around 50% was seen. Overall, the baseline prognostic factors were generally balanced, and the small imbalances of 5-6% seen for ECOG performance status 0 vs.1and Stage I-II vs. III-IV, were in favour of the control arm.

Only 97 (22%) of the 444 patients in the study population had received hormonal therapy at any time prior to randomisation, and only 85 (19%) had received adjuvant hormonal therapy.

The global rate of patients receiving adjuvant (post-surgical) chemotherapy (69%) seems in accordance with the global stage distribution. However, the percentage of patients having received an anthracycline (42%) or a taxane (9%) is very low, compared to what is nowadays indicated in European patients. This low intensity of adjuvant chemotherapy must be commented due to its importance for a correct definition of the studied population.

The prior treatments were generally balanced between treatment arms. The most prominent difference was that 6% more patients in the placebo+paclitaxel arm had received prior chemotherapy at any time and 7% more adjuvant chemotherapy, whereas 4% more of the lapatinib+paclitaxel treated patients had received hormonal therapy at any time and 5% more adjuvant hormonal therapy. Considering that the baseline factors Performance status and Stage were slightly unbalanced in favour of the placebo+paclitaxel arm, this might indicate that patients in the lapatinib arm had received slightly less optimal prior therapy. Whether this would tend to improve the results of the lapatinib arm in relation to the control by being less pre-treated, or decrease the results by being in a poorer baseline status, is difficult to conclude. It is noted that 3-4 % in both arms had received prior systemic therapy for metastatic disease in conflict with the exclusion criteria. However, this is not expected to affect the results in a positive direction.

In the responses to the CHMP questions the MAH has provided data on post-progression therapy, including the lapatinib given in the extension phase of the study. The use of any post-progression therapy was more frequent in the placebo+paclitaxel arm (84%) compared with the lapatinib+paclitaxel arm (67%), primarily due to the cross-over to lapatinib monotherapy at

progression. HER2-target therapy (lapatinib and/or trastuzumab) was received by 73 vs. 12%, respectively. The use of post-progression chemotherapy was essentially the same in both arms, 53 vs 55%, respectively, balanced also with regard to individual agents. The use of hormonal therapy was considerably lower in the placebo+paclitaxel arm, 12 vs. 23%, possibly due to the cross-over to monotherapy lapatinib "postponing" the latter line of (hormonal) treatment, in relation to the lapatinib+paclitaxel arm. Thus, in the comparison between arms, the placebo has received HER2 targeted therapy "instead of" ER targeted. The relative efficacy of HER2 vs. ER targeted therapy is not fully known in any disease setting. It can therefore not be ruled out that the low use of post-progression hormonal therapy resulting from the study design with a substantial proportion of patient's crossing over to active HER2-targeted monotherapy at progression could represent a disadvantage to the patients. However, since the difference between arms is low in absolute frequencies (23-12 => 11% imbalance), the possible effect of this potential relative under treatment of the patients in the control arm would be small on the overall results.

The results of the primary and secondary analysis of the primary endpoint were in overall agreement, with statistically significantly superior results in the lapatinib+paclitaxel arm compared with the placebo+paclitaxel arm.

The HR was thus 0.64 (95% CI: 0.49, 0.82) for lapatinib+paclitaxel vs. placebo+paclitaxel in the (primary) Cox proportional hazards regression model adjusted for the two stratification factors and five pre-specified prognostic factors, and 0.74 (95% CI: 0.58, 0.94) in the (secondary/sensitivity) analysis based on the stratified log-rank test without adjustment for the 5 additional prognostic factors. All sensitivity analyses had HRs with CIs well below 1. The similar findings in the sensitivity analyses and the primary analysis indicated that the OS results are robust.

The difference in median OS was >7 months between treatment arms, despite second line therapy including the monotherapy lapatinib given to 67% of the patients in the placebo+paclitaxel arm. The OS results are based on an event rate of 54% in the lapatinib+paclitaxel arm and 64% in the placebo+paclitaxel arm. The maturity of the data is thus somewhat low and therefore an updated analysis is requested for confirmation of the results.

No conclusion can be made regarding the effect of cross-over on the primary OS analysis. However, due to the large treatment effect seen in the primary analysis and secondary/sensitivity analyses, there is no need to elucidate the effect of cross-over.

Furthermore, a request for routine GCP inspection of the pivotal study EGF104535 has been adopted.

The secondary endpoint progression-free survival HR was 0.52 (95% CI: 0.42, 0.64) for lapatinib+paclitaxel vs. placebo+paclitaxel ($p < 0.0001$), i.e. statistically significant. The 3.2 month difference in median PFS between the treatment arms is most likely an underestimation of the treatment effect, by the look of the Kaplan-Meier curves. The same type of estimation as mentioned for OS might give a more relevant estimation of the treatment effect: Mediancontrol / HR = estimated Median experimental , i.e. 6.5 / 0.52 = 12.5. This would indicate a difference in PFS medians of 6 months (12.5 – 6.5 = 6), which is in line with the results of the OS difference of approximately 7 months. The results are based on an event rate of 85% in the lapatinib+paclitaxel arm and 92% in the placebo+paclitaxel arm, and are thus mature. The sensitivity analyses all show very similar HRs and CIs.

For the secondary endpoint ORR, there was an overall difference in response rate of 20% (69.37% vs. 49.55 = 19.8%) between the lapatinib+paclitaxel and the placebo+paclitaxel arms which was statistically significant, $p < 0.0001$. The odds ratio for response 2.30 for lapatinib vs. placebo was also statistically significant. The test for homogeneity of odds ratios across strata did not reveal any important imbalance in the treatment effect between strata. This was further explored in the analysis

of ORR by stratification factors, which showed a consistent trend for all strata with response rates around 70% in the lapatinib+paclitaxel arm compared with around 50% in the placebo+paclitaxel arm. However, the response rate of 50% in the placebo+paclitaxel arm may be considered as high, and may reflect the relatively low frequency of prior therapy in this population. It cannot be automatically assumed that similar magnitudes of effect would be achieved in a more optimally pretreated population.

The clinical benefit rate (CBR), which included stable disease for > 24 weeks along with complete and partial responses, was also was statistically significantly higher in the lapatinib arm, and the difference between arms (19%) very similar to the ORR (20%). Thus, the difference in ORR is not compensated in the placebo arm by relevantly long periods of stable disease.

With respect to duration of response, it was observed that the patients who received the combination of lapatinib+paclitaxel had a more durable response than those who received placebo+paclitaxel. These findings are in line with the overall findings of OS and PFS. The time to response analysis showed that the response came slightly faster in the responding lapatinib+paclitaxel treated patients (69%) compared with those who responded on placebo+paclitaxel (50%).

The subgroup analysis of demographic and stratification factors showed HR point estimates below 1.0, i.e. favouring the lapatinib arm, for all PFS analyses and for all but two OS analyses.

In the OS analysis of the age group ≥ 65 years of age the HR was 1.0 and the CI wide, which could be explained by a low number of subjects in the subgroup (n= 29). The fact that the median OS in this group was slightly lower in the lapatinib arm compared with the control arm is of little consequence considering the small numbers and the risk of single patients affecting the overall results. The PFS analysis has a similarly wide CI, but HR point estimate well below 1. The only factor with a HR point estimate above 1 was the OS analysis of the subgroup with Non-visceral metastatic sites. Also here the numbers were relatively low (n= 71) and a low number of events (event rate 44%) may explain the aberrant result in this subgroup. This explanation is supported by the corresponding PFS results with a HR and CI below 1.0.

Overall, the wide CIs of some subgroups can generally be explained by small numbers and low event rates. An exception is the large group of patients (n= 224) with hormone receptor positive disease (including unknown receptor status). There is no clear explanation why the PFS results are not carried forward into the OS results, as is seen for the hormone receptor negative group. The hormone receptor positive and negative groups are of equal size and have very similar event rates in both analyses (58 and 60% event rate in OS analysis, respectively, and 87 and 90% event rate in the PFS analysis, respectively).

The supportive study EGF30001 was conducted in first-line metastatic or incurable locally advanced breast cancer, including patients with primary metastatic cancer. No prior therapy with any ErbB1 and/or ErbB2 inhibitor in any setting was allowed. The study was multinational with centres in Europe, North-, Central- and South America, Asia, Australia, New Zealand, Russia, and South Africa. The main problem, methods wise, with assessing the HER2 positive subgroup in Study 30001 for efficacy was that the randomisation of the total study population was not stratified with regard to HER2 status, why (even though treatments of course were randomly assigned) the subgroup as such was not "randomized" in nature and causing some baseline factors to be largely imbalanced. Therefore, normal statistical methods do not formally apply and results are interpreted with caution. Apart from the formal statistical implications, practical problems with imbalances between arms hampered the assessment. Furthermore, due to the small population a small shift in number of events could change the results. The use of prior adjuvant therapy in the HER2 positive subgroup of the supportive Study EGF30001 was very low (48%) compared with a European population. Likewise, the use of post-

progression anti-cancer therapy was low (66%). Since both these factors may affect the results in a positive direction, this will affect the validity of the results in a European context.

The use of placebo as comparator instead of the established alternative HER2-targeting treatment trastuzumab (Herceptin) is problematic. According to the Guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3), the reference regimen should normally be selected from "best available, evidence-based therapeutic options." This recommendation is important from an assessment point of view. The use of trastuzumab in HER2-positive first line metastatic breast cancer is considered standard therapy according to all major international (Western) therapy guidelines, e.g. the National Comprehensive Cancer Network (NCCN) breast cancer guideline Version 2.2011, and the European Society for Medical Oncology (ESMO) clinical practice guideline on locally recurrent or metastatic breast cancer (Cardoso et al 2010).

The distributions of some of the baseline factors in the pivotal study population are not representative of a typical European first-line metastatic breast cancer population, such as:

- Race – 86% were Asian, only 5% were White, and 8% Hispanic.
- Metastatic sites – only 16% had non-visceral disease.
- Prior hormonal therapy – only 22% of all patients (translating into 44% of the hormone receptor positive/unknown patients) had received prior hormonal therapy.
- Prior anti-HER2 therapy – no patient had received adjuvant trastuzumab which is considered standard treatment for HER2 positive patients in Europe (possibly with some exceptions for very small tumours).

Patients with less prior therapy are likely to have a larger treatment effect, and differences in race may imply differences in e.g. pharmacokinetics, interactions, single-nucleotide polymorphism with effect on target receptor structure and affinity of binding to the pharmaceutical compound, as well as cultural differences affecting food interactions etc.

These differences compared with a European population are a major problem with regard to the external validity and relevance to a European population, and constitute grounds for a Major Objection.

Furthermore, the CHMP considered a comparison of the lapatinib studies and the relevant post-hoc HER2 IHC 3+ subgroup of the Herceptin registration study HO648g based on publically available data. This comparison showed a larger difference in response rate between the treatment arms (anti-HER2 agent+paclitaxel vs. placebo+paclitaxel) for trastuzumab (32%) compared with lapatinib (20 and 24%, pivotal and supportive study), despite the fact that a somewhat less efficacious paclitaxel regimen was used and in a much more heavily pretreated population. However, OS medians were very similar. A considerably higher response rate to the paclitaxel backbone therapy was seen in the lapatinib studies compared with the Herceptin trial. This further strengthens the possibility that the observed OS in the lapatinib studies may be higher than they would have been in a more optimally pretreated population, and the results are therefore not automatically generalisable to a European population. The magnitude of treatment effect was similar in the lapatinib and trastuzumab studies, although response rates were higher for trastuzumab despite being more heavily pretreated. Due to the differences in study populations no firm conclusions can be drawn from the comparison across the lapatinib and trastuzumab studies.

Additionally, head-to-head comparisons of lapatinib vs. trastuzumab in the *neo-adjuvant* setting have shown inferior results for lapatinib in 3 out of 4 studies (Study EGF106903/Neo-ALTTO, Study LPT109096, and the GeparQuinto study). While not statistically significant in 2 of them, the trend is consistent. More importantly, following interim results on disease-free survival, the IDMC of the *adjuvant* ALTTO study recommended discontinuation of the lapatinib arm, and patients were instead to

be offered trastuzumab. Therefore, there is a founded concern that lapatinib may be less efficacious than the licensed alternative adding to the uncertainties around using the present studies for support of the sought indication in a European population, where trastuzumab is an available treatment option.

2.5. Clinical safety

The safety assessment is based on the following clinical trials and pooled populations:

Table 43. Subjects treated with lapatinib or placebo in combination with paclitaxel (Safety populations)

Analysed Subject Population Contributing Studies	**Subjects Receiving Lapatinib N=677**	**Subjects Receiving Placebo N=507**	**Total N=1184**
Pivotal Phase III Study in HER2-Overexpressed MBC (EGF104535)	**222**[a]	**221**[a]	**443**[a]
3-Study Pool (paclitaxel dose 80 mg/m²/week)	**328**	**221**	**549**
Pivotal Study in HER2-Overexpressed MBC			
EGF104535 (Phase III)	222	221	443
HER2-Overexpressed MBC			
EGF105764 (Phase II)	57	0	57
Inflammatory Breast Cancer			
EGF102580 (Phase II)	49	0	49
Phase III Study (EGF30001)	**293**[b]	**286**[b]	**579**
4-Study Pool	**621**	**507**	**1128**
Pivotal Study in HER2-Overexpressed MBC			
EGF104535 (Phase III)	222	221	443
HER2 Status Negative or Unknown MBC			
EGF30001 (Phase III)	293	286	579
HER2-Overexpressed MBC			
EGF105764 (Phase II)	57	0	57
Inflammatory Breast Cancer			
EGF102580 (Phase II)	49	0	49
Phase I Solid Tumour Cancer Study with Combined Agent Therapy	**56**	**0**	**56**
Solid tumour			
EGF10009 (Phase I)	56	0	56

a. Of the 444 subjects randomised, 443 received treatment and were included in the safety population.

b. Two subjects (104 and 198) randomised to receive placebo+paclitaxel actually received lapatinib+paclitaxel.

Table 44. Clinical cut-off dates for studies in MBC safety database

EGF104535	EGF30001	EGF105764	EGF102580	EGF10009
18 Jun 2010	25 Aug 2010	18 Jun 2010	24 Jul 2007	25 Feb 2005

A short description of the supportive studies is given below.

Study EGF102580 Phase II, lapatinib + weekly paclitaxel

This was a Phase II, open-label, two-stage, multicentre, single-arm, international study designed to evaluate the efficacy, safety/tolerability, and pharmacodynamic effects of oral lapatinib administered daily in combination with weekly paclitaxel. Subjects were treatment naïve with a clinical diagnosis of inflammatory breast cancer (IBC), histologic confirmation of breast carcinoma, and tumours readily accessible for sequential biopsy.

Forty-nine subjects were enrolled into 2 cohorts: Cohort A (n= 42) comprised subjects with tumours overexpressing HER2, with or without co-expression of EGFR; Cohort B (n=7) comprised subjects with tumours expressing EGFR without overexpression of HER2.

Each cohort received 1500 mg oral lapatinib once daily for the first 14 days, followed by daily lapatinib (1500 mg) and weekly paclitaxel (80 mg/m2/week) for 12 weeks. Key safety assessments included vital signs, clinical laboratory tests (haematology and clinical chemistry), MUGA scan, ECG, ECOG performance status, complete physical examination, and monitoring for adverse events. AEs and toxicities were graded according to the NCI CTCAE, version 3.0.

Study EGF105764 Phase II, lapatinib + weekly paclitaxel

This was an open-label, single-arm, multicentre, Phase II study to evaluate overall tumour response rate of lapatinib administered daily as first-line treatment in combination with weekly paclitaxel in subjects with HER2-overexpressed Stage IV MBC who had not received prior therapy for metastatic disease.

Fifty-seven subjects were enrolled in the study and received a daily dose of lapatinib (1500 mg once daily) until disease progression or withdrawal from study treatment due to unacceptable toxicity or withdrawal of consent. Subjects were treated with paclitaxel (80 mg/m2/week IV for 3 weeks in a 4-week cycle) plus lapatinib for at least 6 cycles and could continue on paclitaxel at the discretion of the Investigator. Another objective of this study was to provide guidance on monitoring for hepatobiliary disorders. Key safety assessments were the same as for Study EGF102580 above.

Study EGF10009 Phase I, Dose-escalating lapatinib + paclitaxel in different regimens

This was a Phase I, open-label, dose-escalation study of the safety, tolerability, and pharmacokinetics of lapatinib in combination with paclitaxel in subjects with advanced solid tumours.

Fifty-six subjects with various solid tumours were enrolled in the study. The starting doses were lapatinib 1250 mg once daily in combination with paclitaxel 135 mg/m2. Forty-four subjects received once daily lapatinib at doses of 1250 mg or 1500 mg in combination with paclitaxel doses ranging from 135 to 225 mg/m2 once every 3 weeks, and 12 subjects received once daily lapatinib at 1500 mg in combination with once weekly paclitaxel at 80 mg/m2/week.

Safety assessments were performed at all clinic visits: Week 1, Week 2 and Week 3 of each cycle in the once every 3 weeks paclitaxel regimen, and on Day 1, 8 and 15 of each cycle in the once weekly paclitaxel regimen. AEs were monitored at all visits. The planned observation period for subjects was approximately 2 months: 1 cycle of treatment and a 28-day follow-up period. Measurements used to evaluate safety included blood pressure and heart rate, clinical laboratory tests (haematology,

chemistry, and urinalysis), 12-lead ECG, monitoring for AEs, Karnofsky performance status, MUGA scan, and atrial natriuretic factor. Toxicities and AEs were graded according to the NCI Common Toxicity Criteria (CTC) version 2.

- ***Patient exposure***

Pivotal study EGF104535

The exposure data for the pivotal study are summarised in Table 45, Table 46 and Table 47 below.

Table 45. Lapatinib/Placebo exposure during the randomised phase (Safety population), Pivotal study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Time on lapatinib/placebo (weeks)	n=222	n=218
Mean (SD)	48.8 (37.22)	31.8 (25.77)
Median (min-max)	40.9 (2-204)	26.5 (1-184)
Daily dose (mg)	n=222	n=218
Mean (SD)	1405.8 (140.84)	1465.0 (83.05)
Median (min-max)	1466.8 (577-1500)	1500.0 (900-1500)
Cumulative dose (mg)	n=222	n=218
Mean (SD)	488600.2 (382941.07)	327426.6 (270707.17)
Median (min-max)	392250.0 (15000-2064000)	270000.0 (6000-1935000)

Table 46. Paclitaxel exposure during the randomised phase (Safety population), Pivotal study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Median number of Cycles[a] (min-max)	6.0 (1-28)	6.0 (1-21)
<6 Cycles; n (%)	73 (33)	85 (38)
6 cycles; n (%)	113 (51)	92 (42)
>6 cycles; n (%)	36 (16)	44 (20)
Number of doses per cycle[b]		
Median (min-max)	2.8 (2-3)	3.0 (1-3)
Mean (SD)	2.7 (0.35)	2.8 (0.40)
Dose intensity[c]; mg/m^2/week		
Median (min-max)	52.0 (31-61)	59.0 (20-62)
Mean (SD);	50.7 (7.75)	55.1 (8.51)

a. Subjects had at least one dose of paclitaxel administered to be counted as a cycle.
b. Number of doses/cycle is defined as the number of non-missing/non-zero actual doses received in a cycle.
c. Planned Dose Intensity is the total planned dose (when the actual dose is not 0) for the cycle divided by the number of weeks in the cycle.

Table 47. Lapatinib/Placebo exposure following discontinuation of paclitaxel (Safety population), Pivotal study EGF104535

	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Time on lapatinib/placebo (weeks) Mean (SD) Median (min-max)	n=219 27.4 (33.51) 16.1 (0-178)	n=212 11.7 (21.03) 2.6 (0-157)
Daily dose (mg) Mean (SD) Median (min-max)	n=219 1440.6 (143.59) 1500.0 (528-1500)	n=212 1491.0 (50.01) 1500.0 (947-1500)
Cumulative dose (mg) Mean (SD) Median (min-max)	n=219 280363.0 (347241.75) 166500.0 (1500-1822500)	n=212 122600.2 (220349.73) 27000.0 (1500-1647000)

Compliance

Compliance was calculated as = [(total no. of tablets dispensed - total no. of tablets returned) /(no. of days in visit interval * no. of tablets prescribed per day)] * 100, where no. of days in visit interval = date returned - date dispensed + 1 in visit interval.

A subject is overall compliant if they are between 80-105% compliant, have not missed > 14 consecutive days, and have no more than one visit interval where compliance was unknown.

Compliance data showed that 16% in the lapatinib arm and 7% in the placebo arm had less than 80% compliance, and 11% vs. 3%, respectively, missed study drug for more than 14 days. Overall compliance, according to the definition above, was seen in 74% of the patients in the lapatinib arm vs. 89% in the placebo arm.

Supportive study EGF30001

Table 48. Summary of exposure to lapatinib and paclitaxel (Safety population) (Cut-off date 25 August 2010), Study EGF30001

Category of adverse event	Exposure to Lapatinib	Exposure to Paclitaxel	Exposure to Paclitaxel
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=293)	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=293)	Paclitaxel 175 mg/m² plus Placebo (N=286)
n evaluable	293	293	286
Duration of treatment period (weeks)			
Mean (standard deviation)	26.7 (26.48)	17.5 (15.62)	19.6 (16.95)
Daily dose	**mg**	**mg/m²**	**mg/m²**
Mean (standard deviation)	1490.5 (55.14)	172.0 (10.62)	173.9 (5.99)
Median (range)	1500.0 (1088 to 1941)	175.0 (82 to 187)	175.0 (102 to 183)

Compliance

Percentage compliance was calculated as [(number of tablets dispensed - number of tablets returned) / (number of tablets prescribed for initial dose per day*number of days on treatment)]*100.

Eleven percent had a lapatinib compliance of less than 80 %, and for seven percent of the patients the data was missing. Discontinuations

Pivotal study EGF104535

Table 49. Summary of investigational product discontinuation during the randomised phase (Safety population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Lapatinib or Placebo Dose Discontinuation		
Ongoing	14 (6)	6 (3)
Discontinued	208 (94)	215 (97)
Primary reason for discontinuation		
Disease progression	170 (77)	184 (83)
Adverse event[a]	14 (6)	16 (7)
Investigator decision	8 (4)	2 (<1)
Subject decided to withdraw from IP	5 (2)	4 (2)
Protocol violation	4 (2)	0
Subject decided to withdraw from study	3 (1)	1 (<1)
Death[b]	2 (<1)	4 (2)
Lost to follow-up	2 (<1)	1 (<1)
Other[c]	0	3 (1)
Paclitaxel Dose Discontinuation		
Ongoing	2 (<1)	2 (<1)
Discontinued	220 (>99)	219 (>99)
Primary reason for discontinuation		
Investigator decision	122 (55)	104 (47)
Disease progression	37 (17)	84 (38)
Adverse event[a]	26 (12)	14 (6)
Subject decided to withdraw from IP	5 (2)	1 (<1)
Protocol violation	4 (2)	0
Subject decided to withdraw from study	2 (<1)	2 (<1)
Lost to follow-up	2 (<1)	1 (<1)
Death[b]	1 (<1)	4 (2)
Other[d]	21 (9)	9 (4)

a) Subject discontinuation due to an AE is as recorded on the Study Completion page of the eCRF (where the investigator can only provide the 'primary' reason for withdrawal). AEs leading to discontinuation of IP as recorded on the Adverse Event page of the eCRF is provided in Table 52.
b) Lapatinib+paclitaxel arm: Subject 1446 died due to disease under study and discontinued lapatinib and paclitaxel, Subject 1069 died due to disease under study and discontinued lapatinib;
c) Placebo+paclitaxel arm: Subjects 1026, 1536, 1597 and 1854 died due to disease under study and discontinued placebo and paclitaxel.
d) 1 subject had two primary cancer sites and was withdrawn from study, 1 subject had PD and SAE and withdrew from study, 1 subject had an SAE.
e) Lapatinib+paclitaxel arm: 10 subjects had completed 6 cycles of treatment, 6 subjects stopped receiving paclitaxel, 4 subjects decided to withdraw/stop paclitaxel, 1 subject could not attend hospital weekly; Placebo+paclitaxel arm: 3 subjects had completed 6 cycles of treatment, 3 subjects stopped receiving paclitaxel, 1 subject decided to withdraw/stop paclitaxel, 1 subject had two primary cancer sites and was withdrawn from study; 1 subject could not attend hospital weekly.

Table 50. Summary of all adverse events leading to permanent discontinuation of investigational product during the randomised phase (Safety population), Pivotal study EGF104535

Preferred term	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Any Event	**29 (13)**	**21 (10)**
Neutropenia	6 (3)	0
AST increased	3 (1)	3 (1)
Ejection fraction decreased	3 (1)	2 (<1)
ALT increased	2 (<1)	0
Leukopenia	2 (<1)	0
Myalgia	2 (<1)	0
Hyperbilirubinaemia	1 (<1)	1 (<1)
Diarrhoea	1 (<1)	0
Epigastric discomfort	1 (<1)	0
Laryngeal oedema	1 (<1)	0
Acute pancreatitis	1 (<1)	0
Vomiting	1 (<1)	0
Hepatitis	1 (<1)	0
Liver injury	1 (<1)	0
Peripheral neuropathy	1 (<1)	0
Negativism	1 (<1)	0
Fatigue	1 (<1)	0
Arthralgia	1 (<1)	0
Rash	1 (<1)	0
Cardiac discomfort	1 (<1)	0
Hypotension	1 (<1)	0
Dyspnoea	0	3 (1)
Interstitial lung disease	0	2 (<1)
Hypersensitivity	0	2 (<1)
Blood bilirubin increased	0	2 (<1)
Presyncope	0	2 (<1)
Hepatic function abnormal	0	1 (<1)
Hepatobiliary disease	0	1 (<1)
Anaphylactic reaction	0	1 (<1)
Anxiety	0	1 (<1)
Completed suicide	0	1 (<1)
Peripheral oedema	0	1 (<1)
Swelling face	0	1 (<1)
Pneumonia	0	1 (<1)
Femur fracture	0	1 (<1)

NB: These are AEs leading to discontinuation of IP as recorded on the Adverse Event page of the eCRF. Subject discontinuation due to AEs as recorded on the Study Completion page of the eCRF (where the investigator can only provide the 'primary' reason for withdrawal) is provided in Table 49.

- **Dose interruptions and reductions**

AE management guidance was provided in the protocol that specified dose interruptions and reductions for managing known and expected AEs to increase the tolerability of the regimen.

Interruptions in the dose of lapatinib or placebo occurred in 70% of subjects in the lapatinib+paclitaxel arm and in 39% of subjects in the placebo+paclitaxel arm In both treatment arms, interruptions were of short duration (median duration of 4 days and 3 days respectively) and mainly due to haematologic toxicities.

Reductions in the dose of lapatinib or placebo were infrequent and occurred in 7% of subjects in lapatinib+paclitaxel arm and <1% of subjects in the placebo+paclitaxel arm. The higher number of dose reductions in the lapatinib+paclitaxel arms was mainly due to non-haematological toxicities. Overall, the majority of lapatinib or placebo dose modifications were performed to manage known toxicities associated with lapatinib.

Supportive study EGF30001

Table 51. Primary reason for discontinuation from treatment (ITT population)(Cut-off date 25 August 2010), Study EGF30001

	Number (%) of subjects		
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=291)	Paclitaxel 175 mg/m² plus Placebo (N=288)	Total (N=579)
Continuing treatment/missing[1]	1 (<1)	0	1 (<1)
Discontinued from study treatment[2]	290 (>99)	288 (100)	578 (>99)
Reason for discontinuation from study treatment			
Adverse event	48 (17)	20 (7)	68 (12)
Consent withdrawn	24 (8)	27 (9)	51 (9)
Lost to follow-up	1 (<1)	2 (<1)	3 (<1)
Protocol violation	4 (1)	2 (<1)	6 (1)
Progression of cancer	186 (64)	216 (75)	402 (70)
Death	4 (1)	1 (<1)	5 (<1)
Other	23 (8)	19 (7)	42 (7)

- **Adverse events**

Pivotal study EGF104535

Table 52. Overall summary of adverse events during the randomised phase (Safety population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo + paclitaxel (N=221)
Number of subjects with AE	**220 (>99)**	**212 (96)**
Number of subjects with treatment-related AE	220 (>99)	202 (91)
Number of subjects with AE leading to withdrawal of IP	29 (13)	21 (10)
Number of subjects with SAE	**66 (30)**	**30 (14)**
Number of subjects with fatal on-therapy AE	0	8 (4)
Number of subjects with treatment-related SAE	61 (27)	19 (9)

Treatment-related=Considered by the investigator to be related to IP (investigational product)

Table 53. On-therapy adverse events regardless of causality reported in 10% or more subjects in any treatment arm (Safety population), Pivotal study EGF104535

System organ class MedDRA preferred term	Number of Subjects (%)					
	Lapatinib+paclitaxel (N=222)			Placebo+paclitaxel (N=221)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia	170 (77)	77 (35)	36 (16)	104 (47)	34 (15)	11 (5)
Leukopenia	117 (53)	50 (23)	7 (3)	74 (33)	18 (8)	1 (<1)
Anaemia	50 (23)	8 (4)	0	22 (10)	3 (1)	0
Skin and subcutaneous tissue disorders						
Alopecia	102 (46)	0	0	113 (51)	1 (<1)	0
Rash	130 (59)	9 (4)	1 (<1)	52 (24)	0	0
Nail disorder	25 (11)	0	0	3 (1)	0	0
Gastrointestinal disorders						
Diarrhoea	172 (77)	45 (20)	0	64 (29)	1 (<1)	1 (<1)
Nausea	66 (30)	1 (<1)	0	41 (19)	0	0
Vomiting	48 (22)	5 (2)	0	26 (12)	3 (1)	0
Nervous system disorders						
Neuropathy peripheral	30 (14)	1 (<1)	0	30 (14)	0	0
Hypoaesthesia	18 (8)	1 (<1)	0	25 (11)	0	0
General disorders and administration site conditions						
Fatigue	48 (22)	4 (2)	0	35 (16)	1 (<1)	0
Pyrexia	32 (14)	1 (<1)	0	30 (14)	1 (<1)	0
Investigations						
ALT increased	24 (11)	4 (2)	0	17 (8)	1 (<1)	0
Haemoglobin decreased	23 (10)	7 (3)	0	4 (2)	1 (<1)	0
Metabolism and nutrition disorders						
Decreased appetite	70 (32)	2 (<1)	0	41 (19)	0	0
Musculoskeletal and connective tissue disorders						
Myalgia	30 (14)	1 (<1)	0	23 (10)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	22 (10)	0	0	19 (9)	2 (<1)	0

Grade 3=severe AE; Grade 4=life threatening or disabling AE.

Febrile neutropenia

The clinically important event of febrile neutropenia was 4 vs. <1% in the lapatinib+paclitaxel and placebo+paclitaxel arms, respectively. Diarrhoea AEs are associated with both lapatinib therapy and paclitaxel therapy, and based on previous lapatinib monotherapy studies, it is generally expected (a 58% incidence has been previously reported for lapatinib monotherapy studies). Diarrhoea treatment guidelines were implemented throughout Study EGF104535 (see guideline in next paragraph). Dose modifications were also used to manage diarrhoea AEs. Overall, diarrhoea events generally occurred early in the treatment regimen, with most subjects that had diarrhoea having their first episode within the first 2 weeks of treatment. The median duration of diarrhoea was 6 days in lapatinib+ paclitaxel arm compared with 3 days in the placebo+paclitaxel arm. Withdrawals due to diarrhoea were < 1%. According to the MAH these diarrhoea management guidelines are proposed to be included in the prescribing information for lapatinib. However, the proposed SmPC text does not include all the measures recommended in the guideline to limit the diarrhoea condition.

Diarrhoea Management Guidelines:

Uncomplicated CTC Grade 1-2 diarrhoea: was to be managed with a standard dose of loperamide: Initial 4 mg dose followed by 2 mg every 4 hours or after every unformed stool, until subjects were diarrhoea free for 12 hours. All lactose containing products were to be stopped. Frequent small meals and 8-10 glasses of clear liquid per day were recommended. For Grade 2 diarrhoea, cytotoxic chemotherapy was to be interrupted and a dose reduction of lapatinib was to be considered.

CTC Grade 3 or 4 diarrhoea or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration): was to be managed with intravenous fluid as appropriate (with hospital admission if required) and prophylactic antibiotics, especially if diarrhoea persisted beyond 24 hours or there was fever or Grade 3-4 neutropenia. Both lapatinib and paclitaxel was to be held.

Cardiac events

In the pivotal study, the only preferred terms reported as AEs for cardiac events were ejection fraction decreased, left ventricular dysfunction and chronic cardiac failure.

Any cardiac event was experienced by 9 vs. 5% of the patients in the lapatinib+paclitaxel arm vs. the placebo+paclitaxel arm. One patient in each arm experienced a ≥ grade 3 cardiac event. Left ventricular ejection fraction (LVEF) changes meeting predefined decreases were observed at a higher rate in the combination treatment arm. These changes were transient. Dose interruption due to cardiac events occurred in 2.7% of the subjects in the lapatinib+paclitaxel arm compared with 0.5% of subjects in the placebo+paclitaxel arm. Only 3 subjects in the lapatinib+paclitaxel arm and 2 subjects in the placebo+paclitaxel arm had study treatment discontinued due to a cardiac event.

Rash and nail changes

Rash events are a known class effect of tyrosine kinase inhibitors (TKIs). Rash events in lapatinib treatment are expected; a 29% incidence has been previously reported for lapatinib monotherapy studies. In the pivotal study aggregated preferred terms for rash were used. Rash occurred more frequently in the lapatinib+paclitaxel arm (in 59% of subjects) than in the placebo+paclitaxel arm (24%); none was reported as serious and none fatal. The majority of events in both treatment arms resolved without any residual sequelae and most subjects did not require dose modifications or disruption of study treatment; 1 subject in the lapatinib+paclitaxel arm had study treatment discontinued due to rash.

Nail changes are associated with lapatinib therapy and also infrequently with paclitaxel. For lapatinib monotherapy studies a 1% incidence has been previously reported. In the pivotal study nail changes were of low grade and did not require any dose modifications or interruptions, and no subjects had study treatment withdrawn due to nail change events.

Interstitial Lung Disease (ILD) is rarely associated with lapatinib, with an incidence of 0.2% incidence previously reported for lapatinib monotherapy studies. In the pivotal study, ILD occurred in <1% in both treatment arms. Thus, 1subject in the lapatinib+paclitaxel arm had a Grade 1 ILD AE, which resolved without any dose modifications. One subject in the placebo+paclitaxel arm had a Grade 2 event that resulted in withdrawal of IP, and resolved without residual sequelae. One other subject in the placebo+paclitaxel arm had a Grade 5 (i.e. fatal) ILD event.

Hepatobiliary events are associated with lapatinib therapy, and the incidence is generally low (a 1.3% incidence has been previously reported for lapatinib monotherapy studies). It should be noted that the incidence of subjects with events in this pivotal Study EGF104535 includes those with abnormal laboratory events, which previous lapatinib studies did not consider (Table 54).

Table 54. Summary of the 56 individual AE preferred terms included in the definition of Hepatobiliary events in the Pivotal study EGF104535

Acute hepatic failure	Hepatic infiltration eosinophilic
Alanine aminotransferase/abnormal/increased	Hepatic necrosis
Ammonia abnormal/increased	Hepatic steatosis
Aspartate aminotransferase/abnormal/increased	Hepatitis/acute/cholestatic/fulminant/toxic
Autoimmune hepatitis	Hepatobiliary disease
Bilirubin conjugated abnormal/increased	Hepatocellular injury
Bilirubin urine	Hepatotoxicity
Blood alkaline phosphatase/abnormal/increased	Hyperammonaemia
Blood bilirubin/abnormal/increased	Hyperbilirubinaemia
Blood bilirubin unconjugated/increased	Hypertransaminasaemia
Cholestatic liver injury	Jaundice/cholestatic/hepatocellular
Cytolytic hepatitis	Liver disorder
Gamma-glutamyltransferase/abnormal/increased	Liver function test/abnormal
Hepatic encephalopathy	Liver injury
Hepatic enzyme abnormal/increased	Subacute hepatic failure
Hepatic failure	Transaminases/abnormal/increased
Hepatic function abnormal	

Table 55. Characteristics of hepatobiliary adverse events during the randomised phase (Safety population), Pivotal study EGF104535

	Number of Subjects (%)	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Number of subjects with events	52 (23)	47 (21)
Number of events	176	92
Event characteristics	n=176	n=92
Serious	0	3 (3)
Investigational product-related	147 (84)	61 (66)
Leading to withdrawal from study	1 (<1)	2 (2)
Fatal	0	2 (2)
Outcome	n=176	n=92
Recovered/resolved	162 (92)	57 (62)
Recovering/resolving	7 (4)	3 (3)
Not recovered/not resolved	7 (4)[a]	27 (29)[b]
Recovered/resolved with sequelae	0	3 (3)
Action taken	n=176	n=92
Investigational product (s) withdrawn	8 (5)	8 (9)
Dose reduced	1 (<1)	0
Dose increased	0	0
Dose not changed	132 (75)	68 (74)
Dose interrupted	32 (18)	11 (12)
Not applicable	3 (2)	5 (5)
Number of occurrences by subject	n=52	n=47
1	22 (42)	30 (64)
2	14 (27)	9 (19)
≥3	16 (31)	8 (17)
Maximum toxicity[c]	n=52	n=47
Grade 1	25 (48)	24 (51)
Grade 2	20 (38)	10 (21)
Grade 3	7 (13)	9 (19)
Grade 4	0	2 (4)[d]
Grade 5	0	2 (4)[e]
Number of interruptions by subject	n=52	n=47
1	11 (21)	5 (11)
2	2 (4)	0
≥3	3 (6)	1 (2)

Footnotes a, b, d, and e refer to subject identification numbers.
c. The denominator of the percentages here is the number of subjects who experienced events.

The 3 hepatobiliary SAEs reported all occurred in the placebo+paclitaxel arm (1 Grade 4 hepatic functional abnormal, 1 Grade 5 hepatobiliary disease and 1 Grade 5 hepatotoxicity).

There were no cases in the study that met Hy's criteria.

Supportive study EGF30001

Table 56. Number (%) of subjects with common adverse events (15% or more in either treatment group) by preferred term (Safety population) (Cut-off date 25 August 2010), Study EGF30001

MedDRA preferred term	Number (%) of subjects	
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m^2 (N=293)	Paclitaxel 175 mg/m^2 plus Placebo (N=286)
Any AE	287 (98)	278 (97)
Diarrhoea	171 (58)	73 (26)
Alopecia	153 (52)	183 (64)
Rash	145 (49)	66 (23)
Nausea	100 (34)	85 (30)
Myalgia	94 (32)	74 (26)
Neutropenia	76 (26)	58 (20)
Vomiting	74 (25)	48 (17)
Arthralgia	70 (24)	58 (20)
Fatigue	65 (22)	61 (21)
Asthenia	62 (21)	36 (13)
Neuropathy peripheral	54 (18)	32 (11)
Decreased appetite	50 (17)	32 (11)
Pain in extremity	50 (17)	50 (17)
Peripheral sensory neuropathy	48 (16)	54 (19)
Pruritus	46 (16)	37 (13)
Paraesthesia	43 (15)	42 (15)
Constipation	35 (12)	48 (17)
Cough	33 (11)	42 (15)

Neutropenia

Neutropenia of Grade 4 was observed in 18% and 10% of subjects suggesting slightly higher rates of myelosuppression in both paclitaxel-containing arms of EGF30001 relative to the weekly paclitaxel experience (5% in the placebo+paclitaxel arm of the Pivotal study). Febrile neutropenia was reported in 4% and 1% of subjects, which is the same frequency as in the Pivotal study. There was 1 death associated with febrile neutropenia and 3 additional deaths of infectious nature (fatal sepsis/fatal septic shock) with Grade 4 neutropenia on the lapatinib+paclitaxel arm. Three of these 4 deaths came early in the study before implementation of diarrhoea management guidelines. Two subjects (1%) in the lapatinib+paclitaxel arm and 1 subject (<1%) from the placebo+paclitaxel arm discontinued treatment due to neutropenia AEs.

Diarrhoea

In the Study 30001, 58% of subjects experienced diarrhoea events in the lapatinib+paclitaxel arm compared with 26% in the placebo+paclitaxel arm. SAEs of diarrhoea were reported for 24 subjects (8%) in the lapatinib+paclitaxel arm and for 2 subjects (<1%) in the placebo+paclitaxel arm.

The median time to onset in the lapatinib+paclitaxel arm was 8 days compared with 22 days in the placebo+paclitaxel arm. The median duration of diarrhoea events in the lapatinib+paclitaxel arm was 4 days and in the placebo+paclitaxel arm was 3 days. In the lapatinib+paclitaxel arm with 464 events, diarrhoea resulted in dose delays in 10% of events and dose adjustments in 2% of events. Thirteen subjects permanently withdrew from treatment due to diarrhoea, all from the lapatinib+paclitaxel arm. At the start of this study, no specific diarrhoea management guidelines were in place. Diarrhoea guidelines were implemented on 31 October 2004.

Cardiac events

There were 5 (2%) cardiac SAEs in lapatinib+paclitaxel arm and 2 (<1%) in the placebo+paclitaxel arm, and 2 in the lapatinib+paclitaxel arm were fatal (cardiac arrest and cardiac failure).

LVEF decrease events (Preferred terms: Ejection fraction decreased and Left ventricular dysfunction) were reported for 10 subjects (3%) in each treatment arm during Study EGF30001.*

The majority of LVEF decrease events were Grade 2 or 3 in both treatment arms. Grade 3 occurred in 5 and 3 subjects, respectively. None of the LVEF events resulted in a dose adjustment or withdrawal. Most of the LVEF events resolved in the lapatinib+paclitaxel arm (71%) and in the placebo+paclitaxel arm (86%). The median time to onset in the lapatinib+paclitaxel arm of the LVEF decreases was 66.0 days, compared with 79.0 days in the placebo+paclitaxel arm. The median duration of the LVEF decrease events in the lapatinib+paclitaxel arm was 12.5 days and in the placebo+paclitaxel arm was 37 days.

However, it was noted that in the text in section 4.5.3.3 of the Summary of Clinical Safety it is stated that "Ten subjects (3%) reported 7 events of LVEF in each treatment arm during Study EGF30001" but in the data source, Table 8.19 in CSR of Study EGF3000 the number of events are 11 and 14 in the lapatinib+paclitaxel and placebo+paclitaxel arms, respectively.

Hepatobiliary events

In Study EGF30001 for the evaluation of hepatobiliary events, the AE Preferred term considered was "hepatobiliary", unlike the pivotal study where additionally a large number of laboratory abnormalities were included. With this definition, 1 subject in each treatment arm experienced hepatobiliary events, none was fatal, both subjects had unresolved events and both discontinued treatment due to a hepatobiliary event.* The patient in the lapatinib+paclitaxel arm had 2 Grade 3 hepatobiliary events and 1 of these was classified as serious. The time to onset of the hepatobiliary event in the lapatinib+paclitaxel arm was 95 days, and of the event in the placebo+paclitaxel arm was 23 days.

However, it was noted that in table 37 of the Summary of Clinical Safety the number of patients discontinuing in the placebo+paclitaxel arm is 0, however in the text above the table, as well as in the data source tables in the CSR of Study EGF30001 (Table 8.6; Table 8.15), the number in the placebo+paclitaxel arm is 1. Thus one subject in each arm experienced hepatobiliary events, and both subjects discontinued.

Clinical chemistry assessments were also evaluated for potential hepatobiliary signals. Four subjects in the lapatinib+paclitaxel arm (<1%) had laboratory results consistent with Hy's criteria, which were pre-defined as > 3xULN for AST and ALT, >2xULN for total bilirubin, and alkaline phosphatase ≤2xULN. The days of event onset for these subjects were Day 33, Day 50, Day 199, and Day 218. All but 1 subject had metastatic liver disease, but none of the events could be attributed to liver metastasis progression. Baseline liver abnormalities were observed in 2 of the 4 subjects. Some of them received other concomitant medications with the potential for liver toxicity. All subjects improved after study drug discontinuation. Although these subjects had many confounding factors which may have contributed to the hepatobiliary events, an association between the events and the administration of lapatinib could not be excluded. None were considered definite Hy's cases as each had some confounding features that could explain the rise in transaminases and bilirubin.

Rash was experienced in 49% of patients in the lapatinib+paclitaxel group compared with 23% in the placebo+paclitaxel in Study EGF30001. Rash SAEs occurred in 6 (2%) patients in lapatinib+paclitaxel arm and 2 (<1%) in the placebo+paclitaxel arm; none were fatal. Rash led to permanent treatment discontinuation in 2% of cases in the lapatinib+paclitaxel group.

No cases of interstitial lung disease were seen in the lapatinib+paclitaxel group; 1 subject (<1%) in the placebo+paclitaxel arm had an SAE of Grade 3 pneumonitis which resulted in the permanent discontinuation of investigational product.

Pooled data from studies EGF104535, EGF105764, and EGF102580 (80mg/m2/week paclitaxel)

The incidence of neutropenia AEs in the integrated 3-study pool was higher in the lapatinib+paclitaxel treatment arm (61%) compared to the placebo+paclitaxel arm (47%).

Laboratory Grade 4 ANC was reported in 15% and 5%, respectively. There were no additional cases of febrile neutropenia in the combined data set for weekly paclitaxel studies. The incidence of subjects with diarrhoea AEs was 76% in the lapatinib+paclitaxel arm and 29% in the placebo+paclitaxel arm, consistent with Study EGF104535. The incidence of subjects with cardiac AEs were similar in both treatment arms, 7% in

the lapatinib+paclitaxel and 5% in the placebo+paclitaxel arm. The incidence of rash in the 3-study pool was not different from Study EGF104535.

All interstitial lung disease AEs in this integrated population were reported by subjects in Study EGF104535.

Pooled data from studies EGF104535, EGF30001, EGF105764, and EGF102580

In the lapatinib+paclitaxel arm, 479 events (53%) required a dose interruption or delay, compared to 185 events (38%) in the placebo+paclitaxel arm. Seven subjects (<1%) in the lapatinib+paxlitaxel arm had study treatment withdrawn, compared with 1 subject (<1%) in the placebo+paclitaxel arm.

The data for diarrhoea for the 4-study pool of data is within the ranges of the 3-study pool and Study EGF30001.

The MAH states that: Across all 4 of these lapatinib+paclitaxel studies, hepatobiliary events and their sequelae were consistent with expectations for combination therapy using cytotoxic agents in treating first-line MBC. Conclusions from the 4-study pool are primarily based on the data from the two Phase III studies, EGF104535 and EGF30001.

All rash SAEs occurred in subjects enrolled in Study EGF30001.

Studies EGF102580 and EGF105764

Table 57. Summary of AEs of interest (regardless of causality) and relation to discontinuations in supportive phase II studies EGF102580 and EGF105764.

Study	**EGF102580, n = 49**	
	AE, n (%)	**Discontinuation due to AE n (%)**
Any	48 (98)	2 (4)
Diarrhoea	34 (69)	1 (2)
Vomiting	28 (57)	0
Rash	5 (10)	1(2)
Neutropenia	2 (4)	0
Ejection fraction decrease	2 (4)	0
AST+ALT decrease	2 (4)	2 (4)
Bilirubin increased	0	0
Study	**EGF105764, n = 57**	
	AE, n (%)	**Discontinuation due to AE n (%)**
Any	57 (100)	6 (11)
Diarrhoea	32 (56)	(1 (2) Dehydration [a])
Vomiting	6 (11)	0
Rash	23 (40)	0
Neutropenia	26 (46)	0
Ejection fraction decrease	0	0
ALT increase	10 (18)	3 (5) ALT±AST increase [b]
AST increase	5 (9)	0
Transaminases increase	1 (2)	0
Bilirubin increased	2 (4)	0
Hyperbilirubinemia	3 (5)	0

[a] Cause for discontinuation was Grade 3 Dehydration following 14 days of Grade 1 diarrhoea.

[b] Two patients discontinued due to elevations in both ALT and AST, for one patient only ALT was reported as cause for discontinuation.

Study EGF10009

Paclitaxel administered on a once every 3 weeks schedule:

All 44 subjects receiving the once every 3 weeks schedule of paclitaxel + once daily lapatinib combination experienced at least one AE during the study. The majority of AEs were Grade 1 or Grade 2 in intensity. The most frequently reported drug-related AEs were diarrhoea (73%), rash (73%), nausea (50%), fatigue (41%), anorexia (32%), vomiting (32%), dyspepsia (18%) and pruritis (16%). Four subjects (9%) experienced a left ventricular ejection (LVEF) decrease ≥20% relative to baseline. All of these events were asymptomatic and none of these subjects were discontinued from therapy due to changes in LVEF.

Forty-one SAEs were experienced by 16 of the 44 subjects (36%) receiving the once every 3 weeks regimen of paclitaxel in combination with once daily lapatinib. Nine SAEs were considered by the investigator to be drug-related and occurred in 3 subjects (7%) as follows: Subject 1193 had fatal

hepatic encephalopathy and Grade 4 leucopenia; Subject 1203 had Grade 2 nausea and vomiting and Grade 3 dehydration; and Subject 1209 had 2 episodes each of Grade 3 nausea and vomiting. There were two deaths on study in subjects who received the once every 3 weeks regimen of paclitaxel with lapatinib. As mentioned above one subject (Subject 1193) experienced fatal hepatic encephalopathy. Although it was considered likely that this event resulted from disease progression, a relationship with the study drug regimen could not be ruled out. The other subject (Subject 1212) died on study due to disease progression.

Paclitaxel administered on a once-a-week schedule for 3 weeks out of 4:

Each of the 12 subjects (100%) receiving the once-weekly paclitaxel and daily lapatinib regimen experienced at least one AE, the majority of which were Grade 1 or 2 in severity. The most frequently reported drug-related events were diarrhoea (92%), vomiting (67%), rash (58%), fatigue (42%), nausea (42%), anorexia (33%), constipation (33%), mucositis(25%) and pruritus (25%).

Thirteen SAEs were experienced by 4 of the 12 subjects (33%) who received the weekly paclitaxel regimen in combination with daily lapatinib. Two of these SAEs i.e., Grade 3 nausea and vomiting, were considered drug-related and occurred in one subject. No deaths occurred on study in subjects on the weekly paclitaxel regimen and no subjects on this regimen experienced relative declines in LVEF that were ≥20% from baseline.

- **Serious adverse event/deaths/other significant events**

Pivotal study EGF104535

Table 58. Summary of all on-therapy serious adverse events during the randomised phase by treatment arm (Safety population), Pivotal study EGF104535

Preferred term	Number of Subjects (%) [Related, n]	
	Lapatinib+paclitaxel (N=222)	Placebo+paclitaxel (N=221)
Any Event, n (%) [related to IP]	**66 (30) [61]**	**30 (14) [19]**
Neutropenia	36 (16) [36]	10 (5) [10]
Ejection fraction decreased	13 (6) [12]	3 (1) [2][a]
Diarrhoea	10 (5) [9]	0
Leukopenia	7 (3) [7]	1 (<1) [1]
Febrile neutropenia	6 (3) [6]	1 (<1) [1]
Granulocytopenia	4 (2) [4]	0
Left ventricular dysfunction	3 (1) [2]	0
Pyrexia	3 (1) [1]	0
Cellulitis	2 (<1) [2]	0
Dyspnoea	1 (<1)	2 (<1)[1][a]
Vomiting	1 (<1) [1]	1 (<1)
Hypokalaemia	1 (<1)	1 (<1)
Neutrophil count decreased	1 (<1) [1]	0
Haemoglobin decreased	1 (<1)	0
Fatigue	1 (<1)	0
Pharyngitis	1 (<1) [1]	0
Lung infection	1 (<1) [1]	0
Escherichia bacteraemia	1 (<1) [1]	0
Acute pancreatitis	1 (<1)	0
Abdominal pain	1 (<1)	0
Acute pyelonephritis	1 (<1)	0
Urinary tract infection	1 (<1)	0
Microlithiasis	1 (<1)	0
Laryngeal oedema	1(<1)	0
Hyperglycaemia	1 (<1) [1]	0
Femur fracture	0	2 (<1)
Deep vein thrombosis	0	1 (<1) [1]
Completed suicide	0	1 (<1)[a]
Increased intracranial pressure	0	1 (<1)
Presyncope	0	1 (<1) [1]
Pleural effusion	0	1 (<1)
Non-cardiac chest pain	0	1 (<1)
Multi-organ failure	0	1 (<1) [1][a]
Viral infection	0	1 (<1)
Pneumonia	0	1 (<1)
Septic shock	0	1 (<1)[a]
Interstitial lung disease	0	1 (<1)[a]
Chronic cardiac failure	0	1 (<1)[a]
Cholecystitis	0	1 (<1)
Abnormal hepatic function	0	1 (<1) [1]
Hepatobiliary disease	0	1 (<1)[a]
Hepatotoxicity	0	1 (<1) [1][a]

a. One event had a fatal outcome.

Cardiac SAEs

Ejection fraction decreases were reported as SAEs in 13 subjects (6%) in the lapatinib+paclitaxel arm and 3 subjects (1%) in the placebo+paclitaxel arm (Table 60). In the lapatinib+paclitaxel arm, 1 event was symptomatic (Grade 3), none of the events were fatal, 3 subjects discontinued study treatment, and the majority of events resolved without residual sequelae. In the placebo+paclitaxel arm 1 subject had a symptomatic (Grade 5) event. All other subjects had events considered by investigator as Grade 1 or 2.

A post-hoc analysis of changes in LVEF was performed to further evaluate the cardiac profile. As defined in the protocol, events with a relative change from baseline in LVEF ≥20% and below LLN were required to be reported as SAEs. This was observed in 15 subjects in the lapatinib+paclitaxel arm and 4 subjects in the placebo+paclitaxel arm; in 3 events LVEF was below 40%. In 6 subjects, the LVEF recovered to between 51% to 55%, and 8 recovered to >60%. This analysis indicates that the majority of subjects had a recovered LVEF to clinically normal values (>55%).

SAEs of left ventricular dysfunction were reported in 3 subjects (1%) in the lapatinib+paclitaxel arm, and in no subjects in the placebo+paclitaxel arm. All events were Grade 1 or 2, and had resolved or were resolving at the safety data cut-off.

Only 1 subject, in the placebo+paclitaxel arm, experienced a symptomatic cardiac failure SAE that was fatal, and was considered by the investigator not to be related to study treatment. The investigator also reported a fatal ejection fraction decrease for this subject, and considered this death to be primarily caused by disease progression.

Supportive study EGF30001

Table 59. Number (%) of subjects with SAEs (1% or more subjects in either treatment group) (Safety population) (Cut-off date 25 August 2010), Study EGF30001

MedDRA preferred term	Number (%) of subjects	
	Lapatinib 1500 mg plus Paclitaxel 175 mg/m^2 (N=293)	Paclitaxel 175 mg/m^2 plus Placebo (N=286)
Any SAE, n (%)[treatment related, n]	103 (35) [61]	63 (22) [29]
Diarrhoea	24 (8) [21]	2 (<1) [2]
Neutropenia	22 (8) [20]	14 (5) [11]
Febrile neutropenia	10 (3) [8]	3 (1) [2]
Pyrexia	7 (2) [1]	2 (<1) [1]
Mucosal inflammation	6 (2) [5]	1 (<1) [1]
Ejection fraction decreased	5 (2) [2]	5 (2) [4]
Vomiting	4 (1) [2]	4 (1) [2]
Hypercalcaemia	4 (1) [1]	3 (1) [0]
Dehydration	4 (1) [3]	0
Rash	4 (1) [4]	0
Dyspnoea	3 (1) [0]	3 (1) [0]
Pneumonia	3 (1) [0]	2 (<1) [0]
Hypotension	3 (1) [1]	0
Pain in extremity	3 (1) [1]	0

Serious adverse events across the lapatinib programme

Preliminary SAE data are available for the lapatinib programme (all phases) up to a cut off date of 12 September 2010. At this time, a total of 26,345 subjects were enrolled in GSK sponsored interventional Phase I, II and III studies, of which approximately 19,642 will have received lapatinib.

Overall, 42.6% (3487/8195) of the SAEs reported were assessed as related to study treatment by the investigator. Most neutropenia/febrile neutropenia events occurred in studies where lapatinib is given in combination with cytotoxic chemotherapies known to be associated with neutropenia. The lapatinib CSI states that combining lapatinib with paclitaxel or docetaxel can increase the incidence and severity of neutropenia.

Table 60.Ten most frequently reported drug-related SAEs from the lapatinib clinical programme (n ≈19,642)

MedDRA Preferred Term	Drug Related[a]	Total (all Causalities)
Diarrhoea[b]	493	564
Neutropenia	288	346
Vomiting[b]	180	313
Alanine aminotransferase increased[b]	178	188
Ejection fraction decreased[b]	164	192
Dehydration[b]	119	204
Nausea[b]	109	172
Febrile neutropenia	95	131
Pyrexia	67	207
Left ventricular dysfunction[b]	63	73

a. Based on the judgement of the investigator.
b. Included in the lapatinib CSI

- **Laboratory findings**

Pivotal study EGF104535

Table 61. Summary of maximum toxicity grade for key haematology parameters during the randomised phase (Safety population), Pivotal study EGF104535

Parameter	Visit	n	Number (%) of Subjects		
			All Grades	Grade 3	Grade 4
Lapatinib+paclitaxel, N=222					
Haemoglobin	Baseline	222	30 (14)	0	0
	Any Post	222	193 (87)	13 (6)	0
Platelets	Baseline	222	2 (<1)	0	0
	Any Post	222	19 (9)	2 (<1)	0
Total WBC	Baseline	222	15 (7)	0	0
	Any Post	222	214 (96)	69 (31)	11 (5)
Neutrophils	Baseline	222	10 (5)	0	0
	Any Post	222	202 (91)	77 (35)	40 (18)
Placebo+paclitaxel, N=221					
Haemoglobin	Baseline	221	26 (12)	0	0
	Any Post	216	132 (61)	4 (2)	0
Platelets	Baseline	221	1 (<1)	0	0
	Any Post	216	19 (9)	0	0
Total WBC	Baseline	221	17 (8)	0	0
	Any Post	216	181 (84)	37 (17)	2 (<1)
Neutrophils	Baseline	221	6 (3)	0	0
	Any Post	216	159 (74)	37 (17)	11 (5)

Table 62. Summary of maximum toxicity grade for clinical chemistry parameters during the randomized phase (Safety population), Pivotal study EGF104535

Parameter	Visit	n	Number (%) of Subjects			
			Grade 1	Grade 2	Grade 3	Grade 4
Lapatinib+Paclitaxel, N=222						
Sodium	Baseline	219	14 (6)	0	0	1 (<1)
	Any Post	220	59 (27)	6 (3)	10 (5)	0
Potassium	Baseline	219	9 (4)	0	0	0
	Any Post	220	57 (26)	7 (3)	18 (8)	1 (<1)
Calcium	Baseline	217	27 (12)	1 (<1)	1 (<1)	4 (2)
	Any Post	220	59 (27)	25 (11)	2 (<1)	7 (3)
Glucose	Baseline	219	33 (15)	4 (2)	0	0
	Any Post	219	91 (42)	17 (8)	5 (2)	1 (<1)
Albumin	Baseline	220	9 (4)	3 (1)	0	0
	Any Post	219	30 (14)	15 (7)	1 (<1)	0
Total bilirubin	Baseline	222	5 (2)	0	0	0
	Any Post	219	46 (21)	18 (8)	3 (1)	0
AST	Baseline	221	45 (20)	5 (2)	1 (<1)	0
	Any Post	220	80 (36)	5 (2)	5 (2)	0
ALT	Baseline	222	36 (16)	5 (2)	0	0
	Any Post	220	86 (39)	19 (9)	4 (2)	0
Placebo+Paclitaxel, N=221						
Sodium	Baseline	217	12 (6)	1 (<1)	0	0
	Any Post	216	50 (23)	2 (<1)	5 (2)	1 (<1)
Potassium	Baseline	217	9 (4)	0	0	0
	Any Post	216	23 (11)	5 (2)	5 (2)	1 (<1)
Calcium	Baseline	216	17 (8)	1 (<1)	1 (<1)	2 (<1)
	Any Post	214	45 (21)	9 (4)	1 (<1)	5 (2)
Glucose	Baseline	219	39 (18)	3 (1)	2 (<1)	0
	Any Post	215	70 (33)	17 (8)	6 (3)	0
Albumin	Baseline	218	6 (3)	3 (1)	0	0
	Any Post	215	19 (9)	8 (4)	0	0
Total bilirubin	Baseline	221	8 (4)	1 (<1)	0	1 (<1)
	Any Post	215	18 (8)	6 (3)	5 (2)	2 (<1)
AST	Baseline	221	42 (19)	13 (6)	1 (<1)	0
	Any Post	215	72 (33)	12 (6)	10 (5)	1 (<1)
ALT	Baseline	221	30 (14)	8 (4)	0	0
	Any Post	215	88 (41)	16 (7)	2 (<1)	0

Supportive study EGF30001

Haematology

The mean values (and ranges) were similar between the 2 treatment groups. For each haematology assessment (haemoglobin, haematocrit, red blood cells, platelets, total WBC, neutrophils, granulocytes, lymphocytes, monocytes, eosinophils and basophils), the mean values remained relatively constant from screening to discontinuation. Neutrophils were the most frequently reported Grade 3 or 4 haematology assessment in both treatment groups post treatment. In the lapatinib+paclitaxel arm 18% had Grade 3 and 18% Grade 4 neutrophil counts, compared with 18% and 10%, respectively, in the placebo+paclitaxel arm.

Clinical chemistry

Grade 4 clinical chemistry assessments were infrequent in both treatment groups. Sodium was the most frequently reported Grade 3 or 4 clinical chemistry assessment in both treatment groups.

Note that Grade 3-4 clinical chemistry values include those that are both higher and lower than normal.

Table 63

Laboratory parameter	Time point	Lapatinib+paclitaxel		Placebo+paclitaxel	
Toxicity grade		All grades	Grade 3-4	All grades	Grade 3-4
Sodium	Screening	9%	< 1%	7%	0
	Max. post-screening	28%	6%	26%	4%
Potassium	Screening	9%	< 1%	5%	< 1%
	Max. post-screening	29%	5%	26%	4%

For hepatobiliary laboratory values, see Table 64.

Table64. Clinical chemistry parameters of maximum toxicity CTCAE grade 3 or 4 at any screening or post-screening visit (Safety population) (Cut-off date 25 August 2010), Study EGF30001

Parameter	Visit	n	Number (%) of subjects	
			Grade 3	Grade 4
Lapatinib 1500 mg plus Paclitaxel 175 mg/m² (N=293)				
Creatinine	Screen	288	0	0
	Any Post[1]	287	2 (<1)	0
BUN	Screen	111	0	0
	Any Post[1]	116	1 (<1)	0
Total bilirubin	Screen	286	0	0
	Any Post[1]	285	4 (1)	0
ALP	Screen	282	4 (1)	0
	Any Post[1]	285	7 (2)	0
AST	Screen	287	1 (<1)	0
	Any Post[1]	285	15 (5)	0
ALT	Screen	287	1 (<1)	0
	Any Post[1]	285	11 (4)	1 (<1)
Paclitaxel 175 mg/m² plus Placebo (N=286)				
Creatinine	Screen	283	0	0
	Any Post[1]	284	0	0
BUN	Screen	118	1 (<1)	0
	Any Post[1]	130	2 (2)	0
Total bilirubin	Screen	280	0	0
	Any Post[1]	284	6 (2)	0
ALP	Screen	278	1 (<1)	0
	Any Post[1]	283	9 (3)	1 (<1)
AST	Screen	280	0	0
	Any Post[1]	283	13 (5)	3 (1)
ALT	Screen	280	0	1 (<1)
	Any Post[1]	283	8 (3)	1 (<1)

- **Safety in special populations**

Pivotal study EGF104535

- **Intrinsic Factors**

Age, Race, and Gender

The following pre-specified subgroups of the Safety population of the Pivotal study EGF104535were analysed to assess the safety profile in key demographic factors: age (<65 years and ≥65 years), racial subgroups, and gender. The majority of subjects in this study were <65 years old (93%), Asian (86%), and female (99%).

Most White subjects were treated with the once every 3 weeks paclitaxel regimen in Study EGF30001, and most Asian subjects were treated with the once weekly regimen for 3 weeks in a 4-week cycle in Study EGF104535.

In studies with different monitoring practices, direct comparisons of rates across race are problematic. As such, the greater reporting of Grade 4 neutropenia seen in EGF104535 (39%) and in the Asian subset of the 4-study pool (58%) may be the result of weekly haematology lab testing, while the predominantly White population in Study EGF30001 with lower frequencies had haematology testing once per q3 weeks cycle. The important event of febrile neutropenia was low in all categories, although the Asian population did have the highest among these subgroups (6% in lapatinib+paclitaxel arm; 1% in placebo+paclitaxel arm).

Hepatobiliary events of low grades were more common in the Asian populations, regardless of lapatinib exposure, as might be anticipated given the high rates of chronic hepatitis observed in some of the regions in which EGF104535 was conducted. High grades of cardiac events and high grades of diarrhoea were similar across races. Although the numbers are relatively small, subjects ≥65 years did appear to have more frequent high-grade diarrhoea events, more frequent ventricular dysfunction events and a higher rate of discontinuation due to AEs than did subjects aged <65 years.

Hepatic Impairment

No data on the combination of lapatinib and paclitaxel in patients with hepatic impairment have been submitted. In summary, the following is known about lapatinib and paclitaxel in hepatic impairment:

Lapatinib is extensively metabolized, primarily by CYP3A present in the intestine and liver.

Moderate and severe hepatic impairment have been associated, respectively, with 56% and 85% increases in systemic exposure of lapatinib. In patients with severe hepatic impairment, a dose reduction to 750 mg daily is predicted to adjust systemic exposure to the normal range and should be considered. However, there is no clinical data at this dose in patients with severe hepatic impairment.

Furthermore, lapatinib inhibits CYP2C8 in vitro at clinically relevant concentrations. In vivo, co-administration of the CYP2C8 substrate paclitaxel with lapatinib was associated with a 23% increase in paclitaxel AUC.

According to the paclitaxel SmPC, paclitaxel when given to patients with hepatic impairment may increase the risk of toxicity, particularly Grade 3-4 myelosuppression. There is no data to recommend dosage alterations in patients with mild to moderate hepatic impairments, but paclitaxel is not recommended in patients with severely impaired hepatic function.

- **Extrinsic Factors**

Diet

Administration of lapatinib with food significantly increases bioavailability. Please refer to discussion in the Clinical pharmacology section.

2.5.1. Discussion and conclusion on clinical safety

In the pivotal study EGF104535, the duration of exposure to lapatinib/placebo was considerably longer in the lapatinib+paclitaxel arm compared with the placebo+paclitaxel arm; correspondingly higher

mean (45% higher) and median (49% higher) cumulative doses were observed, reflecting both effect and tolerability. The vast majority of patients received the intended dose. The daily exposure was 2-4% lower (median and mean) in the lapatinib arm, likely due to tolerability factors, which in this light appear small. Compliance for lapatinib/placebo was however clearly (15%) lower in the lapatinib arm, which could affect the treatment result in individual patients. The paclitaxel exposure was slightly lower in the lapatinib arm compared with the placebo arm. However, the percentage of patients receiving the intended 6 cycles or more was slightly higher in the lapatinib arm compared with the control arm.

In the pivotal study the frequency of discontinuation of lapatinib/placebo due to AEs as primary reason were practically the same in both treatment arms (6 and 7%, respectively), indicating tolerability of lapatinib. The frequency of investigator decisions for discontinuation of both lapatinib/placebo and paclitaxel was slightly higher in the lapatinib+paclitaxel arm, while the frequency of subject decisions for withdrawal were similar in both treatment arms. The fraction of patients discontinuing treatment due to disease progression was considerably lower in the lapatinib+paclitaxel compared with the placebo+paclitaxel arm, reflecting the treatment effect.

Furthermore, the percentage of patients discontinuing with an AE as (a contributing) cause were similar in the two treatment arms, 13 and 10%, respectively. The most common cause in the lapatinib+paclitaxel arm was neutropenia in 6 subjects (3%), plus leucopenia in 2 subjects, compared with no subjects discontinuing for this reason in the placebo+paclitaxel arm. More than one cause appears to be registered for some subjects, judging by the numbers and the "Any event numbers". It is therefore not possible to make an exact calculation on the difference in patient numbers discontinuing due to a certain group of AEs, since some items may have been reported together. Similar items cause discontinuation in both treatment arms, and all at low frequencies. Hepatobiliary related AEs appear as cause for discontinuation in both arms.

Dose interruptions and reductions occurred more frequently in the lapatinib+paclitaxel arm of the pivotal study, but had little effect on total exposure, as discussed above. The compliance with regard to lapatinib treatment was however clearly (15%) lower in the lapatinib arm, which could affect the treatment result in individual patients.

The overall incidence of AEs in the pivotal study EGF104535 was slightly higher in the lapatinib+paclitaxel arm compared with the placebo+paclitaxel arm (approximately 4% difference). The same was seen for treatment-related AEs (8% difference) and AEs leading to permanent discontinuation of study treatment (3% or 1% difference, depending on type of measurement). These differences are considered small.

The main increases in toxicity seen for the combination treatment of lapatinib+ paclitaxel compared with the toxicity from paclitaxel in the placebo+paclitaxel arm, were haematological, gastrointestinal, rash and nail changes.

Specifically, the haematological AEs all increased, most importantly neutropenia, which increased from 47 to 77% in the lapatinib arm compared with the placebo arm, including a relevant increase in grade 3-4 events. Febrile neutropenia also increased relevantly from <1 to 4%.

Also of importance, the gastrointestinal AEs all increased, in particular diarrhoea, which increased from 29 to 77%, including an increase in Grade 3 events from <1 to 20%. The median duration of diarrhoea was 6 days in the lapatinib+ paclitaxel arm. The Grade 3 diarrhoea occurring in 20% is considered very high. However, the discontinuation rate due to diarrhoea was low, < 1%, indicating that it was somehow manageable. It should be noted that Grade 3AEs generally refers to severe conditions. According to the definition of the CTCAE version 3.0 (used in the present study), Grade 3 diarrhoea includes (any of) the following: "Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with

ADL". The guidelines used to manage diarrhoea in the study appears to have been successful, particularly considering the, in this context, relatively low frequency of diarrhoea SAEs (5%). The MAH referred to their successful use of Diarrhoea management guidelines as an important factor, and stated that these are proposed to be included in the SmPC. Following responses to the CHMP questions the MAH has updated the SmPC with a suggestion for more detailed diarrhoea management recommendations.

Additionally, rash increased from 24 to 59%, but this was mainly grade 1-2, and nail disorders increased from 1 to11%, (all grade 1-2).

Cardiac side effects of lapatinib appear low in this setting. SAEs of increased ejection fraction were seen in 6 vs. 1% in the lapatinib+paclitaxel arm and placebo+paclitaxel arm, respectively. In the lapatinib+paclitaxel arm, 1 event was symptomatic (Grade 3), none of the events were fatal, 3 subjects discontinued study treatment, and the majority of events resolved without residual sequelae. There were also 3 patients with SAEs of Grade 1-2 left ventricular dysfunction in the lapatinib arm and none in the placebo arm. Cardiac events of high toxicity grade were rare (one in each arm), discontinuations and dose interruptions due to cardiac events were also uncommon, slightly higher in the lapatinib arm. LVEF changes were transient.

The hepatobiliary AEs (which included laboratory events) in the lapatinib+paclitaxel arm were mostly of low grade (87% of those afflicted had grade 1-2 events), and most resolved completely (>90%). No Hy's law cases were seen. Discontinuation due to hepatobiliary AEs occurred in 1 and 2 patients, respectively, in the two treatment arms. One must also consider that this is a population with 84% visceral disease, where a large proportion of patients with (progressing) liver metastases are included. Thus, the hepatobiliary consequences of lapatinib therapy in this setting appear minor. However, the co-administration of lapatinib and paclitaxel has not been studied in patients with hepatic impairment. Hepatic impairment causes increased exposure to lapatinib and increased risk for toxicity from paclitaxel. Since lapatinib also increases the exposure of paclitaxel, combination therapy could in theory further increase the risks in patients with hepatic impairment, however, data provided by the MAH in the responses to questions show that the pharmacokinetic interaction observed between lapatinib and paclitaxel may not be expected to be exaggerated by hepatic impairment.

The incidence of SAEs was higher in the lapatinib+paclitaxel arm (30%) compared with the placebo+paclitaxel arm (14%), mainly attributable to differences in neutropenia (16 vs. 5%) and other haematological SAEs, diarrhoea (5 vs. 0%), decreased ejection fraction (6 vs. 1%) and 3 cases of increased left ventricular ejection fraction grade 1-2. Judging by the similar discontinuation frequencies primarily due to AEs (6 and 7%) in the two treatment arms one may conclude that the relatively high incidence of SAEs in the lapatinib arm was clinically manageable.

A summary of the 10 most frequent SAEs from across the lapatinib clinical programme included among others the term febrile neutropenia. Based on the clinical relevance of SAEs, and the increased frequency when given in combination with paclitaxel, febrile neutropenia should be mentioned in section 4.8 of the SmPC, should this indication be approved.

Grade 3 - 4 neutrophil and WBC counts were very common, and considerably more common in the lapatinib+paclitaxel arm than in the placebo+paclitaxel arm. This is reflected in section 4.8 of the proposed SPC.

Due to the domination of single sub-groups of age, race and gender in the pivotal study, the impact of these factors on the results cannot be assessed. The co-variation of parameters such as paclitaxel regimen and monitoring routines with race further hampers any assessment. A higher incidence of hepatobiliary events in the Asian populations may be explained/affected by extrinsic factors

contributing to the high rates of chronic hepatitis observed in some of these regions. It is noted that hepatitis was not an exclusion criterion in the study.

Administration of food significantly alters lapatinib bioavailability. The consequences of differences in food culture between geographic regions on lapatinib and thereby also paclitaxel exposure is not known.

In the supportive study EGF30001, the mean duration of lapatinib therapy was 27 weeks, compared with 49 weeks in the pivotal study. Time on placebo was not given. In this study, the duration of paclitaxel therapy was numerically 2 weeks shorter in the lapatinib arm compared with the control arm, (17.5 vs. 19.6 weeks), unlike the pivotal study where the lapatinib treated patients also had longer exposure of paclitaxel. Between 11% (reported) and 18% (worst-case scenario including missing data as low compliers) of the patients received < 80% of the intended cumulative lapatinib dose. However, the median daily dose of lapatinib was 1500 mg, i.e. the intended dose. Whether or not this degree of compliance (>80% of the patients received >80% of the intended dose), should be considered as good can be discussed, and may further depend on how many of the patients with missing data (7%) that were non-compliant. It does point to the compliance problem that comes with oral therapy as opposed to the i.v. alternative of trastuzumab.

In Study EGF30001, the incidence of discontinuation due to AE was more than twice as high as in the in the lapatinib+paclitaxel arm (17%) compared with the placebo+paclitaxel arm (9%), and higher than the AE discontinuation rate in the pivotal study. This may partly reflect the fact that the q3weekly paclitaxel regimen in Study 30001 is more strenuous/toxic than the q1weekly regimen in the pivotal study and the added toxicity of lapatinib thereby harder to endure. As in the pivotal study, the discontinuations due to progression are lower in the lapatinib arm as a result of the treatment effect. The other causes for discontinuation were similar in the two treatment arms.

Four cases with hepatobiliary clinical chemistry values consistent with Hy's criteria for drug induced liver injury were seen in the lapatinib+paclitaxel arm, but none were considered definite Hy's cases by the MAH as each had some confounding features that could explain the rise in transaminases and bilirubin. In this context it should also be remembered that bilirubin could be elevated due to lapatinib inhibition of hepatic uptake by OATP1B1 or inhibition of excretion into bile by Pgp or BCRP, since these transporters are known in vitro to be inhibited by lapatinib. However, narratives were not provided for all 4 subjects.

Study EGF30001 appear to have a lower frequency of several important AEs compared with the pivotal study, but more severe outcomes including deaths related to febrile neutropenia (4 deaths) and cardiac events (2 deaths). The diarrhoea management guidelines developed during this study appear to be an important factor for the safe use of the combination (see previous comment on pivotal study). The overall incidence of SAEs was higher in the supportive Study EGF30001 (35 and 22% in the two treatment arms, respectively) compared with the pivotal study EGF104535 (30 vs.14%, respectively), despite that the main AEs were more frequent in the pivotal study. This could be due a combination of factors including e.g. the different paclitaxel backbone regimens and differences in study populations. Diarrhoea was less frequent than in the pivotal study, the median duration 4 days in the lapatinib+paclitaxel arm. Diarrhoea management guidelines were implemented during the course of study EGF30001, which were then implemented through-out EGF 104535, improving the handling of safety problems.

Overall, the safety data from the two supportive phase II studies EGF102580 and EGF105764, and phase I Study EGF10009 give an impression consistent with the Phase III studies, with GI events, rash and neutropenia as the main tolerability problems. Decreases in ejection fraction occur but appear manageable.

In conclusion, neutropenia and diarrhoea stand out as the most important tolerability and safety problems with the combination of lapatinib with paclitaxel in metastatic breast cancer. Rash and nail changes were increased, as expected. Cardiac and hepatobiliary events were mostly of low grade and appeared manageable. Despite that the incidence of AEs was slightly higher, and SAEs was considerably higher in the lapatinib+paclitaxel arm compared with the control arm, the proportion of patients discontinuing due to AEs were similar. It thus appears that the increased tolerability problems attributable to lapatinib are overall manageable; however, some safety issues as discussed above still require the MAH's attention and amendments of the SmPC.

2.6. Risk Management Plan

The MAH provided an updated RMP (version 11 dated 22 March 2011) to include information regarding the results from the pivotal phase III study EGF104535, supporting phase I combination study EGF10009, and supporting studies EGF102580, EGF105764, and EGF30001.

The MAH proposed an inclusion of neutropenia as an important identified risk based on increased frequency of neutropenia observed in the lapitinib-paclitaxel arm (neutropenia grade 4; 16% compared to 5% in the placebo+paclitaxel arm) and known interaction where lapitinib inhibit CYP2C8 and thereby increase the paclitaxel levels by over 20%. No additional pharmacovigilance activities were proposed and no additional risk minimization activity other than the SmPC wording.

This update is acceptable. The RMP should include the final SmPC wording.

2.7. User consultation

The Package Leaflet for Tyverb in combination with paclitaxel is based on the current Package Leaflet for Tyverb, which has proven readability in October 2006 during the review of the application for Tyverb MAA, thus the MAH argued that readability testing is not warranted.

The CHMP considered that the changes made to the PIL due to product specific information are indeed limited. Since the main issues of the package leaflet have already been tested, the CHMP agreed that no new user testing is considered necessary.

3. Benefit-Risk Assessment

Benefits

Beneficial effects

Two add-on studies have been submitted to support the efficacy of lapatinib in combination with paclitaxel in (first-line) metastatic breast cancer.

Overall, the results of the Pivotal study EGF104535 showed a HR of 0.64 (95% CI: 0.49, 0.82; p=0.0005). The difference in median OS was >7 months between treatment arms, despite second line therapy, including 67% of the patients in the placebo+paclitaxel arm receiving lapatinib monotherapy after disease progression. A routine GCP inspection of the pivotal study EGF104535 was conducted.

Uncertainty in the knowledge about the beneficial effects.

The present studies do not allow to conclude if the combination of paclitaxel and lapatinib is better or poorer than trastuzumab (Herceptin), which has a major bearing on being able to contextualise the benefit-risk assessment.

Furthermore, a number of factors and circumstances point in the direction of the results not being directly generalisable to a European population:

Differences are seen in baseline characteristics compared with what is normally seen in Western study populations including race, metastatic sites, and prior hormonal and anti-HER2 therapy, along with differences in post-progression therapy.

Patients with less prior therapy are likely to have a larger treatment effect, and differences in race may imply differences in e.g. pharmacokinetics, interactions, SNPs affecting the target receptor structure and affinity of binding to the pharmaceutical compound. The MAH's responses to questions have shown that differences exist between Western and Asian populations with regard to metabolic enzymes, and Japanese patients (and thereby possibly also Chinese patients) have a higher exposure to lapatinib than Western patients. SNPs in the *ERBB2* gene and HLA alleles with different allele frequencies in populations are also present, but their effect on efficacy is largely unknown.

A comparison of the present lapatinib studies and the relevant post-hoc HER2 IHC 3+ subgroup of the Herceptin registration study HO648g also showed a larger difference in response rate between the treatment arms (anti-HER2 agent+paclitaxel vs. placebo+paclitaxel) for trastuzumab (32%) compared with lapatinib (20 and 24%, pivotal and supportive study), despite the more heavily pretreated population. OS medians were very similar, however. A considerably higher response rate to the paclitaxel backbone therapy was seen in the lapatinib studies compared with the Herceptin trial. This could be partly be caused by the lapatinib study populations being less optimally pretreated. The differences seen in the study populations of the lapatinib and trastuzumab trials make a comparison across studies unreliable.

Furthermore, head-to-head comparisons of lapatinib vs. trastuzumab in the *neo-adjuvant* setting have shown inferior results for lapatinib in 3 out of 4 studies (Study EGF106903/Neo-ALTTO, Study LPT109096, and the GeparQuinto study), while similar pCR rates for lapatinib and trastuzumab were seen in the fourth study (LAP106988/CHERLOB). While not statistically significant in 2 of the studies, the trend is consistent. More importantly, following interim results on disease-free survival, the IDMC of the *adjuvant* ALTTO study recommended discontinuation of the lapatinib arm, and patients were instead to be offered trastuzumab. Therefore, there is a founded concern that lapatinib may be less efficacious than the licensed alternative.

Risks

Unfavourable effects

In the pivotal study, the incidence of any AEs was slightly higher, and SAEs was considerably higher in the lapatinib+paclitaxel arm compared with the placebo+paclitaxel arm. However, the proportion of patients discontinuing due to AEs were similar (6 vs. 7 % or 13 vs. 10%, depending on method of measurement). Haematological and gastrointestinal AEs were the most prominent AEs and appeared in considerably higher frequency in the lapatinib+ paclitaxel arm compared with the placebo+paclitaxel arm, including grade ≥3 events. Thus 77% vs. 47% experienced neutropenia and 77% vs. 29% had diarrhoea, respectively. Grade 3 diarrhoea was observed in 20% of patients in the lapatinib+paclitaxel arm compared with <1% in the control arm. This is considered a very high frequency, and would appear an important tolerability problem; however, the discontinuation rate due to diarrhoea was low,

< 1%, indicating that it was somehow manageable. The median duration of diarrhoea was 6 days in the lapatinib+ paclitaxel arm vs. 3 days in the control arm – it thus appears to have been a transient problem in most cases. The MAH has now included relevant diarrhoea management guidelines similar to those used during the study in the SmPC. Another tolerability problem is the frequently occurring rash with 59% in the paclitaxel+lapatinib arm compared with 24% in the paclitaxel+placebo arm of Study EGF104535.

The clinically important event of febrile neutropenia was 4% vs. <1% in the lapatinib+paclitaxel and placebo+paclitaxel arms, respectively; the same frequency was seen in the supportive study EGF30001. Discontinuation due to neutropenia occurred in 3 vs. 0% in the pivotal study, and 1 vs. <1% in the supportive study, which is considered low. No neutropenic deaths occurred in the pivotal study, but in the supportive study 4 deaths (i.e. 1.4% of patients in the lapatinib+paclitaxel arm) were associated with febrile or grade 4 neutropenia. Three of these 4 deaths came early in the study before implementation of diarrhoea management guidelines. Febrile neutropenia is currently not mentioned as an adverse reaction in the SmPC, but should be included in case of approval of the proposed indication due to its clinical relevance and since being a consequence of the combination therapy of lapatinib and paclitaxel.

Cardiac events were few and mostly transient in the Pivotal study; even less common in the supportive study, but 2 cardiac deaths were seen in the lapatinib arm of the supportive study.

While the number of hepatobiliary events (including laboratory abnormalities) were higher in the lapatinib+paclitaxel arm of the pivotal study, there was no difference in the number of patients experiencing hepatobiliary adverse events in the lapatinib+paclitaxel arm compared with the placebo+paclitaxel arm; most events were grade 1-2; and discontinuation due to hepatobiliary AEs occurred in 1 and 2 patients, respectively, in the two treatment arms. In the Supportive study, 4 patients in the lapatinib+paclitaxel arm had hepatobiliary clinical chemistry values consistent with Hy's criteria for drug induced liver injury, but other explaining factors were present. Thus in this setting, hepatic toxicity appears manageable.

Uncertainty in the knowledge about the unfavourable effects

The susceptibility to certain AEs may theoretically depend on many factors, including some of those already mentioned with regard to effect, such as race (implying e.g. pharmacokinetic and genetic differences), prior therapy (e.g. cardiac events in patients having received adjuvant therapy with trastuzumab and anthracycline compared with patients without prior cardiotoxic therapy), life style factors (adding to the problem or coping). The differences between populations discussed with regard to effect are thus of concern also for the safety evaluation. The MAH's responses to the CHMP questions have shown that SNPs associated with lapatinib cardiotoxicity is more frequent in White compared with Asian populations, as are certain HLA alleles associated with lapatinib associated ALT elevations. While the overall impact of these factors is difficult to assess, they are at least indications that important population differences may exist and add to the uncertainty of unfavourable effects, although the lower mean lapatinib exposure in White populations compared with Japanese (and possibly other Asian populations) could in theory imply an overall lower level of AEs in a European population.

In the pivotal study the overall compliance for lapatinib/placebo was 15% lower in the lapatinib arm compared with the placebo arm. It is uncertain how a European population would react to the high frequency of diarrhoea in terms of compliance, and the implications thereof for the efficacy of treatment.

Benefit-risk balance

Importance of favourable and unfavourable effects

The treatment effect observed in the pivotal study of 7 months' improved overall survival is clinically relevant in the population where it was performed, but the relevance of these results to a European population has not been established.

The percentage of patients discontinuing due to AEs were similar which gives the impression that the increased tolerability problems attributable to lapatinib are manageable. The large proportion (20%) of patients in the lapatinib arm experiencing grade 3 diarrhoea would however appear to be a great disadvantage in relation to the available treatment option trastuzumab. A high frequency of rash (59%) also affects the overall tolerability of the treatment.

Benefit-risk balance

The generalisability of the results to the EU population is not established. The lack of an active-controlled trial in the applied indication hampers the proper assessment of the benefit-risk balance. Therefore the benefit-risk assessment cannot be adequately assessed.

Overall conclusion

The benefit-risk balance of lapatinib in combination with paclitaxel in metastatic breast cancer in a European population remains negative.