London, 18 February 2010
Doc. Ref No.: EMA/125079/2010

ASSESSMENT REPORT
FOR
Tyverb

International non-proprietary name/Common name:
lapatinib

Procedure No. EMA/H/C/795/II/0004

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 74 18 86 13
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1 SCIENTIFIC DISCUSSION

1.1 Introduction

Lapatinib (Tyverb) is an orally-administered, small molecule, reversible inhibitor of the intracellular tyrosine kinase domains of Epidermal Growth Factor Receptor (EGFR) and of Human Epidermal Receptor Type 2 (HER2) or ErbB2. Lapatinib is a member of the 4-anilinoquinazoline class of kinase inhibitors. Members of this class of molecules have been shown to bind to the ATP binding site of protein kinases and compete with the ATP substrate. This blocks receptor phosphorylation and activation, preventing subsequent downstream signalling events. The rationale for lapatinib use as an anticancer entity is that the blockade of the tyrosine kinase activity of ErbB1 or ErbB2 is expected to block the transforming activity that results from overexpression of these receptors.

In June 2008, lapatinib was granted a conditional Marketing Authorisation (MA) in the EU for combination with capecitabine in the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

The recommended dosage for the approved indication is 1250 mg lapatinib daily, continuously, in combination with capecitabine 2000 mg/m2/day taken in 2 doses 12 hours apart on days 1-14 in a 21-day cycle.

In this application, the Marketing Authorisation Holder (MAH) initially proposed to extend the indication as follows:

> *"Tyverb in combination with an aromatase inhibitor is indicated for the treatment of patients with hormone receptor-positive metastatic breast cancer which overexpresses the ErbB2 (HER2) receptor."*

The MAH proposed to amend SPC sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 accordingly. Minor editorial changes were also made to the SPC. Consequently, the MAH also applied for an additional pack-size of 84 tablets reflecting the proposed daily dose for this indication. SPC section 6.5, labelling and section 6 of the PL have been updated in this respect. Furthermore, the Package Leaflet has been updated in line with the SPC revisions. Annex II has been revised to reflect the latest approved RMP version.

This variation application for lapatinib is based on the results from two clinical studies, one pivotal Phase III study and a supportive Phase I study, in both the medicinal product was combined with an aromatase inhibitor, letrozole.

The daily dose of lapatinib for the proposed new indication in combination with an aromatase inhibitor is 1500 mg (i.e., six 250 mg tablets), in contrast to the currently authorised indication of lapatinib (in combination with capecitabine) for which it is 1250 mg. There are currently three approved aromatase inhibitors, letrozole, anastrozole and exemestane, which work by inhibiting oestrogen biosynthesis.

In addition, the dosing schedule proposed for the new indication (i.e., six 250 mg tablets/day) initially warranted from the MAH point of view the introduction of two new pack sizes (containing 84 and 168 tablets in total), which will provide patients with exactly 14-days and 28-days supply, respectively. The respective changes related to this additional pack size were part of this Type II variation application. However, during the procedure the MAH revised this request for only an additional pack size of 84 tablets. Consequently regarding the additional pack size a change to SPC section 6.5 was suggested and initially a new separate Patient Information leaflet (PIL) for the Tyverb plus aromatase inhibitor indication has been proposed by the MAH for inclusion in the pack.

During the Type II variation procedure the MAH revised its initial position and decided not to pursue with separate package leaflets for lapatinib (5 tablets/day) / with capecitabine and lapatinib (6 tablets/day) / with an aromatase inhibitor.

Requests for Supplementary Information were adopted during the July 2009 and October 2009 CHMP meetings.

1.2 Quality aspects

The dosing schedule proposed for the new indication (i.e., six 250 mg tablets/day) warranted in view of the MAH the introduction of two new pack sizes (containing 84 and 168 tablets in total), which will provide patients with exactly 14-days and 28-days supply, respectively. However, during the procedure the MAH revised this request for only an additional pack size of 84 tablets.

No new quality data were provided in this variation application. The qualitative and quantitative formula remains the same. The container/closure contact materials and the size of the blister pockets remain unchanged, and only the number of blister pockets/strip has increased. Therefore, the MAH considered that the existing ongoing stability data support the approved drug substance retest date and drug product shelf life, and that no additional stability data are required.

Section 6.5 of the SPC as well as the Labelling has been updated to include the new pack size.

In general, the CHMP agreed to the MAH's request to introduce only one new pack size of 84 tablets and considered the proposed changes to the Product Information acceptable.

1.3 Nonclinical aspects

With this application, the MAH has submitted a nonclinical Overview discussing the rationale for the new indication and relevant issues on pharmacology, pharmacokinetics and toxicology mainly based on data from the original marketing authorisation application. One new pharmacology study (non-GLP) and a recently completed *in vitro* haemolytic potential study (conducted according to GLP) have been included in the submission and are discussed below.

Nonclinical studies with the combination of lapatinib with aromatase inhibitors were not conducted.

1.3.1 Pharmacology

The pharmacological rationale for the combined use of lapatinib with aromatase inhibitors is based on the observation that, in addition to its ability to down-regulate the AKT pathway and up-regulate the FOXO3A subpathway, which correlates with its efficacy, lapatinib induces ESR1 and PGR expression in breast cancer cell lines which express moderate basal levels of these receptors. This effect highlights a receptor cross-talk, where the AKT pathway would be down regulating the hormone-related pathways. By down-regulating the AKT pathway, the hormone-related pathways would therefore be expected to be up-regulated as a result of lapatinib action, resulting in increased sensitivity to anti-hormonal therapy. Genes involved in cell cycle control, glycolysis and fatty acid metabolism are also differentially affected by lapatinib.

Primary Pharmacology supportive of the new indication
The study "Delineation of Molecular Mechanisms of sensitivity to GW572016F in Breast Cancer Cell Lines using Global Gene Expression Profiles" intended to provide the proof of concept related to the proposed combined therapy of lapatinib with letrozole, by studying the cascade components of lapatinib mechanism of action, including the effect of lapatinib on the expression of estrogen (ER) and progestagen (PGR) receptors in human breast cancer cell lines responsive and low responsive to lapatinib.

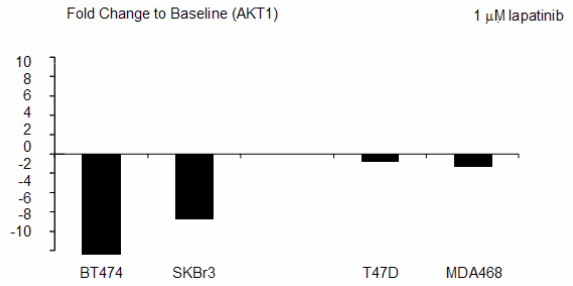
Phosphoprotein and microarray analyses were used to carry out targeted pathway studies of phosphorylation and gene expression changes in human breast cancer cell lines in the presence or absence of GW572016F.

Studies were performed in four breast cancer cell lines, BT474 and SKBr3, which are lapatinib responsive, and MDA-MB-468 and T47D, which are lapatinib non-responsive.

Results

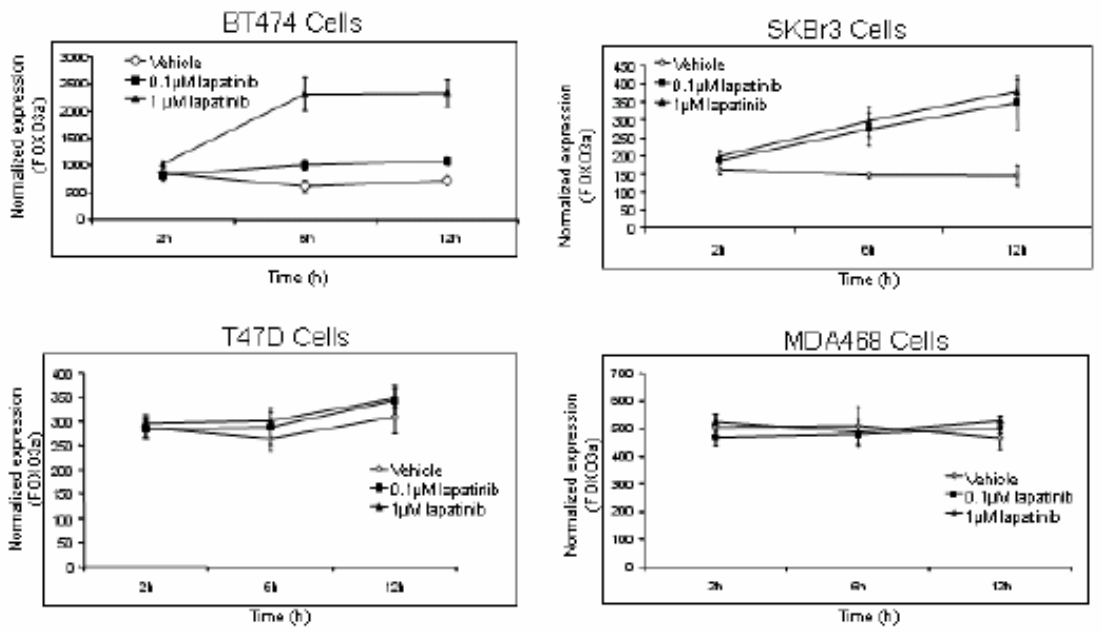
Responsive cell lines, BT474 and SKBr3
These cells constitutively over-express ErbB2 and demonstrated an IC50 for lapatinib of 25 or 32 nM, respectively. ErB2 over-expression was demonstrated in the cell lines.

- Both cell lines exhibited strong differential effects on multiple genes in the AKT pathway. After 12 h exposure to 1.0 µM lapatinib, AKT1, MAPK9, HSPCA, RAK1 and CCND1 transcripts were down-regulated 7 to 25-fold in responsive BT474 and SKBr3 cells. In the figure below, is illustrated the effect obtained on AKT1 expression, in all cell lines used. Only in ErB2 expressing cells the AKT1 was up-regulated by lapatinib.



Expression of AKT1 following treatment with GW572016F at 1µM for 12 hours in BT474, SKBr3, T47D and MDA468 cells. Y-axis represents a pair-wise fold change of AKT1 expression upon treatment with GW572016F compared to baseline untreated cells at 12h

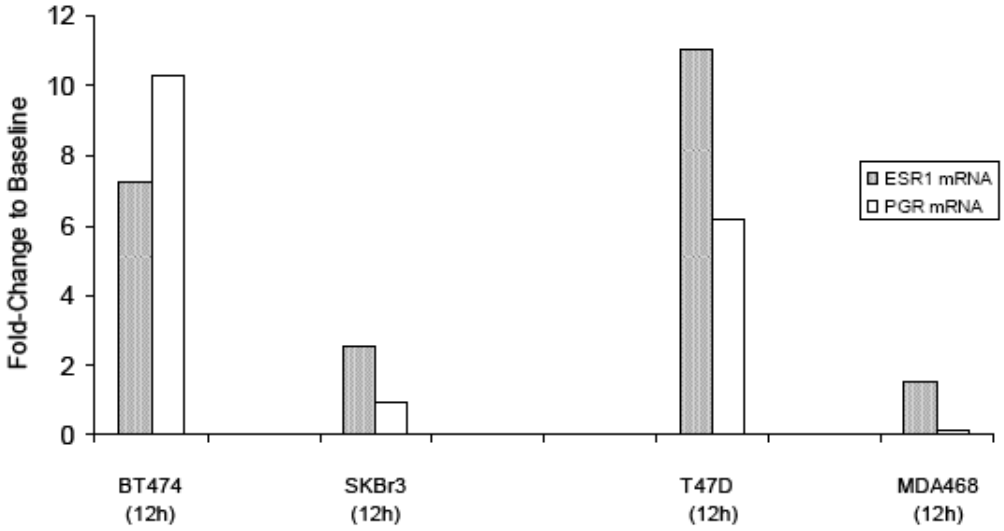
- The proapoptotic gene FOXO3A, which is negatively regulated by AKT, was up-regulated 7-and 25-fold in SKBr3 and BT474 cells, respectively.



- Phosphorylated Akt and Akt-mediated phosphorylation of FOXO3A also decreased in responsive breast cancer cell lines exposed to lapatinib.
- Gene expression profiling also revealed that lapatinib stimulates expression of the estrogen and progesterone receptors and modulates expression of genes involved in cell cycle control, glycolysis and fatty acid metabolism.

Nonresponsive cell lines MDA-MB-468 and T47D

- These cells express a low basal level of ErbB2 and demonstrate IC50 values in the µM range.
- In contrast to the observed in responsive cells, lapatinib weakly down-regulated the AKT pathway (less than 5-fold down-regulation of most genes in the pathway).
- In BT474 and T47D cells, which express moderate basal levels of the estrogen and progesterone receptors, 1.0 µM lapatinib induced expression 7- to 11-fold.



Effect of GW572016F treatment on expression of ESR1 and PGR. Y-axis represents a pair-wise fold-change analysis relative to untreated control cells at the 12h time point for the 1μM dose of GW572016F. A two-fold change to baseline is the minimum fold-change value that is statistically significant.

Discussion

The CHMP commented that the study results are not totally consentaneous with the theory developed by the MAH as a basis of the association of lapatinib with letrozole or other aromatase inhibitor. Indeed, while in BT474 cells, both oestrogen and progestagen receptors showed increased expression as a consequence of lapatinib treatment, in SKBr3 cells, which are also ErB2 expressing cells, only a modest increase in oestrogen receptor was observed without change in progestagen receptor. On the other hand, in T47D cells, which express a low basal level of ErB2, and are low responders to lapatinib, considerable over-expression of both receptors was induced by lapatinib. Therefore, if these *in vitro* results can be applied to the i*n vivo* situation, it would be expected that while in a tumour based on BT474-like cells it would make sense to associate lapatinib with aromatase inhibitor treatments, such might not be the case for a tumour based on SKBr3-like cells. In addition, while lapatinib would not seem appropriate to treat a T47D-like cell based tumour, it still was able to promote a high expression of oestrogen and progestagen receptors. A lack of understanding on the mechanism for these "inconsistencies" has been recognised by the MAH.

In the response to the RSI, the MAH has provided an adequate clarification. A stimulatory effect on ER and PGF is dependent on a basal expression of these genes, and may be observed also in cell lines with a low expression of ERbB2 and a low response to lapatinib. It is agreed that a benefit from the combination of lapatinib and letrozole is only clearly to be expected in ErbB2-positive hormone-receptor positive breast cancer.

1.3.2 Pharmacokinetics

No new data on pharmacokinetics have been submitted with this variation application. The nonclinical Overview presented a discussion of the potential for drug interactions between lapatinib and the approved aromatase inhibitors. The analysis performed by the MAH suggested that there may be a low potential for pharmacokinetic interactions between lapatinib and the aromatase inhibitors addressed, including letrozole. For further evaluation please refer to the section clinical pharmacology.

1.3.3 Toxicology

Lapatinib and the three currently approved aromatase inhibitors, letrozole, anastrozole and exemestane, have been well studied individually both clinically and toxicologically. No nonclinical studies were conducted with the combination of lapatinib with any of the marketed aromatase inhibitors. The principal findings in repeat dose toxicity studies with lapatinib and aromatase inhibitors

are attributed to exaggerated pharmacology. These include epithelial effects with lapatinib, and effects on the adrenals and reproductive organs (atrophy and/or hyperplasia) with aromatase inhibitors. The effects on reproductive organs are probably due to inhibition of estrogen synthesis due to aromatase inhibition and the resulting lack of negative feedback on the pituitary.

Hepatic and renal effects have been seen with both lapatinib and some aromatase inhibitors. The hepatotoxicity of lapatinib has been raised already from the clinical use. The hepatocellular hypertrophy seen in rats with aromatase inhibitors is most probably a result of enzyme induction and the renal tubular changes may relate to interference with steroid synthesis. Hepatic and renal function will need to be routinely monitored in the clinic, and therefore no additional nonclinical studies are considered necessary to investigate possible interactions with the combination(s).

The impurity specifications for the drug product and drug substance have not altered since the initial application for lapatinib. However, the indicated maximum dose of the compound has increased from 1250 mg to 1500 mg. As such, a re-assessment of the impurity profile has been undertaken. All specified impurities remain qualified. 4-(3-fluorobenzyloxy)-3-chloroaniline (GW397339), a starting material in the synthesis of lapatinib, has been shown to be genotoxic both *in vitro* and *in vivo*. GW397339 is present in lapatinib drug substance at levels resulting in exposures greater than the current guideline Threshold of Toxicological Concern (TTC) for genotoxic impurities (1.5 μg/day/person). At the current specification limit for this impurity (≤0.0004%), the increased recommended lapatinib dose of 1500 mg/day would result in a maximum daily GW397339 dose of 6 μg/day; 0.12 μg/kg to a 50 kg patient.

In vitro haemolytic potential in Rat, Dog and Human Peripheral Blood

The study was conducted as a support of intravenous administration of different solutions of lapatinib. Rat, dog and human blood were tested to evaluate the potential for haemolysis.

Lapatinib showed no potential for haemolysis in dog and human blood. Mild haemolysis was seen in rat blood, but only when administered with 30% (w/v) captisol in 25 mM citrate, approximately pH 5.0. This vehicle also demonstrated haemolysis in the absence of lapatinib. Therefore, lapatinib itself demonstrated no haemolytic potential in any species tested. In all species studied, treatment of blood samples with the positive control material saponin and water induced substantial haemolysis.

Mild haemolysis was evident in rat blood for formulations of lapatinib up to 1.0mg/mL in 30% (w/v) Captisol in 25mM Citrate, approximately pH 5.0 (up to 9.7%) and with the vehicle alone (13.3%). The test was therefore deemed positive for this vehicle in rats.

Minimal or no haemolysis was evident in human blood for formulations of lapatinib of up to 1.0 mg/mL in 30% (w/v) Captisol in 25mM Citrate, approximately pH 5.0, or in rat, dog or human blood for formulations of GW572016 in 10% (w/v) aqueous Captisol at 1 mg/mL or with either vehicle alone. The test was therefore deemed negative in dogs and humans for all formulations and vehicles tested, and in rats for formulations of lapatinib in 10% (w/v) aqueous Captisol or with the vehicle alone. The test was deemed positive in rats for all formulations in 30% (w/v) Captisol in 25mM Citrate approximately pH 5.0 (up to 9.7%) and with the vehicle alone (13.3%).

1.3.4 Ecotoxicity/environmental risk assessment

Lapatinib 250 mg tablets were approved in EU for use in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 (ErbB2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

The MAH proposed with the current submission to extend the indication of lapatinib tablets 250 mg to include its use in combination with an aromatase inhibitor for the treatment of patients with hormone receptor-positive metastatic breast cancer which overexpresses the HER2 (ErbB2) receptor. The incidence of patients with hormone receptor-positive breast cancer whose tumours overexpress the HER2 (ErbB2) receptor is significantly higher than the incidence of the currently approved indication. Thus, the proposed new indication represents a significant increase in the extent of lapatinib use and a

further assessment of the environmental risk posed by its use is therefore required according to the CHMP ERA guidance [EMEA/CHMP/SWP/4447/00].

A full Environmental Risk Assessment (ERA) undertaken for lapatinib was previously submitted and reviewed as a part of the original marketing authorisation application. The original ERA has been reviewed and as a consequence of this assessment the MAH has agreed to perform a number of additional studies: OECD305: Bioconcentration study, OECD305: Bioconcentration study, OECD210: Early life stage test on fish, OECD 216: Nitrogen transformation test, OECD 307: Aerobic and anaerobic transformation in soil, OECD 308: Aerobic and anaerobic transformation in aquatic sediment systems, OECD208: Terrestrial plants growth test, OECD 218: Sediment water chironomus riparius toxicity test, ISO 11267: Collembola, reproduction test. These data have been included into a new ERA, which was submitted in response to the Follow-Up Measure FUM005 in May 2009. This FUM has been assessed and the CHMP considered the FUM to be fulfilled. In the assessment of this FUM the CHMP concluded that the ERA is supporting also this new proposed indication.

1.3.5 Conclusion on Nonclinical Aspects

The main nonclinical aspects of lapatinib have been previously evaluated in the context of the original marketing authorisation application, including post approval studies submitted. Only two (*in vitro*) additional studies were submitted as a support of the current extension of indication, one pharmacology study and one toxicology study. The pharmacology study has been intended to provide the plausibility for the proposed combined use of lapatinib with aromatase inhibitors. While the impact of lapatinib on different cellular cascades involved in cell division could be shown (e.g. AKT, FOX3) as up-regulation or-down regulation, with different profile in ErB2 expressing and low expressing cells, a lower consistency was observed in relation to the effect on oestrogen and progestagen receptor expression. Indeed, a relevant induction of both receptors expression could be observed only in one of the two human breast cancer cell lines responsive to lapatinib (high ErB2 expression) while it was also observed in one of the two poor lapatinib responsive cell lines (low ErB2 expression). In the response to the RSI, the MAH provided an adequate clarification. A stimulatory effect on ER and PGF is dependent on a basal expression of these genes, and may be observed also in cell lines with a low expression of ErbB2 and a low response to lapatinib. It is agreed that a benefit from the combination of lapatinib and letrozole is only clearly to be expected in ErbB2-positive hormone-receptor positive breast cancer.

The potential for pharmacokinetic interactions between lapatinib and aromatase inhibitors has been identified as low. Nonclinical studies were not conducted to address this potential and it is expected that further information will be generated in the clinical setting.

One additional toxicology study addressing the haemolytic profile of different lapatinib solutions to be used intravenously was also submitted. No relevant concern was raised from the outcome with the different solutions in relation to human blood.

The previously reported toxicology package for lapatinib is acceptable for this new indication and the higher dose. The absence of combination pharmacology or toxicology studies with the combination of lapatinib and aromatase inhibitor is sufficiently justified. For the genotoxic impurity GW397339 it was stated in the CHMP AR for the first indication that the level above TTC was acceptable, but that this may not be the case if lapatinib is developed for a more benign indication. For the indication now applied for, exceeding TTC remains acceptable. The potential for toxicological interactions of lapatinib and aromatase inhibitors was not studied. In view of the existing clinical experience with both components, potential interactions will be addressed in the clinical setting and nonclinical studies are not considered needed. This applies also to the potential for hepatotoxicity by both types of medicinal products which will demand clinical monitoring.

In conclusion, no additional nonclinical studies are considered necessary to be conducted as a support of the combined use of lapatinib with aromatase inhibitors in the indication proposed, and, from a nonclinical perspective, there are no objections to the use of the proposed combination.

1.4 Clinical aspects

The MAH stated that the clinical trials submitted in the application were conducted according to GCP.

The clinical program supporting the present application conforms to the conditions previewed in CPMP/EWP/2330/99 for applications with one pivotal trial.
The basis for this application is the clinical study EGF30008 and supportive data are provided from a Phase I dose-finding study of letrozole plus lapatinib (EGF10030).

Study	Design	No of centres	Posology	Subjects	Mean age	Diagnosis Incl criteria	Duration	Primary endpoint
EGF 10030	**Phase 1 open label** **3 cohorts**	**3**	**Lapatinib 1250 mg/ letrozole 2,5 mg** **Lapatinib 1500 mg/ Letrozole 2,5 mg**	**39** **12 OTR** **7 OTR 2** **20 PK**	**56.1 (31-73)**	**Postmenopausal women mainly breast (n=18) and ovarian cancer (n=16)**	**11.9 -18.8, weeks**	**Optimally tolerated regimen and safety, tolerability, PK**
EGF 30008	**Phase 3 double blind**	**212**	**Lapatinib 1500 mg/ Letrozole 2,5 mg** **Letrozole 2,5 mg**	**642 combination** **644 monotherapy** **219 HER2 positive** **111 Combination** **108 monotherapy**	**63.1 (31-95)**	**Postmenopausal women. Hormone receptor positive. First-line treatment**	**Until progression**	**Investigator assessed PFS in HER2 positive population**

OTR=optimally tolerated regimen, PK=pharmacokinetics

1.4.1 Clinical pharmacology

There were no new pharmacokinetic studies provided with the current application, but the MAH discussed potential interactions between lapatinib and aromatase inhibitors based on previously submitted studies and literature data.

Lapatinib is eliminated mainly through metabolism by CYP3A4/5 with a minor contribution from CYP2C19 and CYP2C8. The potent CYP3A4 inhibitor ketokonazole increased lapatinib AUC by 3.6-fold.

In *in vitro* studies with lapatinib, the most significant CYP inhibition observed was with CYP2C8 ($K_i = 0.6$ μM) and CYP3A4 ($K_i = 4$ μM). Clinically, lapatinib has a weak interaction with the CYP2C8 substrate paclitaxel (23% increase in paclitaxel AUC) and a moderate interaction with the sensitive CYP3A4 substrate oral midazolam (45% increase in midazolam AUC) .Therefore, the extent of an interaction through lapatinib inhibiting CYP metabolism of AIs would not be expected to exceed the clinical interaction with midazolam.

Lapatinib is an inhibitor of the transporters organic anion transporter polypeptide 1B1 (OATP1B1), P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). The role of these transporters in the disposition of aromatase inhibitors has not been reported.

Letrozole
The pharmacokinetic interaction between lapatinib and letrozole was evaluated in a sub-study of the EGF 100030 dose-escalation study. The interaction sub-study has already been discussed in the assessment report for the renewal procedure EMEA/H/C/795/R/02.

In this study, once the optimally tolerated regimen (OTR) for the combination of lapatinib and letrozole had been determined, 19 additional subjects were enrolled to profile the pharmacokinetics of lapatinib alone, letrozole alone, and lapatinib in combination with letrozole at the OTR doses, i.e. 1500 mg lapatinib and 2.5 mg letrozole. Although the number of subjects was relatively small, the

study design appears appropriate. Letrozole and lapatinib, respectively, was dosed to steady state before their effect on the other substance was evaluated. There were no statistically significant effects of either letrozole on lapatinib or of lapatinib on letrozole in this study. The AUC ratio (90% CI) for letrozole was 0.94 (0.79-1.11) and for lapatinib 0.84 (0.63-1.13). The MAH's conclusion that there is no clinically relevant pharmacokinetic interaction between letrozole and lapatinib at the intended combination dosage is endorsed.

Anastrozole
Anastrozole has been reported to moderately inhibit CYP3A4 (Ki = 10 μM) and CYP2C8 *in vitro*. However, the clinical concentration of anastrozole (0.3 μM) is approximately 30-fold lower than the inhibitory potency and unlikely to cause a significant pharmacokinetic interaction through either CYP3A4 or CYP2C8.

Anastrozole is eliminated mainly by hepatic metabolism, partly via glucuronidation. Approximately 10% of the total clearance of anastrozole occurs by renal elimination. Lapatinib does not inhibit UGT metabolism, therefore the clearance of anastrozole through glucuronidation should remain unaffected. The effect lapatinib would have on the N-dealkylation and hydroxylation pathways are unknown since the specific enzymes involved in that pathway have not been reported. The role that the transporters OATP1B1, Pgp and BCRP may have in the disposition of anastrozole has not been reported.

Examestane
Exemestane does not inhibit any of the major CYP enzymes (CYP1A2, 2C9, 2D6, 2E1, and 3A4) *in vitro* and is unlikely to alter the pharmacokinetics of lapatinib through CYP inhibition.

Exemestane is highly lipophilic and absorption or distribution is not limited by permeability, which suggests an interaction through transporters may be limited. Exemestane is eliminated mainly by hepatic metabolism via CYP3A4 and aldoketoreductases. Clinically, ketoconazole shows no significant effect on exemestane pharmacokinetics, and consequently the effect lapatinib would have on this pathway of elimination should be negligible. The effect of lapatinib on aldoketoreductases has not been characterised.

Conclusion
The MAH has carefully discussed the risk for pharmacokinetic interactions between lapatinib and the currently approved aromatase inhibitors based on their respective *in vitro* interaction potential and the elimination pathways. The lack of interaction with letrozole has been confirmed in a clinical study. Based on the elimination pathways and the lack of reports on significant impact of transporters in the disposition of anastrozole, there is no obvious reason to expect a pharmacokinetic interaction with anastrozole or examestane.

1.4.2 Clinical Efficacy

1.4.2.1 Pivotal study EGF 30008

The pivotal study EGF 30008 was initially planned to evaluate the combination letrozole/lapatinib vs. letrozole in a hormone receptor positive (HR+) postmenopausal breast cancer population with metastatic breast cancer. Due to external data on lapatinib's mode of action and efficacy, i.e. that lapatinib mainly exerted its effect in HER2 positive patients, the population was expanded to ensure the size of this subpopulation. The recruitment of HER2 positive subjects was stable throughout the study.
Study EGF30008 was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase III study comparing lapatinib and letrozole versus letrozole in subjects with estrogen/progesterone receptor-positive advanced or metastatic breast cancer. This trial was conducted at 212 sites in 29 countries in 5 regions (North America, Latin America, Western Europe, Eastern Europe and Asia Pacific) including 12 EU member countries, and enrolled 1286 subjects. The majority of the patients (57%) were recruited from Western and Eastern Europe.

Methods

The inclusion criteria defined a typical population of postmenopausal women with metastatic breast cancer, in good performance status and good cardiac condition, without age restriction. The main inclusion and exclusion criteria for the study participants are listed below:

Main inclusion criteria:
- Post-menopausal women.
- Invasive breast cancer with Stage IV disease (locally advanced was allowed until amendment 3)
- Measurable or non-measurable disease per RECIST.
- ER positive and/or PgR positive tumours (any assay; primary or secondary tumours)
- Subjects had archived tumour tissue available to compare tumour response with intra-tumoural expression of EGFR and HER2.
- Adjuvant therapy with an aromatase inhibitor was allowed; however, must have ended more than 1 year prior start of study therapy.
- Adjuvant therapy with trastuzumab was allowed; however, must have ended more than 1 year prior (>12 months) to the start of study therapy.
- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram (ECHO) (or multi-gated acquisition [MUGA] scan.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Main exclusion criteria:
- Received prior chemotherapy, endocrine therapy, immunotherapy, biologic therapy or anti-EGFR/HER2 therapy for advanced or metastatic disease.
- Bisphosphonate therapy for bone metastases was allowed; however, treatment must have been initiated prior to the first dose of study therapy.

Treatment

The treatment groups in this study were either 2.5 mg letrozole and 1500 mg lapatinib or 2.5 mg letrozole and placebo on a daily basis. Lapatinib/placebo was provided by the MAH and letrozole from commercial stock and reimbursed by MAH except in the US and partly in Russia where the MAH provided letrozole.

One dose reduction and dose delay for up to 14 days was allowed in the lapatinib arm. No dose reductions and only 3 days delay were allowed for letrozole.

Objectives

The study was initially planned to include 760 patients in order to compare letrozole and lapatinib to letrozole and placebo in the ITT population. During the study, external data emerged that lapatinib mainly exerted its effect in HER2 positive population. According to amendment 3 the population was then expanded to 1280 patients (October 2005). In amendment 4 (October 2007, after subject recruitment ended) the populations of interest were decided to be the ITT population and the HER2 positive population. Furthermore from this amendment the HER2-positive population was the primary population of interest. The planned analyses were included in the RAP**,** dated 30 May 2008. The blinding was kept until 10 October 2008.

The primary objective was to evaluate and compare PFS (as assessed by the investigator) in subjects with HER2-positive advanced or metastatic breast cancer. The secondary objectives (all based on investigator assessment apart from OS) were as follows:

- To evaluate and compare PFS in the ITT population.
- To evaluate and compare the two treatment groups with respect to the following:
  - Overall survival (OS)
  - Overall response rate (ORR) [complete response (CR) and partial response(PR)]
  - Clinical benefit response rate (CBR) (confirmed CR or PR or stable disease (SD) for at least 6 months)
  - Time to response
  - Duration of response
  - Time to progression (TTP)
  - Incidence of brain metastases

- To determine the qualitative and quantitative toxicities associated with oral lapatinib when administered with letrozole.
- To evaluate and compare the two treatment groups with respect to change in quality of life (QOL) status, the change of QOL relative to baseline, and quality adjusted survival.
- To compare and correlate tumour response rates following lapatinib and letrozole therapy, with respect to baseline and on treatment serum concentrations of EGFR and HER2. Potentially, proteomic analysis was to be performed to detect other shed tumour proteins and identify changes in the protein profile, which correlate to treatment response and AEs.
- To characterize the subject population by determination of intra-tumoural expression levels of relevant biomarkers from archived tumour tissue such as EGFR, HER2, and potentially other biomarkers that are downstream of EGFR or HER2 receptors.
- To compare and characterize the subject population who convert to HER2 status (using the serum HER2 collections every 4 weeks of serum data). To specifically look at the time to conversion and the relationship to disease progression.
- The PGx research objective investigated 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 safety and tolerability of lapatinib. The results of the PGx assessments will be reported separately.

Comparator and experimental combination:
The choice of comparator by the MAH was based on *in vitro* data suggesting that letrozole was a more potent inhibitor of oestrogen in tissues. The Phase I study EGF10030 showed, as expected, that there was no relevant pharmacokinetic interaction between lapatinib and letrozole, and that full therapeutic doses of both agents could be administered. As such, subjects in both treatment groups of EGF30008 received the accepted standard of care, which is letrozole 2.5 mg administered orally daily.

Therefore, eligible subjects were randomised to receive once daily oral treatment with either letrozole 2.5 mg plus placebo (visually matching lapatinib tablets), or letrozole 2.5 mg plus lapatinib 1500 mg until disease progression or withdrawal from therapy (e.g., due to unacceptable toxicity, withdrawal of consent). Randomization (1:1) was stratified by site of disease (bone only versus soft tissue/visceral disease/other) and time since discontinuation of prior adjuvant endocrine therapy (≥6 months or none versus <6 months).

Outcomes/endpoints
Physical examination, lab-tests, assessment of AEs (NCI-CTC 3.0) and serum ErbB1 and HER2 were done at screening and every 4 weeks. ECG was done at base-line. Echocardiogram or MUGA was followed every 8 weeks. Tumour measurements, which at screening included chest and abdominal CT/MRI and bone scan and, if clinically indicated, pelvic and head CT/MRI, were performed. Positive CT/MRI scans were followed every 12 weeks and bone scans, if positive, every 6 months. QoL (FACT B) was followed every 12 weeks. After 108 weeks all assessments were done every 12 weeks except tumour measurements which were done every 6 months.

There were specific criteria for evaluating cardiac toxicity and hepatic toxicity (from amendment 5, May 2008).

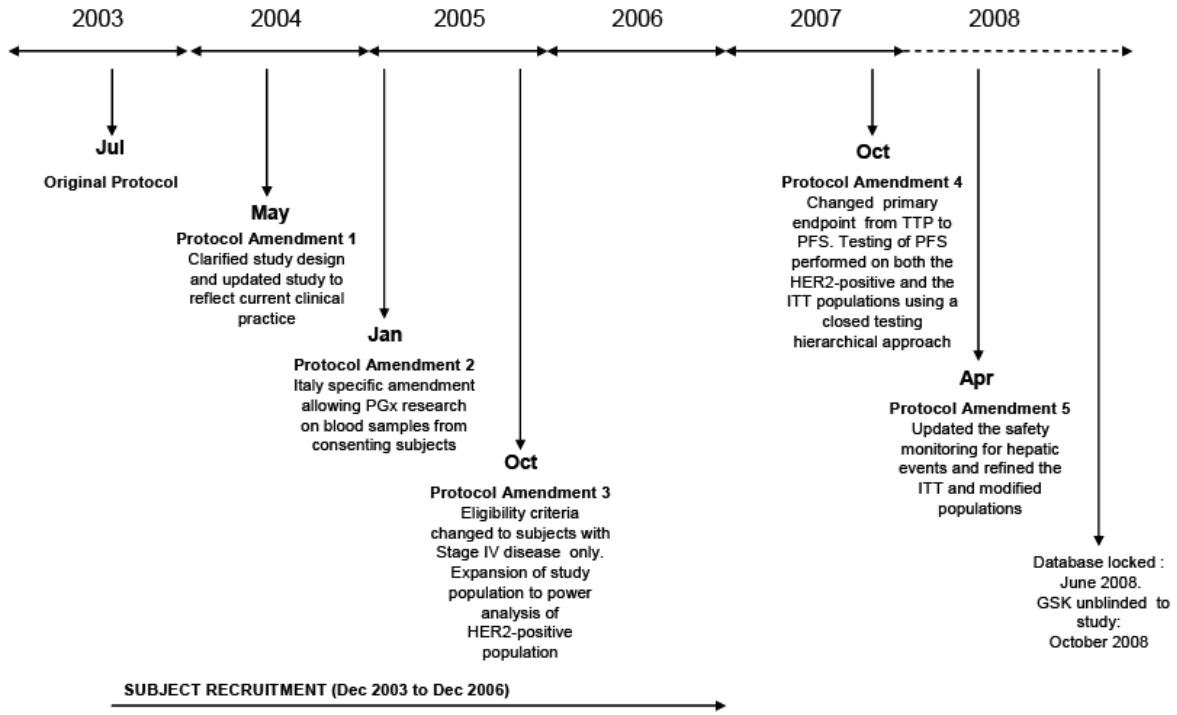
Sample size
The initial sample size 760 was based on assumptions that median time to progression would be 10 and 13 months in the letrozole and letrozole/lapatinib arms, respectively. With a one-sided type I error of 2,5%, there was a 90% chance to detect the 40% increase in median TTP and 5% loss to follow up. With protocol amendment 3 it was decided to expand the population to ensure statistical power for the HER2 positive subgroup. The assumptions for the HER2 positive subgroup was a 10 vs. 15 months TTP for letrozole/ letrozole and lapatinib, respectively. With a one-sided type I error of 2.5%, there was a 80% chance to detect the 55% increase in median TTP and 5% loss to follow up. Altogether 218 HER2 subjects were needed in the study. About 20% of the subjects in the study were HER2 positive.

Randomisation and blinding

The study was double-blind, the blinding was kept from enrolment until 10 October 2008. An IVR system called RAMOS (Registration and Medication Ordering System) was used to randomise and register subject activity. Randomisation was stratified according to

- Site of disease: Soft tissue/ visceral disease (could have bone metastases as well) or bone only
- Interval from discontinuation of adjuvant endocrine therapy ≥ 6 months /< 6 months

Summary of Key protocol amendments



Statistical methods

The primary analysis was PFS assessed by investigators in the HER2 positive population (randomised patients with HER2 positive tumours). PFS was defined as time from randomisation to disease progression or death, whichever occurred first. The secondary endpoint was PFS assessed by investigators in the ITT population. A closed hierarchical testing was done with PFS in the HER 2 positive population as the first endpoint to be tested. A supportive analysis was based on assessments from the IRB.

In amendment 4 the TTP was changed to PFS, however the majority of deaths were breast cancer related, only 11 patients in the ITT population died from other cause than cancer. The primary efficacy population was changed to HER2 positive.

An independent, blinded review of all radiological scans as a supportive analysis was performed by an IRC, and the results used as a confirmatory analysis of the primary efficacy measure of investigator-evaluated PFS. The IRC reviewed all scans and, for subjects with skin lesions, all photographs. The IRC were not given information of symptomatic assessments of PD.

Nevertheless, it must be noted that the clinical assessment of symptomatic progression was also possible by the protocol, more prone to bias and, in principle, not verifiable by the IRC. Although clinically and ethically correct, that possibility obligates great caution in ensuring a rigorous parallelism (in time and means) of assessment of tumoural targets between arms, in order to avoid bias.

A hierarchical closed testing procedure with HER2 positive population was being tested first at α= 0.05 level followed by secondary endpoint if the analysis for the HER2 positive population was significant. There were no adjustments for multiplicity for secondary end-points

The comparisons were between treatment groups: letrozole/placebo vs. letrozole/lapatinib.

A stratified log-rank test was used with stratification as by Site of disease and ≥6 months from discontinuation of adjuvant endocrine therapy. As HER2 status was not known at randomisation the stratification factors in the ITT population was not applied in this population. Cox regression analysis was used with pre-specified base-line prognostic factors (Stage of disease, Site of disease, prior adjuvant chemo ≥6 months, prior adjuvant endocrine therapy, ≥6 months, HR status (categorical), ECOG, Age, disease free interval, number of metastatic sites, EGFR at baseline, Serum HER2 at baseline, Serum HER2 converter post baseline). However "serum HER 2 converter post baseline" was not a baseline prognostic factor per se as it is influenced by treatment.

No interim analysis was performed.

The analyses were performed in three populations: HER2 positive, ITT and HER2 negative.

Results

The figure below presents the participant flow chart for the study.

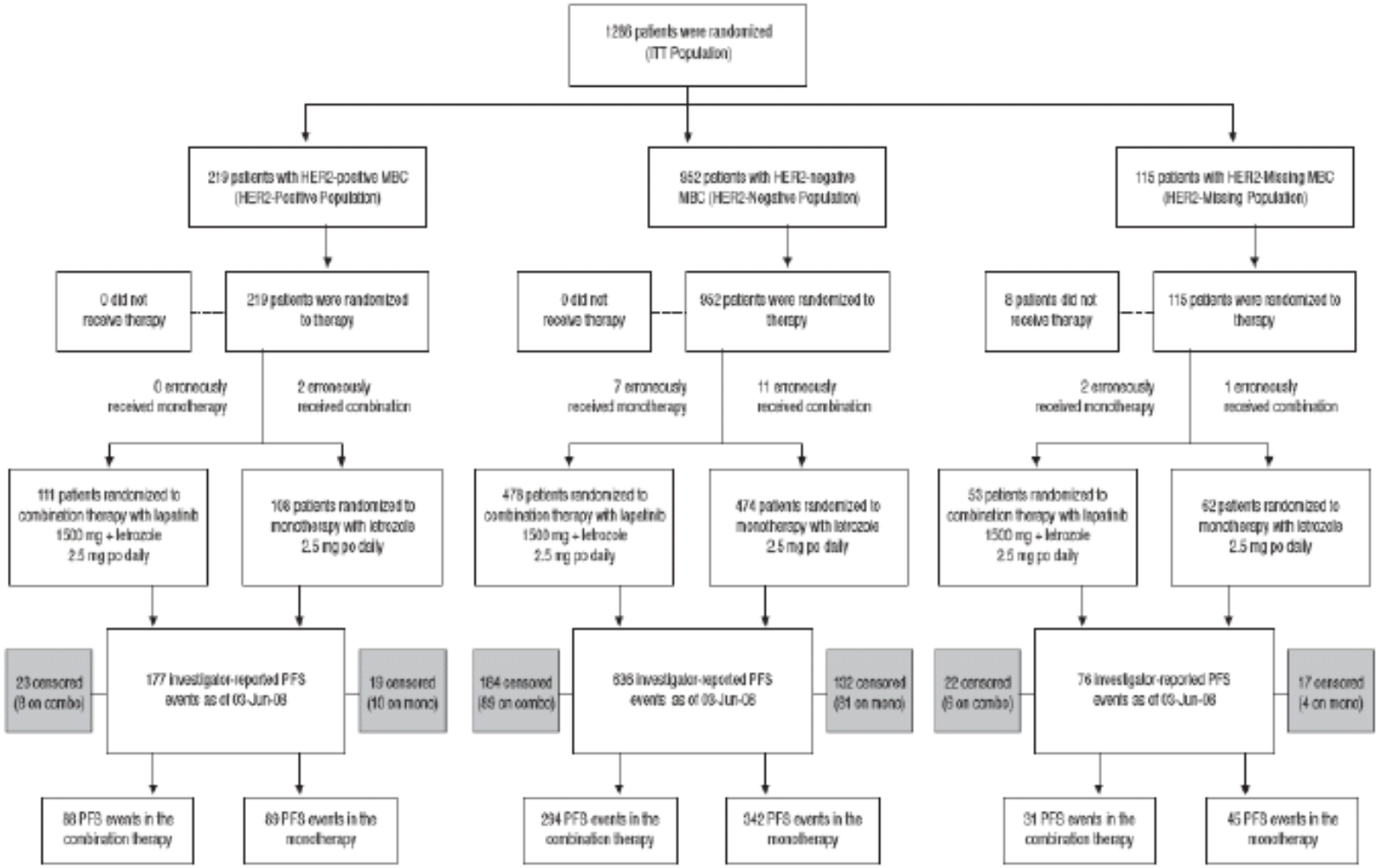
Regarding censoring the following rules applied:

- If not progressed, last radiological scan assessed by investigator was used.
- If new therapy started without evidence of documented disease progression PFS was censored at the date of the last radiological assessment that is no later than 14 days following the date of initiation of therapy.
- If initiation of therapy + 14 day window was prior to progression or death and the therapy start and progression or death was between the first and last of multiple scans, PFS was censored at the first scan date of the previous assessment.
- Subjects with no scans were censored at randomisation.

Conduct of the study

26 patients were excluded from the PP population due to major protocol violations, the most commonly reported was not receiving study treatment and not having metastatic lesions.

One site with 6 patients was closed due to GCP issues, the patients were kept in the ITT population, but not in the PP population.


1286 patients were randomized (ITT Population)
219 patients with HER2-positive MBC (HER2-Positive Population)
952 patients with HER2-negative MBC (HER2-Negative Population)
115 patients with HER2-Missing MBC (HER2-Missing Population)
0 did not receive therapy
219 patients were randomized to therapy
0 did not receive therapy
952 patients were randomized to therapy
8 patients did not receive therapy
115 patients were randomized to therapy
0 erroneously received monotherapy
2 erroneously received combination
7 erroneously received monotherapy
11 erroneously received combination
2 erroneously received monotherapy
1 erroneously received combination
111 patients randomized to combination therapy with lapatinib 1500 mg + letrozole 2.5 mg po daily
108 patients randomized to monotherapy with letrozole 2.5 mg po daily
478 patients randomized to combination therapy with lapatinib 1500 mg + letrozole 2.5 mg po daily
474 patients randomized to monotherapy with letrozole 2.5 mg po daily
53 patients randomized to combination therapy with lapatinib 1500 mg + letrozole 2.5 mg po daily
62 patients randomized to monotherapy with letrozole 2.5 mg po daily
23 censored (8 on combo)
177 investigator-reported PFS events as of 03-Jun-08
19 censored (10 on mono)
164 censored (69 on combo)
636 investigator-reported PFS events as of 03-Jun-08
132 censored (81 on mono)
22 censored (5 on combo)
76 investigator-reported PFS events as of 03-Jun-08
17 censored (4 on mono)
88 PFS events in the combination therapy
89 PFS events in the monotherapy
294 PFS events in the combination therapy
342 PFS events in the monotherapy
31 PFS events in the combination therapy
45 PFS events in the monotherapy

Baseline characteristics

All patients were female. Median age in the HER2 positive population was 60.0 (44-87), in the HER 2 negative population 63.0 (31-94). In the ITT population median age was 63.0 (31-95). The vast majority (94.5%) had metastatic disease only 12 patients in total had locally advanced disease. There were no significant differences between treatment groups. The most common medical condition at baseline was hypertension, 38% in the ITT population.

Baseline disease characteristics of the HER2-positive population

Categorical Covariate	**Strata**	**Letrozole 2.5 mg + Placebo (N=108)**	**Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)**
Histology	Infiltrating ductal	87 (81)	96 (86)
	Lobular invasive	11 (10)	11 (10)
	Other	10 (9)	4 (4)
Site of disease	Visceral/soft tissue	90 (83)	95 (86)
	Bone only	18 (17)	16 (14)
	Liver	37 (34)	33 (30)
	Lung	40 (37)	43 (39)
	Lymph node	43 (40)	57 (51)
	Other	18 (17)	19 (17)
Prior adjuvant chemotherapy	<6 months since discontinuation	2 (2)	4 (4)
	≥6 months since discontinuation	106 (98)	107 (96)
Prior adjuvant endocrine therapy	<6 months since discontinuation	41 (38)	38 (34)
	≥6 months since discontinuation	67 (62)	73 (66)
ECOG performance status at baseline	0	51 (47)	59 (53)
	≥1	57 (53)	51 (46)
Number of metastatic sites	<3	66 (61)	64 (58)
	≥3	42 (39)	47 (42)
Serum ErbB2 (ECD) at baseline	<15 ng/mL	51 (47)	69 (62)
	≥15 ng/mL	53 (49)	35 (32)
Serum ErbB2 converter post-baseline	Yes	0	0
	No	0	0
	Missing	108 (100)	111 (100)
Hormone receptor status	ER positive or PgR positive (reference)	92 (85)	93 (84)
	ER negative and PgR negative	7 (6)	10 (9)
	ER missing and PgR missing	9 (8)	8 (7)
Stage of disease at screening	IIIB/IIIC	7 (6)	5 (5)
	IV	101 (94)	106 (95)
EGFR	3+	2 (2)	0
	0 to 2+	104 (96)	110 (> 99)

Adjuvant therapy

In the ITT population 60% had received adjuvant therapy. HER 2 patients had received both endocrine and chemotherapy to a somewhat higher extent than other populations. The most common hormone therapy was tamoxifen which was used in > 95% in all populations. Only few patients had received aromatase inhibitors and trastuzumab. The most common chemotherapy was anthracyclin based.

Prior systemic therapy HER 2 positive population

	Letrozole/placebo	**Letrozole/laptinib**
Any endocrine	62 (57%)	60 (54%)
Anastrazole, exemestane or letrozole	1 (2%)	1 (2%)
Other hormone	1 (2%)	0 (0%)
Any chemotherapy	51 (47%)	61 (55%)
Anthracyclins	38 (75%)	41 (67%)
Taxanes	0 (0%)	0 (0%)
Anthracyclins and Taxanes	9 (18%)	9 (15%)
Monoclonal antibodies (Trastuzumab)	1(<1%) (100%)	1(<1%) (100%)
Both hormone and chemotherapy	43 (40%)	44 (40%)
Treatment naive	38 (35%)	34 (31%)

Relatively many patients (almost half of them) were endocrine treatment naive. About one-third was treatment naïve; however 19% were initially diagnosed with metastatic disease. Currently more patients receive adjuvant aromatase inhibitors and trastuzumab than at study start.

Hormone receptors

A positive status of ER and PR was most common in all populations followed by ER positive/PR negative.

	HER2+	HER2+	HER2-	HER2-
	Letro/plac	Letro/lap	Letro/plac	Letro/lap
ER+/PR+	69 %	68 %	68 %	71 %
ER+/PR-	25 %	21 %	24 %	18 %
ER-/PR+	2 %	3 %	2 %	3 %
ER-/PR-	0 %	0 %	0 %	<1 %
Missing/unk	4 %	8 %	0 %	0 %

Other current medical conditions:

In the HER2-positive population, the percentage of subjects with current medical conditions was similar between the two treatment groups. The majority of the current medical conditions were Grade 1 or Grade 2 only. At study entry, the most common current medical condition was hypertension (occurring in 32% of subjects overall, grade III 3% in letrozole plus placebo group and <1% in letrozole plus lapatinib), followed by back pain, arthralgia, depression, and fatigue (each occurring in 11% of all subjects). The only Grade 4 current medical condition reported at baseline was obesity (1 subject in the letrozole plus placebo group).

In the letrozole/lapatinib group 26% compared to 35% in the letrozole/ placebo group had a single metastatic site.

Previous medications and concurrent medications

In the HER2-positive population, up to 56% of subjects had received prior chemotherapy or endocrine therapy. Only 2 subjects (1 subject in each treatment group) had previously received trastuzumab. The most common chemotherapy regimen was anthracyclin based, however probably contained as well cyclophosphamide and fluorouracil.

In the HER2-positive population, of the subjects who received prior adjuvant endocrine therapy, approximately 64% and 60% received tamoxifen in the letrozole plus placebo and letrozole plus lapatinib groups, respectively, and approximately 21% and 17% of subjects in the letrozole plus placebo and letrozole plus lapatinib groups, respectively, received tamoxifen citrate. Only 2 patients in the HER2 positive population had received treatment with aromatase inhibitors.

There were more patients in the HER-2 positive group that had discontinued prior endocrine adjuvant treatment < 6 months compared to the ITT population.

Main characteristics of the patients were well balanced between treatment arms in the HER2 population. However, a high serum HER2 (ECD) rate at baseline (≥15 ng/mL) was more frequent in the letrozol plus placebo arm than in the letrozole plus lapatinib arm.

Also, more patients in the letrozole plus lapatinib arm (55%) than in the letrozole plus placebo (47%) arm had received previous chemotherapy; this imbalance was almost entirely due to an imbalance in the number of patients having received CMF adjuvant treatment (4% vs. 10%). However, the distribution between categories of time from discontinuation of chemotherapy is well balanced.

Stratification factors

	Number (%) of subjects					
	HER2-Positive		ITT		HER2-Negative	
	Letrozole 2.5 mg + Placebo (N=108)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)	Letrozole 2.5 mg + Placebo (N=644)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=642)	Letrozole 2.5 mg + Placebo (N=474)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=478)
Site of disease at screening						
Soft tissue or visceral[a]	90 (83)	95 (86)	559 (87)	548 (85)	414 (87)	408 (85)
Bone only disease	18 (17)	16 (14)	85 (13)	94 (15)	60 (13)	70 (15)
Prior adjuvant endocrine therapy						
Discontinuation interval ≥6 months[b]	67 (62)	73 (66)	487 (76)	501 (78)	370 (78)	382 (80)
Discontinuation interval <6 months[c]	41 (38)	38 (34)	157 (24)	141 (22)	104 (22)	96 (20)

Site of disease and ≥6 months interval from discontinuation of endocrine therapy) were basically similar between treatment arms in all populations. In the HER 2 positive population more patients had discontinued endocrine therapy < 6 months before study start compared to the other populations.

Missing HER2 status

115 patients had missing HER2 status, the main reason was insufficient tumour material provided. The HER2 missing subjects were slightly more common in Western and Eastern Europe. In general this population was similar to the other populations, however time since diagnosis was longer compared to the ITT population and there were fewer ductal carcinomas.

Primary reason for discontinuation of study drug HER2 positive population

Primary reason for discontinuation of study drug	**Letrozole/placebo n=108**	**Letrozole/Lapatinib n=111**
Adverse event	3 (3%)	7 (6%)
Consent withdrawn	5 (5%)	9 (8%)
Lost to follow-up	0	0
Protocol violation	3 (3%)	3 (3%)
Radiological progression	71 (66%)	74 (67%)
Symptomatic progression	14 (13%)	8 (7%)
Death	1 (<1%)	1 (<1%)
Discontinuation by sponsor	0	0
Other	1 (<1%)	5 (5%)
Missing	0	0

Primary objective – PFS

Investigator evaluated PFS, HER2 positive population

	Letrozole 2.5 mg + Placebo (N=108)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)
Number (%) of subjects		
Progressed or died due to any cause (event)	89 (82)	88 (79)
Censored, follow up ended	10 (9)	16 (14)
Censored, follow up ongoing	9 (8)	7 (6)
Kaplan-Meier estimate of PFS (weeks)		
1st Quartile (95% CI)	11.0 (8.7, 11.6)	15.4 (12.3, 22.3)
Median (95% CI)	13.0 (12.0, 23.7)	35.4 (24.1, 39.4)
3rd Quartile (95% CI)	48.1 (24.9, 76.1)	60.0 (47.9, 76.4)
Hazard ratio		
Estimate[a] (95% CI)	0.71 (0.53, 0.96)	
Log-Rank p-value[b]	0.019	

Source data: Table 7.2.

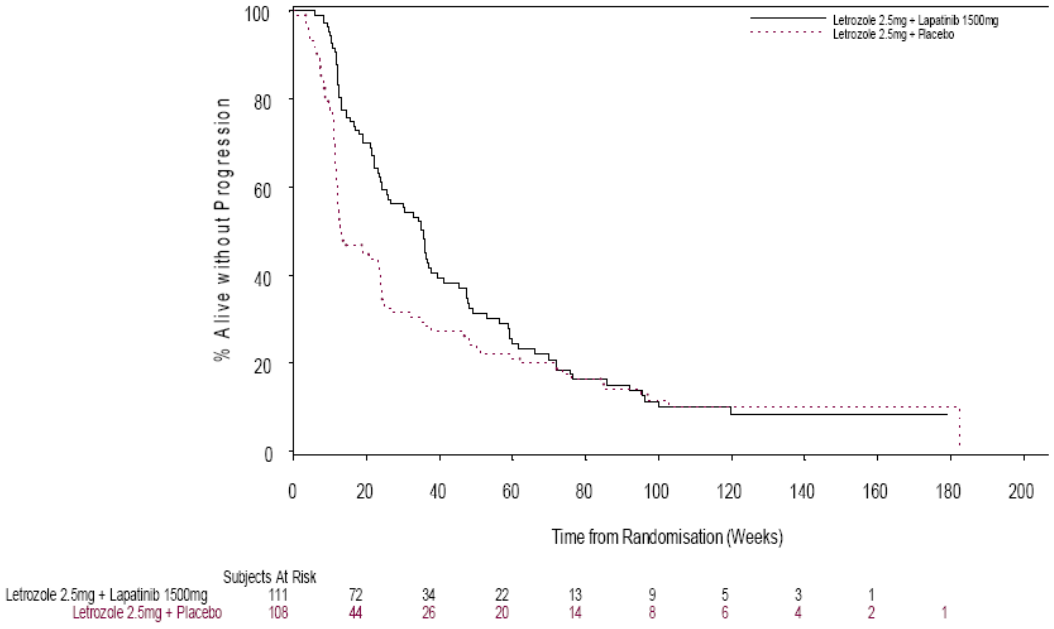
a. Estimate of the treatment HR based on the log-rank test, <1 indicates a lower risk with letrozole 2.5 mg + lapatinib 1500 mg compared with letrozole 2.5 mg + placebo.

b. p-value from stratified log-rank test, stratifying for site of disease and time since prior adjuvant endocrine therapy at screening.

In the HER2-postive population of EGF30008, there were 24 patients with symptomatic progression. There was an imbalance between arms, 15 in the letrozole + placebo arm and 9 in the letrozole + lapatinib arm. Excluding these patients with symptomatic progression, the HR was 0.76 (95% CI: 0.55, 1.04; stratified log rank p=0.075), which was not statistically significant.

The median is at the largest difference in the curve. After about 70 weeks the curves converge. As expected in this selected HER2 positive population the PFS is shorter compared to first-line treatment in other studies with aromatase inhibitors.

Kaplan-Meier estimates for investigator-evaluated PFS, HER2 positive population



Source data: Figure 7.1.

A Cox regression analysis showed a similar difference in PFS. Of the pre-specified co-variates ECOG and Serum HER2 ≥15 had impact on PFS.

Covariate	Effect tested	Hazard ratio (95% CI)	p-value
N/n = 219/192			
Treatment group	Letrozole 2.5 mg + lapatinib 1500 mg / Letrozole 2.5 mg + placebo	0.65 (0.47, 0.89)	0.008
Site of disease	Non-visceral/visceral	0.80 (0.51, 1.28)	0.354
Prior adjuvant endocrine therapy	≥6 months from discontinuation or no prior adjuvant endocrine therapy/<6 months	0.71 (0.49, 1.01)	0.056
ECOG performance status at baseline	≥1/0	1.49 (1.07, 2.06)	0.017
Age	Continuous in years	0.98 (0.96, 1.00)	0.041
Serum HER2 (ECD) at baseline	≥15/<15 ng/mL	2.38 (1.70, 3.33)	<0.001

Source data: Table 7.562.
Note: All main effects were selected using stepwise selection except for treatment, site of disease and time since prior adjuvant endocrine therapy. Interactions were not considered.

The analysis of IRC-evaluated PFS in the HER2-positive population also confirmed the primary analysis, demonstrating the internal consistency of the results in this study. There was a statistically significant improvement in median PFS in subjects receiving letrozole plus lapatinib (60 weeks) compared with subjects receiving letrozole plus placebo (35.4 weeks) (HR: 0.64; 95% CI: 0.43, 0.96, p=0.022).
As a consequence of censoring, the PFS assessed by IRC was longer as compared to the investigator assessments.

PFS HER 2 positive population IRC assessment n (% of treatment arm)

	Letrozole/placebo	**Letrozole /lapatinib**
Number of subjects	(N=108)	(N=111)
Progressed or died due to any cause	52 (48%)	49 (44%)
Censored, follow-up ended	47 (44%)	55 (50%)
Censored, follow-up ongoing	9 (8%)	7 (6%)
Kaplan-Meier estimate of PFS (weeks)		
1st Quartile, 95% C.I.	12.0, (11.4,13.6)	23.4, (14.4,32.9)
Median, 95% C.I.	35.4, (16.0,61.1)	60.0, (42.3,82.6)
3rd Quartile 95% C.I.	155.0, (62.0,-)	107.3, (82.6,-)
Hazard ratio Estimate, 95% C.I.		0.64 (0.43,0.96)
Log-Rank p-value		0.022

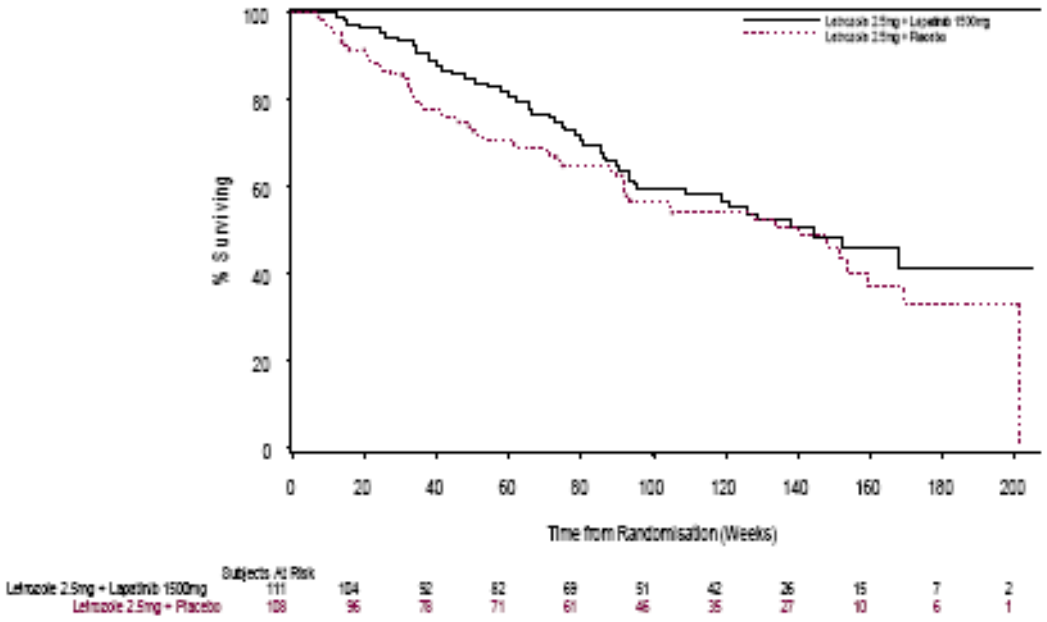
There was a discrepancy between the investigator and IRC assessed PFS regarding the HER2 positive population. Overall concordance is 63% when using a 7 day window. The differences were primarily due to progression being determined by the investigator and censoring of IRC review due to initiation of new anti-cancer therapy by investigator.
As PFS is liable to bias a clarification was provided regarding radiologically versus symptomatically assessed patients which showed that it is admissible that the difference in PFS is maintained.

Comparison of investigator and IRC evaluated PFS using 7 day window for complete agreement.

		Letrozole/ lapatinib	Letrozole/ placebo	Total
Event by IRC	**n**	**52**	**49**	**101**
	Complete agreement with investigator	36 (69)	28 (57)	64 (63)
	PD later by investigator	9 (17)	15 (31)	24 (24)
	PD earlier by investigator	5 (10)	5 (10)	10 (10)
	Event by IRC Censored by investigator	2 (4)	1 (2)	3 (3)
Censored by IRC	**n**	56	62	118
	Complete agreement with investigator	15 (27)	19 (31)	34 (29%)
	Censoring later by investigator	1 (2)	1(2)	2 (2)
	Censoring earlier by investigator	1 (2)	2 (3)	3 (3)
	PD by investigator	39 (70)	40 (65)	79 (67)

Secondary objective – Overall Survival

Overall survival, HER 2 positive population



Source data: Figure 7.25.

The median OS in weeks was 140.3 (92.1, 159.4) vs. 144.7 (95.6, NE) for letrozole/placebo and letrozole/lapatinib respectively.

The response rate was higher in the letrozole/laptinib arm with 27.9% vs. 14.8%; the majority of responses were partial.

Other endpoints, HER 2 positive population

ORR by investigator assessment for subjects with both measurable and non-measurable disease, HER2 positive population

	Letrozole 2.5 mg + Placebo (N=108)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)
Best response, n (%)		
CR	4 (4)	5 (5)
PR	12 (11)	26 (23)
SD	35 (32)	44 (40)
PD	49 (45)	30 (27)
Unknown	8 (7)	6 (5)
ORR (CR or PR)[a]		
Percent response rate (95% CI)	14.8 (8.7, 22.9)	27.9 (19.8, 37.2)
Percent difference in response rate (95% CI)	-13.1 (-25.8, -0.3)	
Estimate of common odds ratio for tumor response		
Estimate (95% CI)	0.4 (0.2, 0.9)	
p-value[b]	0.021	

Source data: Table 7.1070.

a. Subjects with unknown or missing response were treated as non-responders.

b. p-value from exact test that common odds ratio equals 1.

Note: 'Including bone scans' indicates that the assessment of CR or PR required confirmation using bone scans, regardless of the presence of bone disease at baseline.

Overall Response Rate/Complete Response/Partial Response: The data were consistent with the analysis of subjects with measurable disease only. There were only few patients with CR and PRs. Patients aged > 65 years had a higher response rate in both treatment arms, 16.2% and 36.6% respectively.

The IRC evaluated ORR also showed an improved ORR in favour of letrozole/placebo of 27.0% (19.0, 36.3) compared to 9.3 % (4.5, 16.4).

Time to response: 11/16 and 23/31 in the letrozole/placebo and letrozole/lapatinib group respectively had responded by the first assessment (12 weeks).

Duration of response: Duration of response was longer in the letrozole/ placebo group compared to the letrozole/laptinib group (84.4 vs. 47.4 weeks, investigator assessment).

A possible explanation to this finding could be that patients that respond to endocrine treatment only have a more indolent disease.

Brain metastases: There were no differences with regards to brain metastases, however only 3 patients in total in the HER 2 positive population had brain metastases.

Quality of Life: In the HER2-positive population, results for the analyses of OQL change from baseline were similar in the groups with generally stable QOL on all measures for subjects who stayed in the study. In general, mean QOL scores for both treatment groups were higher than their respective baseline values during follow up. At the concluding visit, MIDs occurred in both treatment groups. None of the differences between treatment groups were statistically significant. However, the scales, FACT-B; FACT-G and TOI may not capture all relevant side effects.

Biomarkers: In the HER2 positive population 49% in the letrozole/placebo arm vs. 32% in the letrozole/lapatinib group had with HER2 ECD > 15 ng/mL. In the HER2 positive as well as the HER2 negative group patients with HER2 ECD > 15 ng/mL had shorter PFS irrespective of treatment. In the HER2 positive group subjects with HER2 ECD > 15 ng/mL letrozole/placebo group had significantly shorter PFS compared to the letrozole/lapatinib group.

Sub group analyses:

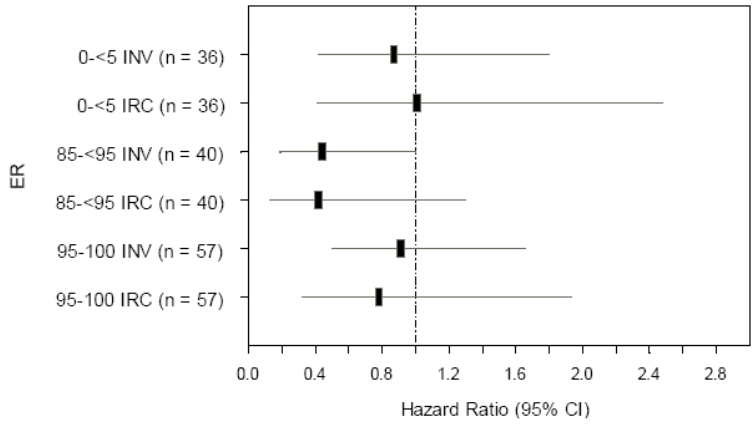
When analysing age groups <65 and >65 there were no differences seen in the HER2 positive population on PFS; ORR was higher in the group aged >65 years. With regards to OS survival in the HER2 positive population in subjects aged <65 years there was a survival of 147.9 weeks in the letrozole/placebo group and 118.7 weeks in the letrozole/lapatinib group. However, the data was not mature. In the group of subjects aged >65 years the median OS was 93.6 weeks in the letrozole/placebo group and data could not be calculated in the letrozole and lapatinib group.

In patients with FISH/ICH2+ or FISH borderline there was no difference in PFS.

With regards to hormone receptors a Cox proportional Hazard Modelling with ER and PR as continuous variables was performed. For the primary endpoint (PFS as assessed by investigators) ER (continuous) had no statistically significant impact on PFS (HR 0.997, p=0.2298). However, when analysed by IRC ER had a statistically significant improvement in PFS HR 0.993, p=0.0266, which translates into a reduction in HR of 0.07 of every 10% increment in ER. The same pattern is seen for PR.

Figure 3

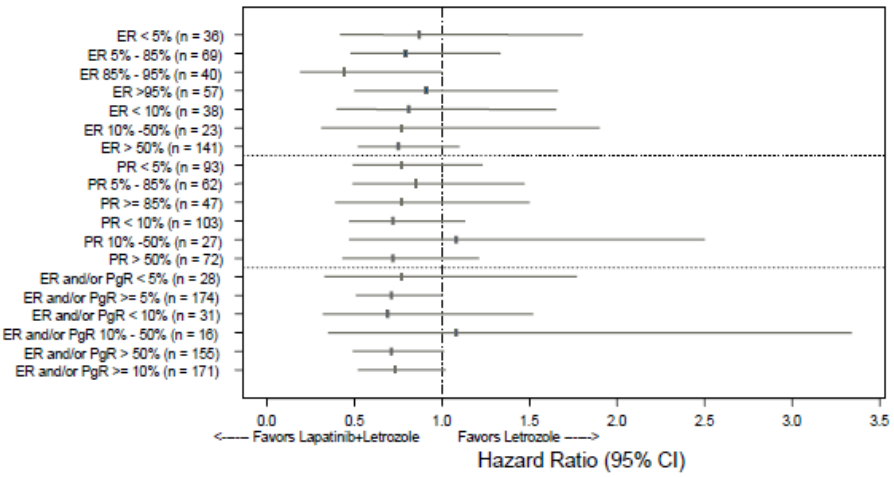
Hazard Ratios of PFS by ER Cuts -- HER2+ Population



In the category 0<5 where lapatinib would be expected to have the largest relative add-on effect the hazard ratio is very close to 1. However the groups were too small to draw any conclusions.

New information provided on effect in different HR cut-off categories (<10%, >10%, 10-50%, >50%) did show consistent results with regards to the hazard ratio.

Figure 3 Forest Plot of Hazard Ratio (95% CI) for Investigator-Assessed PFS for Various ER and PgR Expression Categories in the ErbB2-Positive Population



1.4.2.2 Supportive study EGF10030

EGF10030 was a Phase I, open-label study of the safety, tolerability and pharmacokinetics of GW572016 in combination with letrozole (Femara) in subjects with advanced breast cancer or other solid tumours.

This study was conducted in three phases which included three cohorts of subjects; a dose escalation cohort (Cohort 1) to determine the optimally tolerated dose (OTR), an expansion cohort (Cohort 2) to further evaluate the safety and tolerability of the OTR, and a PK cohort (Cohort 3) to assess the potential for a drug-drug interaction when these two drugs are used in combination.

Methods

The study was a phase 1 open label to determine OTR and PK. Safety was followed by vital signs, laboratory parameters, MUGA and ECG for cardiac safety. Adverse events were collected using NCI-CTC version 3, RECIST criteria were used to assess response when applicable.

39 patients with mainly hormone-receptor positive breast cancer (n=18) and ovarian cancer (n=16) were enrolled. Mean age was 56.1 (31-73) and all subjects were female and white.

12 subjects were included in the optimally tolerated regimen (OTR) dose finding cohort (Cohort 1), seven subjects in the OTR expansion cohort (Cohort 2), and 20 subjects in the PK cohort (Cohort 3). The OTR expansion added patients at OTR to further evaluate the safety and tolerability of the combination.

The dose of lapatinib was escalated in three subjects/dose level in Cohort 1 starting at a lapatinib dose of 1250 mg/day and letrozole 2.5 mg/day. The letrozole dose remained at 2.5 mg at all dose levels.

The doses for lapatinib were chosen from the range administered in EGF 10003 where doses of up to 1800 mg once daily were administered without DLT during the first treatment cycle. The dose of letrozole (2.5 mg once a day) was based on the approved dosage.

Results

Dose limiting toxicity (DLT) was considered a Grade 2 diarrhoea two days after starting lapatinib in one of 8 patients in the 1500 mg cohort.

A total of 5 patients experienced DLTs 4 diarrhoeas 1 grade 1 and 3 grade 3 and one grade 3 rash.

With respect to the efficacy results, two patients achieved PR (one breast cancer, one endometrial cancer), 20 subjects had stable disease, and twelve subjects had progressive disease.

Regarding safety four subjects had a LVEF decrease of greater than or equal to 20% relative to their baseline assessment. One of these subjects had an LVEF decrease of > 20%.

The most commonly reported AEs were: diarrhoea, rash, nausea, vomiting, fatigue, and anorexia. Twenty-one subjects had Grade 3 AEs and two subjects had Grade 4 AEs, all in the 1500 mg lapatinib plus 2.5 mg letrozole treatment group. One patient died due to Grade 4 respiratory failure, this was not considered related by the investigator.

The safety profile was consistent with the known safety profile of lapatinib.

1.4.2.3 Overall Conclusion on Clinical Efficacy

The application targets all postmenopausal, HR+/HER2+ patients in first line treatment for metastatic disease. This group of patients may in fact be treated with chemotherapy instead of hormone therapy. The combination of chemotherapy with trastuzumab is even recommended for patients with good performance status, visceral disease, or rapidly progressing tumours (Prat, 2008), like the majority of the patients included in trial EGF 30008. Therefore, the evidence supporting this application may be considered to respect just one of the possible ways of treating the target population of patients.

For the HER2 population a statistically significant prolongation in PFS was seen by investigator assessed evaluations. In the letrozole/placebo group the median PFS was 13.0 weeks (12.0, 23.7) compared to 35.4 weeks (24.1, 39.4) in the lapatinib/letrozole group which is considered a clinically meaningful improvement. HR was 0.71 (0.53, 0.96) p=0.019 in favour of the letrozole/laptinib arm. Cox regression analysis showed a HR 0.65 (0.47, 0.89) p= 0.008. The majority of the responses were seen within 12 weeks of treatment. The duration of response was 47.7 weeks in the letrozole/lapatinib arm compared to 84.4 weeks in the letrozole/placebo arm. This could tentatively be explained by a more indolent course in tumours responding to single endocrine treatment.

However, as the primary endpoint of PFS is liable to bias, the assessment of the exact magnitude of the efficacy of the combination required a clarification of the distribution of radiologically versus symptomatically assessed patients. The MAH provided data demonstrating that:

- the loss of significance of the difference in PFS when patients with symptomatic progression are excluded from the analysis must be due to a loss of power:
- even in the worst scenario (symptomatic progressions in the control arm being considered to occur at the next fixed assessment date and those in the experimental arm being considered to occur at the preceding fixed assessment date), the difference in PFS keeps its statistical significance.

Therefore, it is admissible that, despite the imbalance between the two arms in the numbers of patients with symptomatic progression, the difference in PFS favouring the lapatinib arm is maintained.
Furthermore, analyses of hormone receptors showed a slight tendency in IRC evaluated PFS towards better effect in patients with higher levels of hormone receptors; however the effect seems to be fairly consistent in all groups. New analyses with regards to different levels of HR cut-off showed consistent results.

There was no significant difference in OS but the data were not considered mature for the analysis of this endpoint. The overall response rate was 27.9 vs. 14.8% respectively in favour of letrozole/lapatinib. The submission of a mature data set has been requested by the CHMP as a Follow-up Measure.

The combination of trastuzumab and an aromatase inhibitor for the treatment of postmenopausal patients with HER2+ metastatic breast cancer is currently approved. To accurately determine the clinical benefit a randomised comparison of the regimens would be needed. However, as the study EGF 30008 had ended subject recruitment before trastuzumab was approved for this indication, this was not feasible at that time. There are no direct comparisons available to explore the difference between lapatinib and trastuzumab concomitant with antihormonal treatment. While not primarily designed to give a direct comparison of lapatinib or trastuzumab in combination with endocrine therapy, study EGF106708 (‘ALTTO’) is testing lapatinib and trastuzumab in the adjuvant setting in patients with early breast cancer. Approximately half of the planned 8000 patients to be enrolled are expected to have hormone receptor (HR)-positive primary

tumours, and therefore to be receiving a concurrent anti-hormonal agent while receiving the investigational targeted therapies (trastuzumab or lapatinib or a sequence of trastuzumab then lapatinib or trastuzumab + lapatinib). It is further estimated that 50% to 75% (approximately 3000 women) of these women with HR-positive tumours will be postmenopausal and hence most likely taking an AI. Results from this study are anticipated in 2012 and the MAH committed to provide these data as a Follow-up Measure.

In addition, the MAH is currently planning to undertake further clinical trials in patients who have received at least adjuvant therapy with trastuzumab for their breast cancer. The design of such trials is currently under consideration within the company. One study may have a randomised, controlled design and be performed in a patient population essentially identical to that of EGF30008 with the exception that subjects must have received prior treatment with trastuzumab. The reference arm for this trial could be trastuzumab + AI, and therefore also address a previous question from the CHMP that a direct comparison of trastuzumab + AI with Tyverb + AI had not been done. The primary and key secondary endpoints of this study may be the same as in EGF30008.
A second, separate study under consideration by the MAH is an uncontrolled trial of Tyverb + AI in the patient population described above. This trial may deliver clinical data in a quicker timeframe to a controlled study.

The CHMP requested the MAH to present the protocol and timelines of the planned studies as Follow-up commitments.

Clinical studies in special populations- Paediatric data

A class waiver decision on the conditions granted for products intended for the treatment of breast carcinoma was issued by the EMEA on 14 July 2008 (EMEA/360425/2008, P/47/2008).

The PDCO confirmed that this waiver applies to lapatinib on 20 May 2008 (EMEA/242695/2008, EMEA/6/2008).

1.4.3 Clinical Safety

This section reviews the safety profile of lapatinib administered in combination with letrozole to subjects with hormone-receptor positive advanced or metastatic breast cancer. The review includes safety data from subjects receiving at least one dose of study treatment in the pivotal study EGF30008 (N=1278) and the supporting dose-finding study EGF10030 (N=39).

Since the supporting Phase I study included subjects with various tumour types, data from the two trials were not integrated.

1.4.3.1 Pivotal study EGF 30008

Patient exposure
In the pivotal study 1286 patients were enrolled, the safety population comprised all patients who have received at least 1 dose of medication which was 1278, 624 patients with letrozole/placebo and 654 with letrozole/lapatinib. 6 patients in the placebo and 2 patients in the lapatinib group did not receive treatment. Furthermore 14 subjects in the letrozole /placebo group received lapatinib.

Nine subjects were randomised to letrozole/lapatinib, but received letrozole+placebo during the treatment period. However, they received at least 1 dose of lapatinib and were included in the lapatinib group for safety. As a conservative approach, these 9 subjects were included in the letrozole+lapatinib arm of the Safety Population, and any adverse events that these subjects experienced were attributed to the letrozole+lapatinib arm.

The mean duration of treatment was about 55 weeks both for lapatinib and letrozole. Treatment compliance was >80% for the majority of patients in both treatment groups.

A Summary of exposure to lapatinib and letrozole (safety population) is presented in the table below.

	Exposure to Lapatinib	Exposure to Letrozole	
	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Duration of treatment period (weeks)			
Mean (standard deviation) Median (range)	55.10 (47.034) 40.14 (0.3 to 213.6)	54.53 (48.313) 37.57 (0.9 to 216.1)	55.22 (46.984) 40.29 (0.1 to 213.6)
Percentage treated days during treatment period[a]			
Median 0 to <20, n (%) 20 to <40, n (%) 40 to <60, n (%) 60 to <80, n (%) 80 to <100, n (%) 100, n (%)	100.0 0 0 4 (<1) 6 (<1) 205 (31) 439 (67)	100.0 0 0 0 0 82 (13) 542 (87)	100.0 0 0 0 2 (<1) 118 (18) 534 (82)
Daily dose (mg)[b]			
Mean (standard deviation)	1461.6 (102.30)	2.49 (0.031)	2.49 (0.052)
Median (range)	1500.0 (672 to 1500)	2.50 (2.1 to 2.5)	2.50 (1.8 to 2.5)
Cumulative dose (mg)			
Mean (standard deviation)	564,683.1 (482,387.55)	951.22 (842.646)	961.81 (818.262)
Median (range)	417,000.0 (3000 to 2,143,500)	655.00 (15.0 to 3780.0)	705.00 (2.5 to 3737.5)

Source data: Table 8.1 and Table 8.2.

a. Percent treated days was calculated as [(date of last dose – date of first dose) +1- days of 0 mg dose] / (date of last dose – date of first dose) +1 x 100. If the last study treatment dose recorded was 0 mg, this was excluded from the calculation.

b. The average daily dose calculation includes only known doses (i.e., 0 or greater).

Adverse events (AEs)

A higher incidence of AEs was reported with the combination therapy compared with the monotherapy arm (96% vs. 86%).

Category of adverse event	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
All AEs	536 (86)	628 (96)
Fatal AEs	8 (1)	8 (1)
Fatal AEs related to study treatment[a]	2 (<1)	1 (<1)
SAEs	94 (15)	144 (22)
SAEs related to study treatment[a]	27 (4)	54 (8)
AEs leading to permanent discontinuation of study treatment[a, b]	35 (6)	95 (15)
AEs related to study treatment[a]	343 (55)	548 (84)
AEs of special interest[c]	228 (37)	533 (81)

Source data: Table 8.11.

a. Assessed by the investigator.

b. Note the numbers of subjects with AEs leading to permanent discontinuation of study treatment presented in this table are different from those presented in Table 9. This is because the primary reason for discontinuation from treatment was not listed as AE on the case report form for some subjects.

c. Included rash, diarrhea, nail changes, hepatotoxicity, LVEF decreases, and pulmonary events (AEs thought to be associated with EGFR and HER2 inhibition) (see Section 8.6.3).

The majority of AEs were grade 1-2 in both groups. The most common AEs (see table below) were gastrointestinal and skin related. Diarrhoea was 3 times more common in the letrozole/lapatinib group compared to the letrozole/placebo group. Also rash was about 3 times more frequent in the letrozole/lapatinib group compare to letrozole/placebo group. Of the events, 84% in the letrozole/lapatinib vs. 55% in the letrozole/placebo arm were classified as treatment related. Also for treatment related AEs gastrointestinal and skin events dominated. There were only minor differences in AEs between <65 and >65 years old and <75 and >75 years old. Peripheral edema and urinary tract infections were more

common in older age groups and hot flushes were reported more commonly among the younger age groups.

Most common adverse events by treatment group

Event	Letrozole/placebo	Letrozole/lapatinib
Diarrhoea	124 (20%)	419 (64%)
Rash	83 (13%)	293 (45%)
Nausea	129 (21%)	200 (31%)
Arthralgia	145 (23%)	128 (20%)
Fatigue	108 (17%)	134 (20%)
Back pain	97 (16%)	105 (16%)
Vomiting	68 (11%)	109 (17%)
Headache	83 (13%)	91 (14%)
Cough	90 (14%)	80 (12%)
Hot flush	92 (15%)	69 (11%)
Asthenia	69 (11%)	80 (12%)

AEs occurring in 10% or more subjects, and at a higher incidence in the lapatinib/letrozole group

System organ class MedDRA preferred term	Number (%) of subjects					
	Letrozole 2.5 mg + Placebo (N=624)			Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Metabolism and nutrition disorders						
Anorexia	54 (9)	2 (<1)	0	72 (11)	5 (<1)	0
Nervous system disorders						
Headache	83 (13)	3 (<1)	0	91 (14)	2 (<1)	0
Gastrointestinal disorders						
Diarrhea	124 (20)	6 (<1)	0	419 (64)	58 (9)	2 (<1)
Nausea	129 (21)	4 (<1)	0	200 (31)	6 (<1)	0
Vomiting	68 (11)	4 (<1)	1 (<1)	109 (17)	7 (1)	1 (<1)
Skin and subcutaneous tissue disorders						
Rash[a]	83 (13)	0	0	290 (44)	7 (1)	0
Pruritus	55 (9)	1 (<1)	0	80 (12)	2 (<1)	0
Alopecia	45 (7)	0	0	85 (13)	1 (<1)	0
Dry skin	27 (4)	0	0	87 (13)	1 (<1)	0
Nail disorder	6 (<1)	0	0	73 (11)	1 (<1)	0
General disorders and administrative site conditions						
Fatigue	108 (17)	3 (<1)	0	134 (20)	10 (2)	0
Asthenia	69 (11)	5 (<1)	0	80 (12)	5 (<1)	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11 (2)	1 (<1)	0	70 (11)	1 (<1)	0

Source data: Table 8.12, Table 8.13 and Table 8.15.

a. In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment group had a rash under "Infections and infestations"; none were Grade 3 or 4. This table includes events that coded to the preferred term of rash.

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

Other AEs with >10% in the lapatinib/letrozole arm were atralgia 31% (vs. letrozole/placebo 21%), back pain 16% (vs. 16%), headache 14% (vs. 13%), cough 12% (vs. 14%), hot flush 11% (vs. 15%) and pain in extremity 10% (vs. 12%).

AEs leading to discontinuation

In the letrozole/laptinib group 12% had any dose reduction and 18 % had dose delays. There were more AEs leading to permanent discontinuation of study drug in the letrozole/laptainib arm. Diarrhoea was most common reason in the letrozole/lapatinib arm, in the letrozole/placebo arm the most common events were ejection fraction decreased/left ventricular dysfunction. However "ejection fraction decreased" was more common in the letrozole/lapatinib arm in total. In the age group >65 years slightly more patients discontinued due to treatment 20% and 8% for letrozole/laptinib and letrozole/placebo respectively.

The most common AEs leading to permanent discontinuation of investigational medicinal products are shown in the table below.

The most common adverse events leading to permanent discontinuation of investigational drugs

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

Source data: Table 8.18 and Table 8.92.

a. The primary reason for discontinuation from treatment was not listed as AE on the case report form for some subjects.

b. A subject could have had more than 1 event leading to discontinuation of study treatment.

Serious adverse events (SAEs) and deaths

The overall rate of death was similar in the two treatment groups (37% each) for the safety population. The primary cause of death in both groups was disease progression (35% in each group).

MedDRA preferred term	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Subjects who died[a,b]	231 (37)	243 (37)
Primary cause of death		
Progression of cancer	217 (35)	228 (35)
Fatal adverse event	6 (<1)	7 (1)
Other[c]	8 (1)	8 (1)

a. In the ITT population, 234 subjects and 240 subjects died in the letrozole plus placebo and letrozole plus lapatinib groups, respectively. The difference in the number of subjects is due to 3 subjects who died in the letrozole plus placebo group but who received lapatinib and have thus been presented according to the treatment they actually received.

b. The number of subjects who died differs from that presented in Table 5. Only subjects who were listed as withdrawing from study treatment due to death are presented in Table 5, not the total number of deaths.

c. See the Study EGF30008 CSR (Section 8.3) for subjects that were included in this category.

There were more SAEs in the letrozole/lapatinib group compared to letrozole/placebo, 144 (22%) and 94 (15%), respectively. The most common events were decreased ejection fraction and diarrhoea.

Of the SAEs 8% vs. 4% in letrozole/laptinib and letrozole/placebo respectively were considered treatment related. Infections were noted in 17 (12%) compared to 6 (6 %) subjects in the letrozole/laptinib and letrozole/placebo arm respectively.

Age did not have a large impact on the frequency or distribution of SAEs.

Serious adverse events reported by three or more subjects in either treatment group

MedDRA preferred term	Number (%) of subjects [n related events]	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any SAE	94 (15) [27]	144 (22) [54]
Ejection fraction decreased	8 (1) [7]	17 (3) [14]
Diarrhea	2 (<1) [1]	15 (2) [10]
Vomiting	7 (1) [3]	10 (2) [4]
Dehydration	2 (<1) [1]	7 (1) [3]
Urinary tract infection	1 (<1) [1]	6 (<1) [0]
Anemia	2 (<1) [2]	5 (<1) [0]
Left ventricular dysfunction	1 (<1) [0]	5 (<1) [5]
Cellulitis	0	5 (<1) [0]
Dyspnea	4 (<1) [1]	5 (<1) [0]
Nausea	4 (<1) [1]	5 (<1) [3]
Abdominal pain	2 (<1) [0]	4 (<1) [0]
Erysipelas	2 (<1) [1]	4 (<1) [1]
Pyrexia	4 (<1) [1]	4 (<1) [0]
Asthenia	1 (<1) [0]	3 (<1) [2]
Chest pain	3 (<1) [0]	3 (<1) [0]
Femur fracture	1 (<1) [0]	3 (<1) [0]
Pulmonary embolism	3 (<1) [0]	3 (<1) [1]
Back pain	5 (<1) [0]	2 (<1) [1]
Pneumonia	3 (<1) [0]	2 (<1) [0]

Source data: Table 8.19 and Table 8.20.

Fatal SAEs occurred in 8 patients in each treatment group. In the letrozole/placebo group there were 2 septic chocks and 1 sepsis and 2 renal failures. In the letrozole/lapatinib group there were one cerebrovascular accident and 2 myocardial infarctions.

Number (%) of Subjects with Fatal serious adverse events (safety population)

MedDRA preferred term	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any Fatal SAE[a, b]	8 (1)	8 (1)
Septic shock	0	2 (<1)
Breast cancer metastatic	0	1 (<1)
Hepatic function abnormal	0	1 (<1)
Intestinal ischemia	0	1 (<1)
Lung infection	0	1 (<1)
Multi-organ failure	0	1 (<1)
Rhabdomyolysis	0	1 (<1)
Renal failure	0	1 (<1)
Renal failure acute	0	1 (<1)
Sepsis	0	1 (<1)
Cerebrovascular accident	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	0
Cardio-respiratory arrest	1 (<1)	0
Dyspnea	1 (<1)	0
Hypotension	1 (<1)	0
Lymphoma	1 (<1)	0
Myocardial infarction	1 (<1)	0
Pancreatitis hemorrhagic	1 (<1)	0
Road traffic accident	1 (<1)	0
Small intestinal obstruction	1 (<1)	0

Source data: Table 8.21.

a. A subject could have more than 1 SAE leading to death i.e., although there are 8 subjects with fatal events in each treatment group, there are more events listed because subjects had more than 1 reported event that attributed to the fatality.

b. This includes 3 subjects who were not listed in the fatal AE category in Table 61; 2 subjects with progression of disease and 1 subject who was involved in a car crash.

Laboratory findings

Of haematology findings neutropenia was the most common and occurred in grade 3 and 4 in 4% for letrozole/placebo and 2% for letrozole/lapatinib.

The most common chemistry grade 3 or 4 events were AST/ALT changes which occurred in 6 and 5% respectively in the letrozole/lapatinib and 2 and 1% respectively in the letrozole placebo group.

1.4.3.2 Supportive study EGF10030

The AE profile of letrozole plus lapatinib in trial EGF 10030 was generally similar to that seen in the pivotal study and consistent with lapatinib clinical experience.

Eighteen of the 39 enrolled subjects had breast cancer. Most subjects (95%) experienced at least one AE and in 87%, the event was treatment-related. The most common treatment-related toxicities were diarrhoea (77%), rash (62%), nausea (46%), and fatigue (26%), but most AEs were Grade 1 or Grade 2, and reversible.

Two subjects discontinued investigational product each due to a single AE; Grade 4 respiratory failure and Grade 3 rash.

Treatment related SAEs were low, with 2 subjects reporting Grade 3 anaemia, Grade 3 diarrhoea and Grade 2 nausea.

One subject died during the follow-up period from serious Grade 4 respiratory failure that was not treatment related.

1.4.3.3 Adverse events of interest

The following categories of AEs have been analysed as AEs of special interest as these are known to be associated with inhibition of either ErbB2 or ErbB1 based on the MAH's prior clinical experience:

- diarrhoea (due to inhibition of ErbB1)
- rash (due to inhibition of ErbB1)
- hepatobiliary events (attributed to inhibition of tyrosine kinase)
- cardiac events (due to inhibition of ErbB2)
- pulmonary events (due to inhibition of ErbB1)
- nail disorder

Number (%) of subjects with adverse events of interest

MedDRA preferred term	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any AE of interest[a]	228 (37)	533 (81)
Diarrhea	124 (20)	419 (64)
Rash	93 (15)	328 (50)
Hepatotoxicity	50 (8)	98 (15)
Nail changes	6 (<1)	73 (11)
Decreased LVEF	15 (2)	32 (5)
Pulmonary events	0	1 (<1)

Source data: Table 8.14.
a. See Section 5.6.3.2 for the MedDRA preferred terms included.

Diarrhoea: Sixty-four % in the letrozole/lapatinib arm had an event of diarrhoea. No action was taken in the majority of the events (90% in the letrozole/placebo and 85% in the letrozole/lapatinib arm). The median time to onset was 14.0 days in the letrozole/lapatinib group and 58.5 days in the letrozole/placebo group. The median duration was 24 days and 8 days respectively. Grade 3 or 4 diarrhoea was reported in 14% of the letrozole/lapatinib group.

Rash: The analysis of rash as an event of special interest included the following preferred terms: dermatitis acneiform, eczema, exfoliative rash, photosensitivity reaction, rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and skin ulcer.

In study EGF30008 in the letrozole/lapatinib group 328 patients experienced rash. Of these 89% of the events resolved. Medication was needed in 35% of the subjects. The median time to onset was 2.86 weeks and the duration 51 days.

In Study EGF10030, 36 rash events were reported for 25 subjects (64%); 3 (75%) subjects who received letrozole 2.5 mg plus lapatinib 1250 mg and 22 (65%) subjects who received letrozole 2.5 mg plus lapatinib 1500 mg. Most rash events reported were considered to be treatment-related by the investigator and most were Grade 1 or Grade 2 in toxicity. No SAEs of rash were reported during the study. One subject who received letrozole 2.5 mg plus lapatinib 1500 mg had a Grade 3 AE of rash that led to discontinuation of investigational product; the event later resolved with sequelae.

Hepatotoxicity: In study EGF30008, the incidence of hepatobiliary AEs was higher in the letrozole/lapatinib group (15% vs. 8%); however, the frequencies of hepatic SAEs were similar between the treatment groups (2% vs. 4%). There was one death due to a liver related SAE in the letrozole/lapatinib group.

In Study EGF10030, five treatment-related Grade 1 hepatic AEs occurred in 3 subjects (9%); all the events resolved without dose modification.

Cardiac events: The most common cardiac events were palpitations, left ventricular dysfunction, atrial fibrillation, tachycardia and cardiac failure. Cardiac events of specific interest were cardiac failure, decreased ejection fraction, left ventricular dysfunction and ventricular dysfunction. In study EGF30008, in the letrozole/laptinib group 32 patients (5%) had 39 events reported. In the letrozole/placebo group 15 subjects (2%) had 16 events reported.

In Study EGF10030, 1 subject (who received letrozole 2.5 mg plus lapatinib 1250 mg) had an event of decreased ejection fraction during the study (70% at screening to 48% [31% decline] on Study Day 51).

This Grade 2 event was reported as an AE and was considered to be treatment-related by the investigator. The event resolved without dose modification. An additional 3 subjects had a ≥20% decrease in LVEF relative to their pre-treatment values but the LVEF measurement was not below 50%.

Pulmonary events: One patient in each treatment group experienced pneumonitis. Two additional subjects in the letrozole/laptinib group had AEs suggestive of pneumonitis.

Nail disorder: Nail disorders were reported for 11 % in the letrozole/laptinib and <1% in the letrozole/placebo group.

1.4.3.4 Overall conclusion on Safety

In the pivotal study, there were more subjects who had side-effects in the letrozole/lapatinib group (96%) than in the letrozole/placebo group (86%). The majority of side effects were grade 1-2. The most common side effects were diarrhoea and rash that occurred in 64% and 45 % in the subjects treated with letrozole/laptinib. The majority of the adverse effects, 84% were classified as treatment related in the letrozole/laptinib group. Although most events were grade 1-2 they can impact patients well-being as an example grade 2 diarrhoea is described as "increase of 4-6 stools/ day or nocturnal stools".
Adverse events of interest were except diarrhoea and rash, hepatobiliary events, cardiotoxicity and pulmonary events. Cardiac events were recorded in the letrozole/placebo group in 15 subjects (2%) reported. In the letrozole/laptinib group 32 patients (5%) had 39 events reported.

Hepatobiliary events were more common in the letrozole/laptinib arm and recorded in 15% of the patients.

One patient in each treatment arm was diagnosed with pneumonitis, and further two cases in the lapatinib arm were suggestive of pneumonitis.

The number of SAEs were higher in the letrozole/lapatinib group compared to the letrozole/placebo group, 144 (22%) and 94 (15%), respectively. The most common serious adverse events were decreased ejection fraction and diarrhoea.

Of the SAEs 8% vs. 4% in letrozole/laptinib and letrozole/placebo respectively were considered treatment related.

Fatal SAEs occurred in 8 patients in each treatment group.

There were no different safety signals in older age groups. In general the safety profile is consistent with the known safety profiles of letrozole and lapatinib.

1.4.4 Risk Management plan

Hepatobiliary events, decreased LVEF, pneumonitis/ILD, diarrhoea, rash and interactions with other drugs are important identified risks. Cardiac, hepatobiliary, and pulmonary events are matters of concern due to the potential seriousness, warranting risk-management measures to allow the detection of a pre-existent deficit predisposing to adverse events (such as in the case of cardiac toxicity) or early diagnosis of toxicity manifestations. QTc changes and food effect on bioavailability are potential risks.

Additional risk minimisation activities are proposed for the following safety concerns: Hepatobiliary events, decreased LVEF, diarrhoea and rash, in form of core risk management information.

The RMP has been updated as requested during the assessment. The updated RMP version 8 follows the template for EU-risk management plan and all relevant areas have been covered. Interactions with other drugs were added as an important potential risk. The section for Pharmacological Class Effects was updated. Key elements from Core risk management information were added into the revised proposed SPC and PIL. In addition, the following responses have been submitted: Data from epidemiological and pharmacogenetic studies concerning hepatobiliary events have been submitted and results of an epidemiology study concerning pneumonitis/ILD were shown. A study to evaluate the effect of lapatinib on QT/QTc interval was proposed by the MAH. Data on cardiac and hepatobiliary events in elderly patients was shown. In the SPC, more safety information was added concerning the following topics:

decreased LVEF, pneumonitis/ILD, study results and additional information concerning possible impact on QT interval.

Four epidemiology studies and three pharmacogenetic studies have been undertaken to date regarding hepatobiliary toxicities, and these studies were summarised by the MAH. Timelines for the epidemiology studies were provided. The pharmacogenetic studies revealed strong genetic associations for a Class II MHC locus (centred on HLA-DQA1*0201) with ALT elevation, and the Gilbert´s syndrome variant UGT1A1*28 with TBL elevation. The MAH committed to discuss possible clinical implications of these findings as a follow-up measure (please reefer to section IV for a complete list of the follow-up measures to be undertaken by the MAH).

Summary of the Risk Management Plan for lapatinib

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Hepatobiliary events	Routine pharmacovigilance as detailed in Section 3.1 Targeted follow up questionnaires to ensure complete documentation of reports Regular quarterly evaluations of hepatobiliary events by the SRT until the rate stabilises. Pharmacogenetics studies of subjects who experienced hepatobiliary events (EGF113892/PGX240, EGF113895/PGX272, and EGF113896/PGX275). Epidemiological studies of hepatobiliary events and compliance with LF monitoring (WEUKSTV3635 and WEUKSTV4275).	**Routine activities:** IDMCs are instructed to review hepatobiliary events for the studies they monitor. Warning in Section 4.4 of the SmPC: "*Hepatotoxicity has occurred with Tyverb use and may in rare cases be fatal. Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and monthly thereafter, or as clinically indicated. Tyverb dosing should be discontinued if changes in liver function are severe and patients should not be retreated."* Adverse Reaction in Section 4.8 of the SmPC: "*Hepatobiliary disorders: Common - hyperbilirubinaemia, hepatotoxicity*" **Additional activities:** Core hepatic risk management information for prescribers on the importance of monitoring liver function.
Decreased LVEF	Routine pharmacovigilance as detailed in Section 3.1 Targeted follow up questionnaires to ensure complete documentation of reports Regular routine evaluations of cardiac events by the SRT.	**Routine activities:** IDMCs are instructed to review cardiac events for the studies they monitor. Warning in Section 4.4 of the SmPC: "*Lapatinib has been associated with reports of decreases in left ventricular ejection fraction (LVEF). Lapatinib has not been evaluated in patients with symptomatic cardiac failure. Caution should be taken if Tyverb is to be administered to patients with conditions that could impair left ventricular function (including coadministration with potentially cardiotoxic agents).* *Evaluation of cardiac function, including LVEF determination, should be conducted for all patients prior to initiation of treatment with Tyverb to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with Tyverb to ensure that LVEF does not*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		decline to an unacceptable level. In some cases, LVEF decrease may be severe and lead to cardiac failure. Fatal cases have been reported, causality of the deaths is uncertain". Adverse Reaction in Section 4.8 of the SmPC: ―*Cardiac Disorders: Common - Decreased left ventricular ejection fraction.* Also information in Section 4.2, posology/administration. **Additional activities:** Core cardiac risk management information to inform prescribers on the importance of cardiac monitoring (see Appendix 8).
Pneumonitis/ILD	Routine pharmacovigilance as detailed in Section 3.1 Targeted follow up questionnaires to ensure complete documentation of reports Study of lapatinib/capecitabine combination safety in Japanese patients (EGF109749, estimated completion 3Q 2010)	**Routine activities:** IDMCs are instructed to review pulmonary events for the studies they monitor. Warning in Section 4.4 of the SmPC: "*Lapatinib has been associated with reports of pulmonary toxicity including interstitial lung disease and pneumonitis. Patients should be monitored for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. Pulmonary toxicity may be severe and lead to respiratory failure. Fatal cases have been reported, causality of the deaths is uncertain."* Adverse Reaction in Section 4.8 of the SmPC: "*Respiratory, thoracic and mediastinal disorders: Uncommon – Interstitial lung disease/pneumonitis*". Regular routine evaluations of pulmonary events by the SRT. **Additional activities:** None
Diarrhoea	Routine pharmacovigilance as detailed in Section 3.1 An ongoing CRT (NCS/Keefe) looking at the development of an animal model to study the mechanism of tyrosine kinase inhibitor-induced mucosal injury and diarrhoea.	**Routine activities:** Warning in Section 4.4 of the SmPC: "*Diarrhoea, including severe diarrhoea, has been reported with Tyverb treatment. At the start of therapy, the patients bowel pattern and any other symptoms (e.g. fever, cramping pain, nausea, vomiting, dizziness and thirst) should be determined, to allow identification of changes during treatment and to help identify patients at greater risk of diarrhoea. Patients should be instructed to promptly report any change in bowel patterns. Proactive management of diarrhoea with anti-diarrhoeal agents is*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of Tyverb therapy." Adverse Reaction in Section 4.8 of the SmPC: "*Gastrointestinal disorders: Very common – diarrhoea, which may lead to dehydration.*" **Additional activities:** Core diarrhoea risk management information for prescribers and patients (see Appendix 9).
Rash	Routine pharmacovigilance as detailed in Section 3.1 Review data from completed CRT (NU08-CC2) which retrospectively compared the histological and immunohistochemical alterations of lapatinib-induced skin rash to other approved epidermal growth factor (EGFR) inhibitors (cetuximab, panitumumab, erlotinib).	**Routine activities:** Adverse reaction in Section 4.8 of the SmPC: "*Rash occurred in approximately 28 % of patients who received lapatinib in combination with capecitabine and in 45 % of patients who received lapatinib in combination with letrozole. Rash was generally low grade and did not result in discontinuation of treatment with lapatinib. Prescribing physicians are advised to perform a skin examination prior to treatment and regularly during treatment. Patients experiencing skin reactions should be encouraged to avoid exposure to sunlight and apply broad spectrum sunscreens with a Sun Protection Factor (SPF) 30. If a skin reaction occurs a full body examination should be performed at every visit until one month after resolution. Patients with extensive or persistent skin reactions should be referred to a dermatologist".* **Additional activities:** Core rash risk management information for prescribers and patients (see Appendix 10).
Nausea/Vomiting	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Adverse reactions in Section 4.8 of the SmPC: "*Gastrointestinal disorders: Very common – nausea, vomiting.*" **Additional activities:** None
Interactions with other Drugs	Routine pharmacovigilance as detailed in Section 3.1 Studies planned to evaluate effects of digoxin (EGF110557), and gastric acid lowering drugs on the bioavailability of lapatinib (EGF109275).	**Routine activities:** Activity to be determined if safety signal is identified. **Additional activities:** None
QTc prolongation	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Warning in section 4.4 of the SmPC: "*There has*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Study EGF114271, a multicentre, single-blind, single sequence crossover study planned to assess the potential for lapatinib to prolong QT interval.	*been no dedicated study to assess the potential for lapatinib to prolong the QT interval. A small, concentration dependent increase in QTc interval was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients, such that an effect on QT interval cannot be ruled out. Caution should be taken if Tyverb is administered to patients with conditions that could result in prolongation of QTc (including hypokalemia, hypomagnesaemia, congenital long QT syndrome, or coadministration of other medicines known to cause QT prolongation). Hypokalemia or hypomagnesaemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be considered prior to administration of Tyverb and throughout treatment".* Further Activity to be determined if safety signal is identified. **Additional activities:** None
Food effect	Routine pharmacovigilance as detailed in Section 3.1 Bioavailability studies on the effects of food (EGF111582) and gastric acid lowering drugs (EGF109275).	**Routine activities:** Warning in section 4.4 of the SmPC: "*Grapefruit juice should be avoided during treatment with lapatinib.*" Comment in Section 4.2: "*Lapatinib should be taken either at least one hour before, or at least one hour after food. To minimise variability in the individual patient, administration of lapatinib should be standardised in relation to food intake, for example always be taken before a meal*", and Section 4.5: "*The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat content in the meal. Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with lapatinib*". **Additional activities:** None
Children	Routine pharmacovigilance as detailed in Section 3.1 Paediatric study PBTC 016 in recurrent or refractory medulloblastoma, malignant glioma, or ependymoma ongoing	**Routine activities:** Comment in Section 4.2 of the SmPC: "*TYVERB is not recommended for use in paediatrics due to insufficient data on safety and efficacy.*" **Additional activities:** None
The Elderly	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Comment in Section 4.2 of the SmPC:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		"*There are limited data of the use of Tyverb and capecitabine in patients aged ≥65 years. In the phase III clinical study of Tyverb in combination with letrozole, of the total number of hormone receptor positive metastatic breast cancer patients (Intent to treat population N=642), 44 % were ≥65 years of age. No overall differences in efficacy and safety of the combination of Tyverb and letrozole were observed between these subjects and subjects <65 years of age."* **Additional activities:** None
Pregnant or lactating females	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Warning in Section 4.6 of the SmPC: "*There are no adequate data from the use of Tyverb in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is not known. Tyverb should not be used during pregnancy unless clearly necessary. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with Tyverb. The safe use of Tyverb during breast-feeding has not been established. It is not known whether lapatinib is excreted in human milk. In rats, growth retardation was observed in pups which were exposed to lapatinib via breast milk. Breast-feeding must be discontinued in women who are receiving therapy with Tyverb.""* **Additional activities:** None
Patients with hepatic disease	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Warning in Section 4.2 of the SmPC: "*Lapatinib should be discontinued if changes in liver function are severe and patients should not be retreated. Administration of lapatinib to patients with moderate to severe hepatic impairment should be undertaken with caution due to increased exposure to the medicinal product. Insufficient data are available in patients with hepatic impairment to provide a dose adjustment recommendation.*" **Additional activities:** None
Patients with renal disease	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Warning in Section 4.2 of the SmPC: "*No dose adjustment is necessary in patients with*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		mild to moderate renal impairment. Caution is advised in patients with severe renal impairment as there is no experience of lapatinib in this population." **Additional activities:** None
Patients with low cardiac ejection fraction	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Warning in Section 4.4 of the SmPC: "*Caution should be taken if Tyverb is to be administered to patients with conditions that could impair left ventricular function. (including coadministration with potentially cardiotoxic agents).*" Also comment in Section 4.2 of the SmPC. **Additional activities:** None
Patients of different racial and/or ethnic origins	Routine pharmacovigilance as detailed in Section 3.1 Studies EGF104535 and EGF109749 ongoing, estimated completion 2010 and 3Q 2010 respectively.	**Routine activities:** Activity to be determined if safety signal is identified **Additional activities:** None
Potential for medication errors	Routine pharmacovigilance as detailed in Section 3.1	**Routine activities:** Section 4.1 and Section 4.2 of the SmPC: "*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." And "Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2): 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."* Section 4.2 of the SmPC: "*Tyverb treatment should only be initiated by a physician experienced in the administration of anti-cancer agents."* **Additional activities:** None

1.5 Overall Conclusion and Benefit-Risk Assessment

Benefit:
In patients with HER 2 positive metastatic disease the treatment of choice is generally chemotherapy in combination treatments that target HER 2. However not all patients are candidates for chemotherapy. In postmenopausal women with hormone receptor and HER 2 positive metastatic breast cancer the combination of letrozole and lapatinib has shown a modest increase in PFS compared to letrozole/placebo. The Hazard Ratio (HR) was 0.71 (0.53, 0.96), p= 0.019. The median PFS in the letrozole/lapatinib group was 35.4 weeks compared to 13.0 weeks. This could however be an overestimation a, estimated from HR it should be rather 5-10 weeks. The effect can be acceptable from a clinical point of view.

Uncertainties:
Breast cancer treatment has changed from study start and substantially more patients are receiving aromatase inhibitors and trastuzumab as adjuvant treatment. A concern is how the new treatment standard would affect the results of the studied combination. In the study only very few patients have received previous adjuvant therapy with aromatase inhibitors or trastuzumab which are current treatment standard for many patients in the proposed population. Data provided to support the effect of the lapatinib/aromatase inhibitor combination after progression on trastuzumab are only data from other settings and not regarding the combination.
As pointed out by the MAH, use of sequential endocrine/aromatase inhibitor treatment is in many cases endorsed and as aromatase inhibitors are widely used a clinical interpretation of the registration study without clear information in the indication could be that addition of lapatinib to an aromatase inhibitor after progression was studied which is misleading.
Furthermore the population failed on trastuzumab and aromatase inhibitors could be a different population both with regards to prognosis and with regards to receptor status and other biologic markers than the population studied where the majority of patients had failed on tamoxifen or were endocrine naive. Data were provided which showed a consistency in Hazard Ratios in different HR levels.

The pivotal trial provided evidence for the superiority of efficacy in terms of PFS of lapatinib+letrozole against letrozole alone, but the application targeted all the postmenopausal, HR+/HER2+ patients in first line treatment for metastatic disease. However, the combination of chemotherapy with trastuzumab is generally recommended for patients with good performance status, visceral disease, or rapidly progressing tumours (Prat, 2008). In the study the majority of patients received chemotherapy on progression. Therefore, the evidence supporting this application may be considered to respect just one of the possible ways of treating the target population of patients. There are no direct data to compare lapatinib+letrozole against combination chemotherapy with trastuzumab.

The combination of trastuzumab and an aromatase inhibitor for the treatment of postmenopausal patients with metastatic breast cancer whose tumours overexpress HER2 is currently approved. To accurately determine the clinical benefit of lapatinib in this context comparisons of lapatinib vs. trastuzumab, each in combination with an aromatase inhibitor are needed. Data provided refer to phase II-III studies investigating the effect of lapatinib in combination with antihormonal treatment in neodadjuvant and metastatic setting. No studies in either setting were comparing the effect of lapatinib and letrozole in combination with an aromatase inhibitor.
The MAH is now planning for further clinical trials in the endocrine setting with patients pretreated with trastuzumab.

The endpoint PFS is liable to bias, the assessment of the exact magnitude of the efficacy of the combination required a clarification of radiologically versus symptomatically assessed patients. Data and sensitivity analyses showed that it is admissible that despite the imbalance between the numbers of patients with symptomatic progression, the difference is maintained.

No statistically significant difference was seen in the OS, but the data are immature and results may be further diluted after prolonged follow up and use of next-line therapies. Even though currently available survival data are considered reassuring, an update is asked for.

Risk:

The combination of letrozole/lapatinib revealed no new safety signals of importance compared to what was known previously. However the high frequency of grade 1-2 diarrhoea and rash is clearly a concern from a tolerability perspective.

The most common serious adverse events were decreased ejection fraction and diarrhoea; however, the event rates were sufficiently low to be seen as acceptable in the context of treatment of metastatic breast cancer.

Nevertheless, cardiac, hepatobiliary, and pulmonary events, although relatively rare, are matters of concern due to the potential seriousness, warranting continuous monitoring and risk-management measures to allow the detection of a pre-existent deficit predisposing to premature adverse events (case of the cardiac toxicity), or the early diagnosis of toxicity manifestations.

No different safety signals were revealed in older patients, which is reassuring with regards to the population intended.

Balance:
A modest to moderate effect in terms of PFS prolongation has been shown. In individual patients tolerability problems led to discontinuation of therapy. The difference in adverse drug reactions associated with the combination consisted mainly in drug reactions of mild or moderate severity and is not considered to outweigh the benefits observed. In conclusion, the benefit – risk ratio is considered favourable.

1.6 Product Information

Taking into account the documentation submitted and the assessment of the data as discussed above, the CHMP agreed to extend the indication in SPC section 4.1 as follows:

"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 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)."*

SPC sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 have been revised as a consequence of the extension of indication. Furthermore, SPC section 6.5, labelling and section 6 of the PL have been updated to reflect the additional pack-size of 84 tablets as applied by the MAH. Minor editorial changes were also made to the SPC. In addition, the Package Leaflet has been updated in line with the SPC revisions. Annex II has been revised to reflect the latest approved RMP version. Please refer to Annex 1 for the complete revised Product Information

The CHMP considered the request from the MAH acceptable to not pursue the initially proposed separate package leaflets for the two indications taking into account the MAH proposed changes to SPC section 4.1, PL section 1 as well as the proposed restructuring in PL section 3. These revisions should guide the potential user to more easily identify the relevant prescribed dose by stressing the relevant type of combination therapy (keeping the same type of terminology structure) as in section 1 of the PL. The CHMP considered all this information vital to eliminate possible confusion for the user of the leaflet and yet to be medically correct.

However, during the assessment the MAH mentioned plans to introduce bottle packaging for Tyberb in the second half of 2010 with a future variation application. The committee pointed out that in view of the agreed combined leaflet it should be considered by the MAH that the bottle size would suit both dosing regimens.

User consultation

The Package Leaflet (PL) for Tyverb in combination with capecitabine is based on the current approved PL, which has proven readability in October 2006 during the review of the initial marketing authorisation application, thus the MAH is of the opinion that readability testing is not warranted.

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

Braille

In accordance with Article 56a of Directive 2001/ 83/ EC, the name of the medicinal product will be expressed in Braille on the secondary packaging.

For the present variation the invented name in Braille will be included on the outer boxes. The outer boxes contain the invented name in the different strengths, which is acceptable.

The following information appears in the submitted Product Information, annex IIIA:

tyverb 250 mg

This information appears with dots on the proposed mock-ups as submitted with this application and the location of the Braille dots could be acceptable.

2 CONCLUSION

On 18 February 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.