28 June 2018
EMA/515162/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tyverb

International non-proprietary name: lapatinib

Procedure No. EMEA/H/C/000795/II/0051

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE Adverse event

AI Aromatase inhibitor

ALT Alanine aminotransferase

CHMP Committee for Medicinal Products for Human Use

CRO Contract Research Organization

CT Chemotherapy

EMA European Medicines Agency

FDA Food and Drug Administration

HR Hormone receptor

HER2 Human epidermal growth factor receptor 2

ITT Intent-to-treat population

L Lapatinib

MBC Metastatic breast cancer

OS Overall survival

PFS Progression free survival

SAEs Serious adverse events

SmPC Summary of Product Characteristics

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 21 November 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and II

Update of sections 4.1 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 listed as a condition (ANX027.4) in the Annex II; a Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II has been updated accordingly. A revised RMP version 34.0 has also been submitted as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics and Annex II and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Bruno Sepodes

Timetable	Actual dates
Submission date	21 November 2017
Start of procedure:	23 December 2017
CHMP Co-Rapporteur Assessment Report	21 February 2018
CHMP Rapporteur Assessment Report	20 February 2018
PRAC Rapporteur Assessment Report	20 February 2018
PRAC members comments	28 February 2018
Updated PRAC Rapporteur Assessment Report	1 March 2018
PRAC Outcome	8 March 2018
CHMP members comments	12 March 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 March 2018
Request for supplementary information	22 March 2018
Submission date	24 May 2018
Re-start of procedure:	30 May 2018
PRAC Rapporteur Assessment Report	31 May 2018
PRAC members comments	06 June 2018
CHMP Rapporteur Assessment Report	14 June 2018
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 June 2018
CHMP members comments	18 June 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2018
Opinion	28 June 2018

2. Scientific discussion

2.1. Introduction

Lapatinib (Tyverb) is a protein kinase inhibitor of EGFR (ErbB1) and HER2 (ErbB2) receptors. Lapatinib was first approved in the United States (US) on 13-Mar-2007 under the trade name of Tykerb® and in the EU on 10-Jun-2008 under the trade name of Tyverb in the following indications:

Tyverb is indicated for the treatment of adult 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 trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy (see section 5.1).*

● *In combination with an aromatase inhibitor (AI) 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 AI (see sections 4.4. and 5.1). No data are available on the efficacy of this combination relative to trastuzumab in combination with an AI in this patient population.*

The combination of L+AI for the treatment of postmenopausal patients with HR-positive, HER2-positive MBC was approved in 2010 based on the Phase III EGF30008 study which was a randomised, double-blind study comparing L+AI versus placebo+AI (letrozol) as 1st line therapy for metastatic disease. Notably, the patients in the registrational study had not received prior trastuzumab and furthermore the period of enrolment into the study (December 2003 – December 2006) preceded the adoption of trastuzumab in combination with an AI. Both the lack of lapatinib/trastuzumab comparative data and the fact that the patients enrolled in the EGF30008 study were essentially previously trastuzumab naïve were reflected in the indication. As a post-approval commitment (ANX027.4) the MAH was required by the CHMP and the FDA to conduct a study in a patient population essentially identical to that of EGF30008 except that subjects must have received prior treatment with trastuzumab and with trastuzumab+AI included as the reference arm. The CHMP highlighted that combination of trastuzumab and an AI for the treatment of postmenopausal patients with HR -positive MBC whose tumours overexpress HER2 was already approved, hence to accurately determine the clinical benefit of lapatinib in this context, comparisons of lapatinib vs. trastuzumab, each in combination with an AI were needed. A study was required to include trastuzumab in combination with an AI as the reference arm.

To fulfil the post-authorization measure, the MAH has now submitted the final analysis of the primary efficacy endpoint PFS of the EGF114299 study designed to address these commitments. An update to the PI is further proposed including a change to the indication to delete the sentence "*The patients in the registration study were not previously treated with trastuzumab or an AI (see sections 4.4. and 5.1). No data are available on the efficacy of this combination relative to trastuzumab in combination with an AI in this patient population".*

Due to new therapies becoming available in HER2 positive metastatic breast cancer changing the treatment landscape for this patient population, the MAH has encountered significant challenges in terms of enrolment rate into the EGF114299 study since the launch in 2010. Therefore, on the 15 of October 2015 the MAH met with the regulatory agencies MPA (Rapporteur), INFARMED (CoRapporteur) and the EMA to discuss how to proceed with the study. In summary, the regulatory agencies did not support the proposal from the MAH to terminate the study since in particular data on dual HER2 blockade is of interest. As it was agreed that it was unlikely that the study would show differences in OS due to next line therapies, it was proposed that the MAH should consider changing the primary endpoint to PFS. Subsequent to the meeting the MAH submitted an amended protocol for the EGF114299 study where they had essentially adhered to the scientific advice given (assessed in the ANX 027.3 procedure).

In May 2017, a scientific advice meeting with MPA was held during which the MAH shared the final results of the primary endpoint of the study and it was agreed that the available data from this study could be appropriate to fulfil the ANX027.4 commitment. This has now been submitted whereby changes to the SmPC, Annex II and to the RMP are proposed.

The MAH proposes removal of the statement relevant to the L+AI indication wording in 4.1 where the absence of trastuzumab comparative data and the fact that patients in the EGF30008 study were essentially trastuzumab naïve, is reflected. Furthermore they propose to include information from the submitted final analysis for PFS in section 5.1 and changes to the RMP based on the submitted data.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

One study was submitted in support of this application. Study EGF114299 (CLAP016A2307) is a Phase III, randomized (1: 1: 1), open-label, three-arm study of lapatinib (L) + trastuzumab (T) + aromatase inhibitor (AI), T+AI or L+AI to evaluate the efficacy and safety of these regimens as 1st or 2nd line therapy in postmenopausal patients with HR-positive, HER2-positive MBC who had received prior trastuzumab containing chemotherapy (CT) regimens and endocrine therapies.

2.3.2. Pharmacokinetics

No new information on Clinical pharmacokinetics was submitted.

2.3.3. Pharmacodynamics

No further data on clinical pharmacology were submitted.

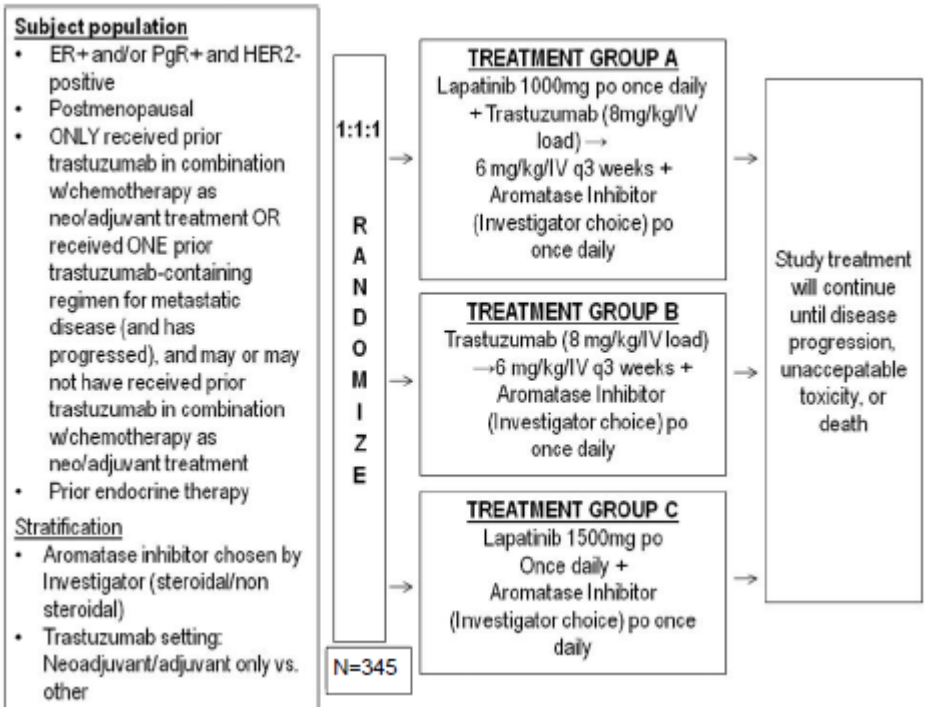
2.4. Clinical efficacy

2.4.1. Main study

Study EGF114299 (ALTERNATIVE/ CLAP016A2307)

Methods

Study schematic diagram



Study participants

Key inclusion criteria

Subjects eligible for enrolment in the study were to meet all of the following criteria:

1. Signed written informed consent

2. Postmenopausal female subjects ≥ 18 years of age. Postmenopausal as defined by any of the following:

- Subjects at least 60 years of age.
- Subjects < 60 years of age and amenorrhic for at least 12 consecutive months AND follicle-stimulating hormone and estradiol levels in postmenopausal range (utilizing ranges from the local laboratory facility).
- Prior bilateral oophorectomy
- Prior radiation castration with amenorrhea for at least 6 months

3. Subjects were to have a history of histologically confirmed breast cancer, with a clinically confirmed diagnosis of metastatic disease (confirmed by histology, cytology or other clinical means (e.g. computed tomography (CT), magnetic resonance imaging (MRI)). Subjects could have either measurable or non-measurable disease per RECIST 1.1 (Eisenhauer et al 2009)

4. Tumours that were ER+ and/or PgR+ by local laboratory

5. Documentation of HER2 overexpression or gene amplification, in the invasive component of either the primary tumour or metastatic disease site as defined as:

- 3+ by immunohistochemistry and/or
- HER2/neu gene amplification by FISH, CISH or SISH; >6 HER2/neu gene copies per nucleus or a FISH, CISH or SISH test ratio (HER2 gene copies to chromosome 17 signals) of ≥ 2.0)

6. Subject had received at least one prior regimen containing trastuzumab in combination with chemotherapy for breast cancer:

- Subject had ONLY received prior trastuzumab in combination with chemotherapy as neoadjuvant and/or adjuvant treatment.

OR

- Subject had received one prior trastuzumab-containing regimen for metastatic disease (and progressed), and could or could not have received prior trastuzumab in combination with chemotherapy as neoadjuvant and/or adjuvant treatment.

7. Subject had received prior endocrine therapy (such as aromatase inhibitors or selective estrogen receptor modulators).

8. Subjects who had a life expectancy of >6 months as assessed by the treating Investigator

9. Subjects had baseline left ventricular ejection fraction ≥ 50% measured by echocardiography or multi-gated acquisition scan

10. Subject had an ECOG performance status of 0 to 1

11. All prior treatment related toxicities were CTCAE (Version 4.0) ≤ grade 1 at the time of randomization

13. Adequate baseline organ functions

14. Subjects met all of the following criteria:

- QTc <450 msec or
- QTc <480 msec for subjects with bundle branch block

Key exclusion criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

1. History of another malignancy with the exceptions of subjects who had been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma were eligible.

2. Subjects with extensive symptomatic visceral disease including hepatic involvement and pulmonary lymphangitic spread of tumour, or the disease is considered by the Investigator to be rapidly progressing or life threatening (subjects who are intended for chemotherapy)

3. Serious cardiac illness or medical condition including but not confined to:

- Uncontrolled arrhythmias
- Uncontrolled or symptomatic angina
- History of congestive heart failure
- Documented myocardial infarction <6 months from study entry

4. Known history of, or clinical evidence of, central nervous system metastases or leptomeningeal carcinomatosis

5. Had acute or currently active/requiring anti-viral therapy hepatic or biliary disease (with the exception of subjects with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per Investigator assessment)

6. Had a concurrent disease or condition that may interfere with study participation, or any serious medical disorder that would interfere with the subject's safety (for example, active or uncontrolled infection or any psychiatric condition prohibiting understanding or rendering of informed consent)

7. Had any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels

8. Had a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to any of the study agents or their excipients that, in the opinion of the Investigator or medical monitor, contraindicated their participation

9. Any prohibited medication as described in Section 9.4.7.2

10. Administration of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.

Treatments

- **Treatment group A**: lapatinib (L) 1000 mg orally once daily plus trastuzumab (T) (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole, or exemestane).

- **Treatment group B**: trastuzumab (T) (loading dose of 8 mg/kg followed by maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole or exemestane).

- **Treatment group C**: lapatinib (L) 1500 mg orally once daily plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole or exemestane).

Objectives / Outcomes / endpoints

Primary objective: Demonstration of superiority of lapatinib+trastuzumab+AI combination (treatment group A) vs. trastuzumab+AI combination (treatment group B) for PFS (by Investigator assessment).

Secondary objectives:

- To compare PFS in treatment group B (trastuzumab+AI) vs. treatment group C (lapatinib+AI) and treatment group A (lapatinib+trastuzumab+AI) vs. treatment group C (lapatinib+AI)

- To compare overall survival in treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI) and treatment group C (lapatinib+AI) vs. treatment group B (trastuzumab+AI)

- To compare overall response rate (ORR; complete or partial response), time to response, and duration of response in treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI) and treatment group C (lapatinib+AI) vs. treatment group B (trastuzumab+AI)

- To compare clinical benefit rate (CBR; complete response, partial response, or stable disease for at least 6 months) in treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI) and treatment group C (lapatinib+AI) vs. treatment group B (trastuzumab+AI)

- The safety objective is to evaluate the safety and tolerability of all three treatment groups (lapatinib+trastuzumab+AI, trastuzumab+AI, lapatinib+AI)

- To compare treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI) and treatment group C (lapatinib+AI) vs. treatment group B (trastuzumab+AI) with respect to change in quality of life (QoL) status relative to baseline

Exploratory objectives

- To identify tumour-derived biomarkers (DNA, RNA, and protein) associated with clinical outcome
- To evaluate biomarkers known to predict sensitivity or resistance to lapatinib and trastuzumab (e.g. p95HER2, PIK3CA mutations, PTEN aberrations and other markers associated with these pathways) and determine the relationship with clinical outcome
- To examine pre- and post-treatment circulating free DNA (cfDNA) to determine whether mutations (e.g. PI3KCA) in cfDNA correlate with that in the tumor tissue from which it is derived
- To investigate the relationship between genetic variants in host DNA and safety and tolerability of lapatinib and/or comparator drugs
- To investigate the relationship between genetic variants in host DNA and efficacy following treatment with lapatinib and/or comparator drugs

Sample size

The total sample size of the study was approximately 345 randomized subjects in a 1:1:1 randomization for the 3 arms (115 subjects/arm).

Randomisation

Patients were randomized in a 1:1:1 design. Stratification factors were:

- AI chosen by the Investigator for on study treatment
- Exposure to prior trastuzumab (neo-adjuvant/adjuvant only or other)

Blinding (masking)

N/A, the EGF114299 study is open-label.

Statistical methods and sample size

The sample size calculation was performed using East software version 5.4. The analysis for PFS was performed when enough events have occurred in treatment group A and treatment group B in order for the test to have 80% power.

To show a 67% improvement (a HR of 0.60) in PFS, the required number of total events to achieve a power of 80% of rejecting the null hypothesis if the alternative hypothesis was true is 121. The following assumptions were made in the estimation of the required sample size:

- Exponential survival distributions
- Approximately 50% of subjects were receiving 1st line metastatic therapy and 50% were receiving 2nd line metastatic therapy in the study. In the trastuzumab+AI arm, median PFS was assumed to be 9 months for 1st line subjects and 5 months for 2nd line subjects. Overall, median PFS times of 7 months

in the trastuzumab+AI arm and 11.7 months in the lapatinib+trastuzumab+AI arm (i.e. a hazard ratio of 0.6).

- A 1:1:1 randomization scheme across the 3 arms.
- An overall 2.5% one-sided risk of erroneously claiming superiority of lapatinib+trastuzumab+AI in the presence of no true underlying difference (overall type I error).
- The actual accrual rate of 0.8, 3.4, 4.5, 9.4 and 11.8 subjects/month for Years 1 to 5 respectively was assumed.
- A minimum of 121 subjects with an event (progression disease or death) were required in the two arms: Treatment group A and treatment group B. To achieve this, an estimated total of 230 subjects were needed to be enrolled in these two arms.
- The primary endpoint was the comparison of the two treatment arms lapatinib+trastuzumab+AI vs. trastuzumab+AI. A third treatment arm of lapatinib+AI was also enrolled for the secondary endpoint comparisons. The total sample size of the study was approximately 345 randomized subjects in a 1:1:1 randomization for the 3 arms (115 subjects /arm).

A total of 355 subjects were enrolled by data cut-off date of 11-Mar-2016. Fourteen (14) additional subjects enrolled after the cut-off date were not included in this analysis.

Results

Participant flow

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=120 n (%)	Lapatinib (1500 mg) +AI N=118 n (%)	Trastuzumab (6 mg/kg) +AI N=117 n (%)	Total N=355 n (%)
Subject status				
Completed	21 (18)	31 (26)	30 (26)	82 (23)
Withdrawn from study	9 (8)	12 (10)	8 (7)	29 (8)
Ongoing	90 (75)	75 (64)	79 (68)	244 (69)
On study treatment	31 (26)	18 (15)	20 (17)	69 (19)
In follow-up	59 (49)	57 (48)	59 (50)	175 (49)
Primary Reason for Study Withdrawal				
Lost to follow-up	4 (3)	7 (6)	5 (4)	16 (5)
Investigator discretion	2 (2)	0	0	2 (<1)
Withdrew consent	3 (3)	5 (4)	3 (3)	11 (3)
Other	0	0	0	0

In total, 284 subjects (80%) had discontinued treatment with 89 subjects (75%) in the lapatinib+trastuzumab+AI arm, 100 subjects (84%) in the lapatinib+AI arm, and 95 subjects (82%) in the trastuzumab+AI arm, and the primary reason for treatment discontinuation was due to disease progression.

Recruitment

A total of 355 subjects were enrolled in the study at the time of the cut-off date for analysis (11-Mar-2016), 120 subjects in the lapatinib (1000 mg)/trastuzumab arm, 118 subjects in the lapatinib (1500 mg) arm, and 117 subjects in the trastuzumab arm from 112 centers in 29 countries worldwide. After the cut-off date, 14 additional subjects were enrolled.

Conduct of the study

The study protocol was amended six times; Amendments 1, 2, 3, 4 and 6 are not considered to have affected the interpretation of study results.

Amendment 5 (18-Mar-2016) was a global amendment: Since study EGF114299 is a post-approval commitment to both the CHMP and the FDA, these regulatory agencies were consulted in light of the study enrolment challenges in this subject population (CHMP in October 2015 and FDA in September 2015). Overall survival in the EGF114299 subject population had substantially increased since the trial was initiated with many new therapies available. As a consequence, at the time the required numbers of survival events would have been reached, the results would not have been relevant from the clinical practice standpoint. Furthermore, next line therapies in this trial would dilute any survival differences, making OS an inappropriate primary endpoint. The primary endpoint was therefore changed from OS to PFS. The protocol was endorsed by the CHMP in Mar-2016 and finalized on 18-Mar-2016. In addition, secondary endpoints were updated, and survival follow-up removed and the revised sample size was changed to approximately 345 subjects.

Baseline data

Summary of demographics and baseline characteristics (ITT)

		Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI	Lapatinib (1500 mg) +AI	Trastuzumab (6 mg/kg) +AI	Total
		N=120	N=118	N=117	N=355
Age (years)	Mean (StD)	56.8 (10.88)	57.2 (9.94)	55.2 (9.78)	56.4 (10.23)
	Median (Min, Max)	57.0 (32, 80)	57.0 (33, 82)	54.0 (30, 84)	56.0 (30, 84)
Age group (years), n (%)	18-64	89 (74%)	88 (75%)	97 (83%)	274 (77%)
	65-74	26 (22%)	24 (20%)	17 (15%)	67 (19%)
	≥ 75	5 (4%)	6 (5%)	3 (3%)	14 (4%)
Sex, n (%)	Female	120 (100%)	118 (100%)	117 (100%)	355 (100%)
Ethnicity, n (%)	Hispanic/Latino	23 (19%)	23 (19%)	20 (17%)	66 (19%)
	Not Hispanic/Latino	97 (81%)	95 (81%)	97 (83%)	289 (81%)
Race, n (%)	American Indian or Alaska Native	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
	Asian	31 (26%)	31 (26%)	32 (27%)	94 (26%)
	Black or African American	2 (2%)	3 (3%)	2 (2%)	7 (2%)
	White	86 (72%)	81 (69%)	80 (68%)	247 (70%)
	Multiple	0	2 (2%)	2 (2%)	4 (1%)
Height (cm)	Mean (StD)	159.9 (6.01)	158.3 (6.37)	160.3 (6.53)	159.5 (6.35)
	Median (Min, Max)	160.0 (143, 176)	158.0 (144, 176)	159.0 (145, 178)	159.0 (143, 178)
ECOG performance status, n (%) [1]	0	74 (63)	72 (61)	74 (64)	220 (62)
	1	44 (37)	47 (39)	42 (36)	133 (38)
Child-bearing potential, n (%)	Post menopausal	120 (100%)	118 (100%)	117 (100%)	355 (100%)

StD: standard deviation

[1] Number of subjects from the Safety Population is used as the denominator of the percentages.

Source: Table 14.1-3.1, Table 14.3-6.1

Summary of disease characteristics at screening (ITT)

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=120	Lapatinib (1500 mg) +AI N=118	Trastuzumab (6 mg/kg) +AI N=117	Total N=355
Time since initial diagnosis (Months)				
N	120	116	113	349
Median (Min, Max)	39.5 (0, 266)	44.5 (3, 203)	41.0 (4, 203)	41.0 (0, 266)
Stage at initial diagnosis, n (%)				
0	1 (<1%)	0	0	1 (<1%)
I	4 (3%)	8 (7%)	7 (6%)	19 (5%)
Ia	2 (2%)	4 (3%)	3 (3%)	9 (3%)
Ib	0	1 (<1%)	2 (2%)	3 (<1%)
Ic	3 (3%)	1 (<1%)	2 (2%)	6 (2%)
II	12 (10%)	12 (10%)	8 (7%)	32 (9%)
IIa	19 (16%)	14 (12%)	19 (16%)	52 (15%)
IIb	15 (13%)	21 (18%)	12 (10%)	48 (14%)
III	6 (5%)	7 (6%)	5 (4%)	18 (5%)
IIIa	20 (17%)	20 (17%)	23 (20%)	63 (18%)
IIIb	15 (13%)	16 (14%)	10 (9%)	41 (12%)
IIIc	9 (8%)	6 (5%)	6 (5%)	21 (6%)
IV	12 (10%)	8 (7%)	17 (15%)	37 (10%)
Unknown	2 (2%)	0	3 (3%)	5 (1%)
Histology at initial diagnosis, n (%)				
Adenocarcinoma	11 (9%)	12 (10%)	13 (11%)	36 (10%)
Ductal carcinoma in situ	16 (13%)	12 (10%)	9 (8%)	37 (10%)
Infiltrating ductal NOS	71 (59%)	68 (58%)	74 (63%)	213 (60%)
Infiltrating lobular carcinoma	8 (7%)	11 (9%)	10 (9%)	29 (8%)
Inflammatory breast carcinoma	4 (3%)	5 (4%)	4 (3%)	13 (4%)
Lobular carcinoma in situ	1 (<1%)	0	0	1 (<1%)
Mucinous adenocarcinoma	2 (2%)	1 (<1%)	0	3 (<1%)
Other	7 (6%)	9 (8%)	7 (6%)	23 (6%)
Histological grade at initial diagnosis, n (%)				
Grade cannot be assessed	27 (23%)	23 (19%)	21 (18%)	71 (20%)
Well differentiated	21 (18%)	12 (10%)	9 (8%)	42 (12%)
Moderately differentiated	37 (31%)	43 (36%)	46 (39%)	126 (35%)
Poorly differentiated	27 (23%)	31 (26%)	30 (26%)	88 (25%)
Undifferentiated	8 (7%)	7 (6%)	11 (9%)	26 (7%)

Continued,

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=120	Lapatinib (1500 mg) +AI N=118	Trastuzumab (6 mg/kg) +AI N=117	Total N=355
Missing	0	2 (2%)	0	2 (<1%)
TNM primary tumor staging at initial diagnosis, n (%)				
T0	1 (<1%)	0	0	1 (<1%)
T1	9 (8%)	12 (10%)	13 (11%)	34 (10%)
T1a	0	0	1 (<1%)	1 (<1%)
T1b	1 (<1%)	5 (4%)	3 (3%)	9 (3%)
T1c	12 (10%)	6 (5%)	9 (8%)	27 (8%)
T2	59 (49%)	49 (42%)	42 (36%)	150 (42%)
T2a	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
T2b	0	1 (<1%)	1 (<1%)	2 (<1%)
T2c	0	1 (<1%)	0	1 (<1%)
T3	11 (9%)	15 (13%)	20 (17%)	46 (13%)
T3a	0	0	1 (<1%)	1 (<1%)
T3b	0	1 (<1%)	0	1 (<1%)
T3c	0	1 (<1%)	0	1 (<1%)
T4	23 (19%)	23 (19%)	23 (20%)	69 (19%)
TIS	0	1 (<1%)	0	1 (<1%)
TX	2 (2%)	1 (<1%)	2 (2%)	5 (1%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
Time since last recurrence (Months)				
N	119	117	116	352
Median (Min, Max)	1.0 (0, 40)	1.0 (0, 34)	1.0 (0, 77)	1.0 (0, 77)
Stage at Screening				
IV	120 (100%)	118 (100%)	116 (>99%)	354 (>99%)
Missing	0	0	1 (<1%)	1 (<1%)
Measurable disease at screening, n (%)				
Yes	89 (74%)	80 (68%)	83 (71%)	252 (71%)
No	31 (26%)	38 (32%)	34 (29%)	103 (29%)
Non-target lesions at screening, n (%)				
Yes	107 (89%)	113 (96%)	104 (89%)	324 (91%)
No	13 (11%)	5 (4%)	13 (11%)	31 (9%)

Source: Table 14.1-3.10

Prior trastuzumab exposure (ITT)

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=120	Lapatinib (1500 mg) +AI N=118	Trastuzumab (6 mg/kg) +AI N=117
In the (neo)-adjuvant setting only	**89 (74%)**	**84 (71%)**	**76 (65%)**
Adjuvant trastuzumab only	75 (63%)	65 (55%)	60 (51%)
Neo adjuvant trastuzumab only	3 (3%)	6 (5%)	6 (5%)
Neo and adjuvant trastuzumab	11 (9%)	13 (11%)	10 (9%)
In the metastatic setting	**31 (26%)**	**34 (29%)**	**41 (35%)**
Metastatic and adjuvant trastuzumab	4 (3%)	4 (3%)	8 (7%)
Metastatic and neo and adjuvant trastuzumab	0	2 (2%)	2 (2%)
Trastuzumab for metastatic disease only	27 (23%)	28 (24%)	31 (26%)

Source: Table 14.1-3.41

Numbers analysed

Subject disposition (ITT)

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=120 n (%)	Lapatinib (1500 mg) +AI N=118 n (%)	Trastuzumab (6 mg/kg) +AI N=117 n (%)	Total N=355 n (%)
Subject status				
Completed	21 (18)	31 (26)	30 (26)	82 (23)
Withdrawn from study	9 (8)	12 (10)	8 (7)	29 (8)
Ongoing	90 (75)	75 (64)	79 (68)	244 (69)
On study treatment	31 (26)	18 (15)	20 (17)	69 (19)
In follow-up	59 (49)	57 (48)	59 (50)	175 (49)
Primary Reason for Study Withdrawal				
Lost to follow-up	4 (3)	7 (6)	5 (4)	16 (5)
Investigator discretion	2 (2)	0	0	2 (<1)
Withdrew consent	3 (3)	5 (4)	3 (3)	11 (3)
Other	0	0	0	0

Source: [Study A2307-Table 14.1-1.1]

Outcomes and estimation

Primary efficacy results – PFS (ITT)

Primary objective to demonstrate superiority of lapatinib+trastuzumab+AI vs. trastuzumab+AI for PFS (radiological progression based on Investigator assessment or death).

Summary of progression-free survival (ITT)

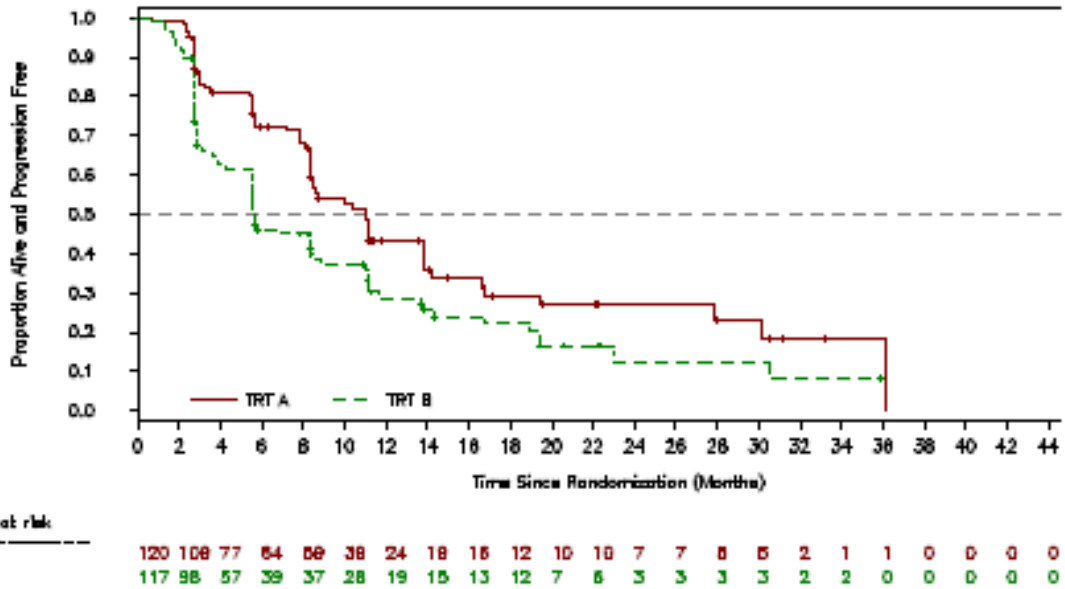
	Lapatinib (1000 mg)+ Trastuzumab (6 mg/kg) + AI N=120	Trastuzumab (6 mg/kg) + AI N=117
Number of subjects, n (%)		
Disease progression or died (event)	62 (52%)	75 (64%)
Censored, follow-up for disease progression ended	7 (6%)	3 (3%)
Censored, follow-up for disease progression ongoing	51 (43%)	39 (33%)
Kaplan Meier estimates for progression-free survival [1] (months)		
1st Quartile	5.7	2.8
95% Confidence Interval	(3.3, 8.3)	(2.8, 3.6)
Median	11.0	5.7
95% Confidence Interval	(8.3, 13.8)	(5.5, 8.4)
3rd Quartile	27.8	14.3
95% Confidence Interval	(13.9, 36.1)	(11.1, 23.0)
Stratified hazard ratio for experimental treatment compared to trastuzumab + AI [2]		
Estimate	0.62	
95% Confidence Interval	(0.45, 0.88)	
Two sided p-value	0.0064	

[1] Progression-free survival is defined as the time from randomization to the earliest date of disease progression (with radiological evidence) or death from any cause, or to the date of censor.

[2] Pike estimate of the treatment hazard ratio, <1 indicates a lower risk compared with trastuzumab + AI. Pike estimate is adjusted for actual strata: AI chosen by the Investigator for this study (steroidal (exemestane) and non-steroidal (letrozole or anastrozole)) and exposure to prior trastuzumab (neoadjuvant/adjuvant only and other).

Source: [Study A2307-Table 14.2-2.1]

Plot of Kaplan-Meier progression-free survival curves (ITT)



TRT A = Lapatinib (1000 mg) + trastuzumab (6 mg/kg)+AI;

TRT B = Trastuzumab (6 mg/kg) + AI;

Source: [Study A2307-Figure 14.2-1.1]

Ancillary analyses

Sensitivity analysis

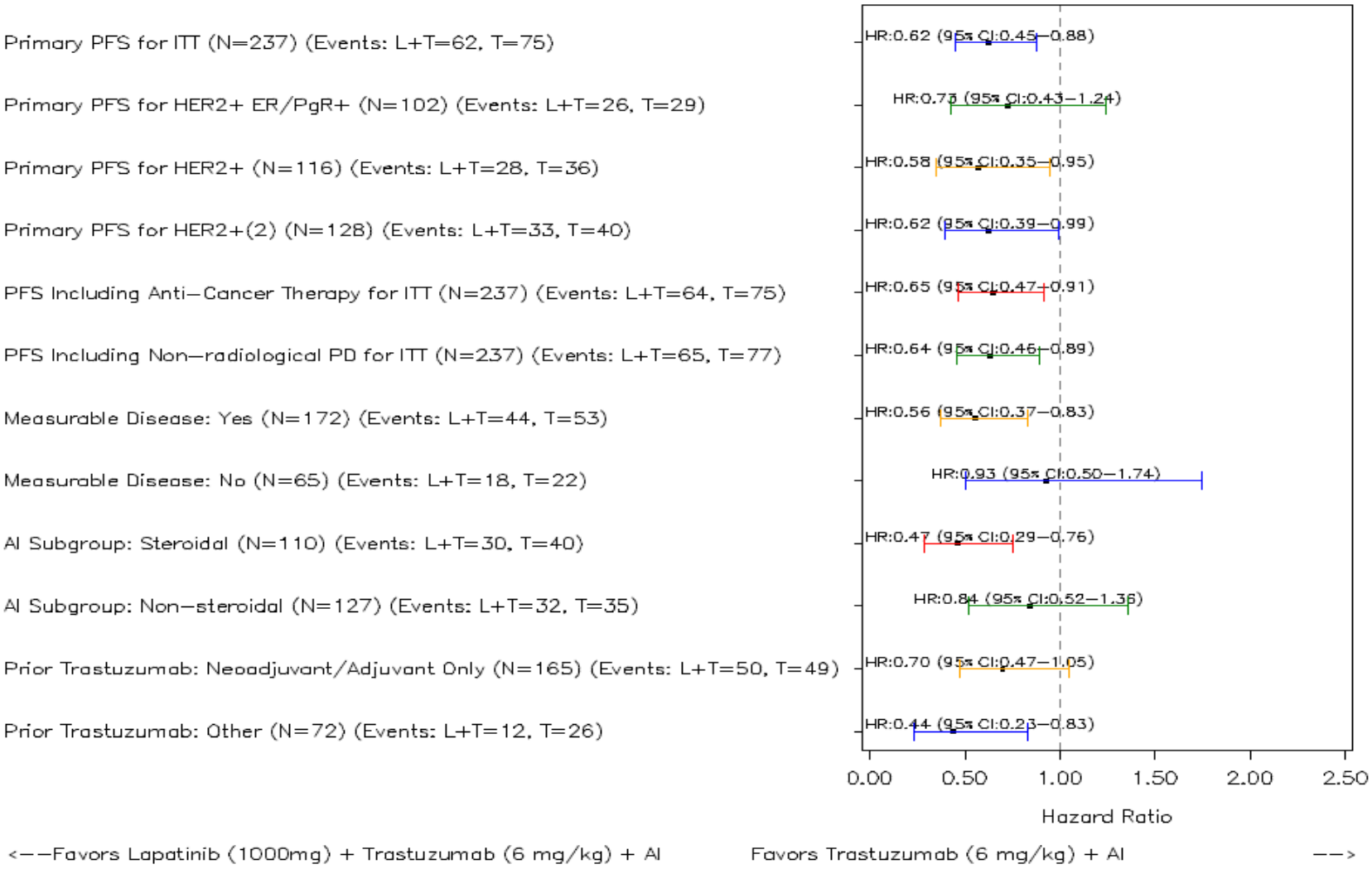
Two sensitivity analyses were performed:

- In the first sensitivity analysis, patients receiving alternative anti-cancer therapies before a PFS event were not censored. For this analysis, there were 53 % and 64 % progressions or deaths in the L+T arm and T arm respectively. The median PFS (95% CI) was 11 months (8.3, 13.8) and about 6 months (5.5, 8.5) respectively with an HR of 0.65 (95% CI: 0.47, 0.91) (p=0.0129) in favour of the combination arm. The rate (95% CI) of progression-free patients at 12 months was 0.44 (0.33, 0.54) in the L+T arm and 0.30 (0.20, 0.40) in the T arm. At 18 months this was 0.29 (0.18, 0.40) and 0.23 (0.14, 0.33) respectively.

- The second sensitivity analysis, non-radiological progressions (as assessed by the Investigator) were included as events. For this analysis, there were 54% and 66 % progressions or deaths in the L+T arm and T arm respectively. The median PFS (95% CI) was 10 months (8.3, 13.8) and about 6 months (5.5, 8.3) respectively with an HR of 0.64 (95% CI: 0.46, 0.89) (p=0.0085) in favour of the combination arm. The rate (95% CI) of progression-free patients at 12 months was 0.40 (0.30, 0.51) in the combination arm compared to 0.28 (0.18, 0.38) in the T arm. At 18 months this was 0.27 (0.17, 0.38) and 0.21 (0.12, 0.31) respectively.

Subgroup analyses (pre-defined)

HRs and 95% CI's for PFS comparing lapatinib+trastuzumab+AI vs. trastuzumab+AI (ITT)



Secondary efficacy results

L+AI arm vs. T+AI arm: The median PFS was about 8 months (95% CI: 5.8, 11.2) in the L+AI arm compared to 6 months (95% CI: 5.5, 8.4) in the T+AI arm with HR 0.71 (95% CI: 0.51, 0.98) (p=0.0361) in favour of the L+AI arm.

L+T+AI arm vs. L+AI arm: The median PFS was 11 months (95% CI: 8.3, 13.8) in the L+T+AI arm compared to 8 months (95% CI: 5.8, 11.2) in the L+AI arm with HR 0.76 (95% CI: 0.54, 1.06) (p=0.1041) in favour of the L+T+AI arm.

Overall response rate (ORR, ITT population)

The response rate (CR+PR) for the L+T+AI arm, L+AI arm and T+AI arm were approximately 32 % vs. 19 % and 14 %, respectively. The odds ratio for the comparison between L+T+AI and T+AI was 2.83 (p-value 0.0017) indicating an improved ORR with the combination of L+T+AI compared to T+AI.

Clinical benefit rate (CBR, ITT population)

The clinical benefit rate (defined as the percentage of subjects with evidence of CR, PR, or SD for at least 6 months) was higher in the L+T+AI arm (41 %) compared to 33 % and 31 % in the L+AI and T+AI arms respectively.

Time to response and duration of response (ITT population)

The median time to response was comparable in the treatment arms. The median duration of response (95% CI) was longer in the L+T+AI arm (14 months [5.7, 33.1]) than in the T+AI arm (8 months [2.8, NE]) and was 11 months (5.6, 22.0) in the L+AI arm.

Overall survival

Survival data are immature. In the ITT population, a total of 82 OS events were observed as of the cut-off date (21 events (18%) in the L+T+AI arm, 31 events (26%) in the L+AI arm, and 30 events (26%) in the T+AI arm). It is noted that the study was not powered for OS. For the OS comparison between L+T+AI vs. T+AI, the HR was 0.60 (95% CI: 0.35, 1.04) in favour of L+T+AI. The median OS was 46 months and 40 months respectively. For the OS comparison between L+AI and T+AI, the HR was 0.82 (95% CI: 0.49, 1.36) in favour of L+AI with a median OS of 45 months and 40 months respectively.

Summary of main study

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

Table 1. Summary of Efficacy for trial EGF114299 (LAP016A2307, acronym ALTERNATIVE)

Title: A Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies		
Study identifier	EGF114299 (LAP016A2307)	
Design	Phase III, randomized (1:1:1), open-label, three-arm comparative study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable not applicable

Hypothesis	Superiority of lapatinib + trastuzumab + AI combination		
Treatments groups	• **Treatment group A**: lapatinib (L) + trastuzumab (T) + aromatase inhibitor (AI)		L 1000 mg orally once daily plus T (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole, or exemestane). Until disease progression, death, or withdrawal, number randomized: 152 patients
	• **Treatment group B**: T + AI		T (loading dose of 8 mg/kg followed by maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole or exemestane). Until disease progression, death, or withdrawal, number randomized: 152 patients
	• **Treatment group C**: L + AI		L 1500 mg orally once daily plus an AI of Investigator's choice orally once daily (either letrozole, anastrozole or exemestane). Until disease progression, death, or withdrawal, number randomized: 152 patients
Endpoints and definitions	Primary endpoint	PFS by Inv	L+T+AI vs. T+AI
	Secondary	PFS PFS	L+AI vs. T+AI L+T+AI vs. L+AI
Database lock	Ongoing		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent-To-Treat Population Cut-off date of the primary analysis 11-Mar-2016			
Descriptive statistics and estimate variability Effect estimate per comparison	Treatment group	Group A	Group B	Group C
	Number of subject	120	118	117
	PFS (median) [months]	11.0	5.7	N/A
	95% CI of median PFS [months]	8.3, 13.8	5.5, 8.4	
	Secondary endpoint PFS	Comparison groups	L+AI vs. T+AI	
		Hazard Ratio (HR)	0.71	

		95% CI of HR 0.51, 0.98
		p=0.0361
	Secondary Endpoint PFS	Comparison groups L+T+AI vs. L+AI
		Hazard Ratio (HR) 0.76
		95% CI of HR 0.54, 1.06
		p=0.1041

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study EGF114299 (CLAP016A2307, acronym ALTERNATIVE) is a Phase III, randomized (1: 1: 1), open-label, three-arm study of lapatinib (L) +trastuzumab (T)+aromatase inhibitor (AI), T+AI or L+AI to evaluate the efficacy and safety of these regimens as 1st or 2nd line therapy in postmenopausal patients with HR-positive, HER2-positive MBC who had received prior trastuzumab containing chemotherapy (CT) regimens and endocrine therapies.

The respective posologies of lapatinib when combined with trastuzumab and/ or AIs are in accordance with the EU approved label (Tyverb SmPC). The trastuzumab posology is in line with clinical practice.

A total of 120, 118 and 117 patients were enrolled in the L+T+AI, L+AI and T+AI arms respectively.

Base-line characteristics are fairly well balanced between the arms. All patients had received trastuzumab prior to enrolment; about 70 % in the (neo)adjuvant setting only and 30 % in the metastatic setting whereof the majority receiving trastuzumab in this setting only (about 25 %).

Stratification factors were “AI chosen by the Investigator for on study treatment” and “Exposure to prior trastuzumab (neo-adjuvant/adjuvant only or other)” and are deemed appropriate.

The protocol was amended six times with the most important being Amendment 5 (18-Mar-2016) where it was agreed with regulatory agencies to change the primary endpoint from overall survival to PFS with OS as secondary endpoint. The amended protocol was endorsed by the CHMP in Mar-2016 and finalized on 18-Mar-2016 (ANX027.3).

Efficacy data and additional analyses

The study met its primary objective demonstrating a 38% risk reduction in PFS in favour of treatment with L+T+AI in comparison with T+AI (HR 0.62, 95% CI: 0.45, 0.88, p=0.0064). About 5 months prolongation in median PFS was observed for the L+T+AI arm compared to T+AI (mPFS of 11 months and about 6 months respectively).

Sensitivity analyses were consistent with the results of the primary analysis which was also supported by the pre-defined subgroups.

The PFS benefit with L+T+AI was supported by the results of secondary endpoints such as ORR and CBR favouring this combination arm.

Of note is the PFS comparison of L+AI vs. T+AI (secondary endpoint) where a 29 % risk reduction in PFS in favour of treatment with L+AI was observed (HR 0.71, 95% CI: 0.51, 0.98, p=0.0361) with

median PFS of 8 months and 6 months respectively. This outcome is in contrast with other randomized studies and in this study likely driven by the fact that all patients were to have received trastuzumab prior to enrolment as per eligibility criteria and thus, constitutes a population of patients that may have begun to developed trastuzumab resistance/ refractoriness as well as patients that may be still trastuzumab responsive.

The median time to response was comparable in the treatment arms. The median duration of response was longer in the L+T+AI arm (14 months) than in the T+AI arm (8 months) and was 11 months in the L+AI arm.

Survival data are immature. In the ITT population, a total of 82 OS events were observed as of the cut-off date (21 events (18%) in the L+T+AI arm, 31 events (26%) in the L+AI arm, and 30 events (26%) in the T+AI arm). The MAH is recommended to provide an update of PFS and mature survival data when available (tentatively planned for September 2020).

Additional data from exploratory ad hoc analyses

Outcome by time categories according to time to disease progression <6 months (indicative of increased risk of trastuzumab resistance, N=50) and ≥ 12 months (indicative of trastuzumab sensitivity, N=156) after (neo)adjuvant trastuzumab has been provided. A time category of ≥ 6 months to < 12 months was also presented but due to limited number of patients/ events, data is non-reliable and not further discussed.

Compared to T+AI, a longer PFS was observed in the L+T+AI arm (median PFS 10 months [95% CI 7.9, 30.2] with HR 0.67 [95% CI 0.28, 1.60]) and in the L+AI arm (6 months [95% CI 2.8, 8.8] with HR 0.47 [95% CI 0.18, 1.25]). Median PFS in the T+AI arm was about 3 months.

Due to immature OS data no conclusion can be drawn but there might be at least numerically a favourable trend for the L+T+AI combination compared to the other two regimens.

In addition, PFS data comparing L+AI to T+AI was presented according to subgroup of patients who received prior trastuzumab in the (neo)adjuvant setting only (84 patients in the L+AI arm and 76 patients in the T+AI arm) versus patients who received prior trastuzumab in the metastatic setting (34 patients in the L+AI arm and 41 patients in the T+AI arm). In the first subgroup a longer PFS was observed in the L+AI arm with a HR of 0.59 (95% CI: 0.39, 0.89). The median PFS was 11 months (95% CI 7.1, 13.9) and 6 months (95% CI 5.5, 11.2) in the L+AI arm and the T+AI arm, respectively. In the subgroup of patients who received prior trastuzumab in the metastatic setting (34 patients in the L+AI arm and 41 patients in the T+AI arm) there was no difference in PFS outcomes between the two treatment arms (HR 0.99, 95% CI 0.57, 1.74). The median PFS was about 6 months in both arms.

2.4.3. Conclusions on the clinical efficacy

The MAH has submitted data from the final analysis of the primary endpoint of PFS from the EGF11499 study to support the fulfilment of the ANX027.4 commitment. A clinically relevant risk reduction of progressive disease or death as well as a relevant prolongation of PFS by the L+T+AI combination as compared to the T+AI regimen has been shown. Further exploratory ad hoc analyses reveal that the licensed L+AI combination compared favourably to the T+AI regimen whilst not being inferior to the L+T+AI combination. Altogether available efficacy data are considered to support the benefit of the licensed L+AI regimen.

2.5. Clinical safety

Introduction

The study population consisted of postmenopausal women with HR+/HER2+ MBC who had received prior trastuzumab containing CT regimens and endocrine therapies.

At the time of the cut-off date of the primary analysis (11-Mar-2016), a total of 355 patients were enrolled in the study. The safety population included 353 patients (two patients randomized to trastuzumab were excluded from the safety population as they did not receive any study treatment). Two patients randomized to the lapatinib+trastuzumab group received only lapatinib or trastuzumab, respectively, and therefore, they were included in the lapatinib+trastuzumab group and in the safety population.

Patient exposure

Summary of exposure to lapatinib (Safety set)

		Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118	Lapatinib (1500 mg) +AI N=119
Daily dose (mg) [1]	Mean (StD)	956.6 (91.15)	1436.6 (135.36)
	Median (Min, Max)	1000.0 (483, 1000)	1500.0 (622, 1500)
Cumulative dose (mg)	Mean (StD)	285389.8 (229603.77)	357250.0 (322933.53)
	Median (Min, Max)	246500.0 (10000, 1079000)	253500.0 (1500, 1709500)
Duration of treatment (weeks) [2]	Mean (StD)	42.21 (33.39)	35.82 (33.20)
	Median (Min, Max)	35.8 (1.4, 154.3)	24.7 (0.1, 197.6)

StD: standard deviation
[1] Daily dose is the cumulative dose divided by the duration of exposure (days).
[2] The duration of treatment period (weeks) is calculated as (the treatment end date - the first dose date + 1)/7.
Source: Table 14.3-1.1

Summary of exposure to trastuzumab (Safety set)

		Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118	Trastuzumab (6 mg/kg) +AI N=116
Number of cycles	n	118	116
	Mean	13.8	10.6
	SD	11.18	10.54
	Median	12.0	6.0
	Min.	1	1
	Max.	52	55

Source: Table 14.3-1.2

Summary of exposure to aromatase inhibitor (Safety set)

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118 n (%)	Lapatinib (1500 mg) +AI N=119 n (%)	Trastuzumab (6 mg/kg) +AI N=116 n (%)
Anastrozole			
N (%)	16 (13.6%)	12 (10.1%)	10 (8.6%)
Median cumulative dose (mg)	200.5	135.500	114.000
Median time on study (weeks)	29.0	19.350	16.500
Letrozole			
N (%)	46 (39.0%)	49 (41.2%)	54 (46.6%)
Median cumulative dose (mg)	756.3	582.5	472.5
Median time on study (weeks)	43.3	33.3	27.0
Exemestane			
N (%)	56 (47.5%)	58 (48.7%)	52 (44.8%)
Median cumulative dose (mg)	5275.0	3825.0	2512.5
Median time on study (weeks)	30.7	22.3	14.4

Source: Table 14.3-1.3

Adverse events

Adverse event overview (Safety set)

	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118 n (%)	Lapatinib (1500 mg) +AI N=119 n (%)	Trastuzumab (6 mg/kg) +AI N=116 n (%)	Total N=353 n (%)
Number of subjects with any on-therapy AE	**109 (92)**	**109 (92)**	**86 (74)**	**304 (86)**
AEs related to study treatment	98 (83)	88 (74)	49 (42)	235 (67)
AEs leading to permanent discontinuation of study treatment	4 (3)	11 (9)	7 (6)	22 (6)
Number of subjects with any on-therapy SAE	**16 (14)**	**20 (17)**	**12 (10)**	**48 (14)**
SAEs related to study treatment	6 (5)	5 (4)	2 (2)	13 (4)
Fatal SAEs	1 (<1)	4 (3)	3 (3)	8 (2)
Fatal SAEs related to study treatment	0	1 (<1)	0	1 (<1)

On-therapy period is defined as the date of first dose of study treatment until the minimum of 30 days post last dose of study treatment, last contact or death.

Source: [Study A2307-Table 14.3.1-1.1]

Adverse events regardless of causality by primary system organ class (Safety set)

System Organ Class	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118 n (%)	Lapatinib (1500 mg) +AI N=119 n (%)	Trastuzumab (6 mg/kg) +AI N=116 n (%)
Number of subjects with any event	109 (92)	109 (92)	86 (74)
Gastrointestinal disorders	89 (75)	76 (64)	36 (31)
Skin and subcutaneous tissue disorders	78 (66)	70 (59)	14 (12)
Infections and infestations	58 (49)	44 (37)	28 (24)
Musculoskeletal and connective tissue disorders	43 (36)	41 (34)	37 (32)
General disorders and administration site conditions	41 (35)	38 (32)	34 (29)
Investigations	39 (33)	39 (33)	25 (22)
Respiratory, thoracic and mediastinal disorders	37 (31)	31 (26)	25 (22)
Metabolism and nutrition disorders	39 (33)	27 (23)	15 (13)
Nervous system disorders	25 (21)	33 (28)	22 (19)
Vascular disorders	13 (11)	11 (9)	16 (14)
Blood and lymphatic system disorders	13 (11)	15 (13)	11 (9)
Injury, poisoning and procedural complications	14 (12)	13 (11)	5 (4)
Psychiatric disorders	6 (5)	13 (11)	11 (9)
Cardiac disorders	9 (8)	5 (4)	4 (3)
Eye disorders	5 (4)	10 (8)	3 (3)
Reproductive system and breast disorders	4 (3)	6 (5)	7 (6)
Renal and urinary disorders	9 (8)	3 (3)	1 (<1)
Hepatobiliary disorders	3 (3)	5 (4)	3 (3)
Immune system disorders	5 (4)	0	4 (3)
Ear and labyrinth disorders	1 (<1)	3 (3)	4 (3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (3)	1 (<1)	2 (2)

Adverse Events (AEs) were grouped by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 19 dictionary.

Source: Table 14.3.1-1.2

AEs (all grades) regardless of causality by preferred term (common defined as an incidence greater than or equal to 10% in any treatment group) (Safety set)

Preferred Term	Lapatinib (1000 mg) +Trastuzumab (6 mg/kg) +AI N=118 n (%)	Lapatinib (1500 mg) +AI N=119 n (%)	Trastuzumab (6 mg/kg) +AI N=116 n (%)
Number of subjects with any common AEs	**104 (88)**	**97 (82)**	**62 (53)**
Diarrhoea	81 (69)	61 (51)	10 (9)
Rash	43 (36)	33 (28)	2 (2)
Nausea	26 (22)	26 (22)	11 (9)
Paronychia	35 (30)	18 (15)	0
Arthralgia	15 (13)	17 (14)	14 (12)
Fatigue	14 (12)	17 (14)	12 (10)
Decreased appetite	21 (18)	16 (13)	4 (3)
Stomatitis	20 (17)	15 (13)	4 (3)
Aspartate aminotransferase increased	7 (6)	20 (17)	10 (9)
Headache	6 (5)	19 (16)	12 (10)
Cough	10 (8)	9 (8)	17 (15)
Alanine aminotransferase increased	8 (7)	18 (15)	7 (6)
Vomiting	12 (10)	17 (14)	1 (<1)
Dermatitis acneiform	15 (13)	10 (8)	2 (2)
Pain in extremity	8 (7)	12 (10)	4 (3)
Palmar-plantar erythrodysaesthesia syndrome	12 (10)	10 (8)	1 (<1)
Alopecia	12 (10)	8 (7)	2 (2)

Adverse events were grouped by preferred term using MedDRA version 19.

Source: [Study A2307-Table 14.3.1-1.3]

Summary of AEs by maximum toxicity grade (with an incidence of greater than 10% in grade 1 in any treatment group) (Safety set)

	Maximum Grade, n (%)					
	1	2	3	4	5	Total
Lapatinib+trastuzumab+AI (N=118)						
Number of subjects with any event	24 (20)	44 (37)	38 (32)	2 (2)	1 (<1)	109 (92)
Diarrhoea	45 (38)	21 (18)	15 (13)	0	0	81 (69)
Rash	31 (26)	12 (10)	0	0	0	43 (36)
Paronychia	17 (14)	18 (15)	0	0	0	35 (30)
Nausea	20 (17)	6 (5)	0	0	0	26 (22)
Decreased appetite	13 (11)	8 (7)	0	0	0	21 (18)
Stomatitis	19 (16)	1 (<1)	0	0	0	20 (17)
Dermatitis acneiform	14 (12)	1 (<1)	0	0	0	15 (13)
Fatigue	11 (9)	2 (2)	1 (<1)	0	0	14 (12)
Vomiting	10 (8)	2 (2)	0	0	0	12 (10)

Continued,

	Maximum Grade, n (%)					
	1	2	3	4	5	Total
Lapatinib+AI (N=119)						
Number of subjects with any event	22 (18)	45 (38)	32 (27)	6 (5)	4 (3)	109 (92)
Diarrhoea	37 (31)	17 (14)	7 (6)	0	0	61 (51)
Rash	27 (23)	3 (3)	3 (3)	0	0	33 (28)
Paronychia	5 (4)	11 (9)	2 (2)	0	0	18 (15)
Nausea	18 (15)	6 (5)	2 (2)	0	0	26 (22)
Decreased appetite	11 (9)	5 (4)	0	0	0	16 (13)
Stomatitis	13 (11)	1 (<1)	1 (<1)	0	0	15 (13)
Dermatitis acneiform	8 (7)	1 (<1)	1 (<1)	0	0	10 (8)
Fatigue	13 (11)	2 (2)	2 (2)	0	0	17 (14)
Vomiting	16 (13)	1 (<1)	0	0	0	17 (14)
Trastuzumab+AI (N=116)						
Number of subjects with any event	21 (18)	36 (31)	22 (19)	4 (3)	3 (3)	86 (74)
Diarrhoea	7 (6)	3 (3)	0	0	0	10 (9)
Rash	1 (<1)	1 (<1)	0	0	0	2 (2)
Paronychia	0	0	0	0	0	0
Nausea	8 (7)	3 (3)	0	0	0	11 (9)
Decreased appetite	3 (3)	1 (<1)	0	0	0	4 (3)
Stomatitis	3 (3)	1 (<1)	0	0	0	4 (3)
Dermatitis acneiform	2 (2)	0	0	0	0	2 (2)
Fatigue	6 (5)	6 (5)	0	0	0	12 (10)
Vomiting	0	0	1 (<1)	0	0	1 (<1)

Adverse events (AEs) were graded according to the CTCAE, version 4.0.

Adverse events (AEs) were grouped by preferred term (PT) using MedDRA version 19

A subject with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade.

Source: [Study A2307-Table 14.3.1-1.5]

Serious adverse event

The frequency of reported SAEs was 14% in the L+T+AI arm, 17% in the L+AI arm and 10% in the T+AI arm. No single SAE had a frequency higher than 1% except for ejection fraction decreased and cellulitis.

Deaths

A total of 14 on-treatment deaths (defined as on treatment and up to 30 days after discontinuation of study treatment) were reported: three patients in the L+T+AI arm, six patients in the L+AI, and five patients in the T+AI group. All deaths were due to disease progression with the exception of one death due to cardiogenic shock and one death due to organ failure in the L+AI arm and one death due to cardiopulmonary arrest in the T+AI arm.

Discontinuation due to adverse events

AEs leading to discontinuation of study treatment occurred in 3% of the patients in the L+T+AI arm, 9% in the L+AI arm and 6% in the T+AI arm.

The AEs leading to discontinuation occurring in more than one patient each were ALT increased (2%), AST increased (3%) and diarrhoea (2%) in the L+AI arm and ALT increased (2%), ejection fraction increased (2%), and dyspnoea (2%) in the T+AI arm.

AEs requiring study drug interruption of lapatinib and/or AI

AEs requiring study drug interruption of lapatinib and/or AI were reported in a higher proportion of patients in the L+T+AI arm and L+AI arm as compared to the T+AI arm (25% and 27% vs. 3%). The most frequently reported AEs requiring interruption of study drug were diarrhoea (13% and 8% vs. 0%), vomiting (3% and 2% vs. 0%) and paronychia (2% and 3% vs. 0%).

AEs requiring dose delays of trastuzumab

Thirteen patients (11%) in the L+T+AI arm experienced AEs requiring dose delays of trastuzumab infusion; five patients (4%) with diarrhoea and two patients (2%) with respiratory tract infection while in the remaining six patients other events were experienced by single individuals. Five patients (4%) had grade 3 AEs. Two patients (single events) in the T+AI arm had AEs requiring dose delays.

Adverse events of special interest (AESI)

The AESIs were analysed by a MedDRA search strategy combining relevant preferred terms:

● Diarrhoea occurred in 81 subjects (69%) in the L+T+AI arm, 61 subjects (51%) in the L+AI arm and in 10 subjects (9%) in the T+AI arm. The number of diarrhoea events was 191, 121 and 10, respectively. Of note, only in the L+AI arm investigational treatment was withdrawn due to three (2%) events of diarrhoea. The majority experienced grade 1 or 2 events, with grade 3 diarrhoea in 19%, 11% and 0% of the patients, respectively. The median time to onset of diarrhoea was 5, 8, and 74.5 days for the L+T+AI arm, L+AI arm, and T+AI arm and the median duration was 11, 14.5 days and 2 days, respectively.

● Rash events occurred in 64 patients (54%) in the L+T+AI arm, 52 patients (44%) in the L+AI arm, and six subjects (5%) in the T+AI arm. The number of rash events was 107, 79 and 6, respectively. Few events required study treatment dose reduction (4%, 4%, and 0%) or interruption (<1%, 6%, and 0%). The majority were grade 1 or 2 except for four patients (8%) with rash in the L+AI arm that were grade 3. The median time to onset was 16.5, 18.0, and 90.5 days for the L+T+AI arm, L+AI arm, and T+AI arm and the median duration was 40, 56 and 15 days, respectively.

● Hepatobiliary events occurred in 19 patients (16%) in the L+T+AI arm, 25 patients (21%) in the L+AI arm, and 18 patients (16%) in the T+AI arm. The number of hepatobiliary events was 25, 60 and 34, respectively. The median time to onset was 85, 87, and 43 days for the L+T+AI arm, L+AI arm, and T+AI arm, respectively. No subject discontinued study treatment in the L+T+AI arm due to hepatobiliary events, while in the L+AI arm and in the T+AI arm, study treatment was withdrawn due to five events (8% of the events) and three events (9% of the events) respectively. In the L+T+AI arm the majority of patients with hepatobiliary events experienced grade 1 or 2 events, and one patient out of 19 (5%) had a grade 3 event. The number of patients with grade 3 events was higher in the L+AI arm (6 out of 25 patients, 24%) and T+AI arm (8 out of 18 patients, 44%). In the L+AI arm, two of the events were serious (one grade 3 SAE of ALT increase related to study treatment, and one fatal SAE of hepatic failure). There were no cases of Hy's law.

● Cardiac events occurred in 7 % in the L+T+AI arm, 2 % in the L+AI arm, and 3 % in the T+AI arm, for a total of 16 cardiac events:

- Seven patients presented with ejection fraction decreased (four outcome recovered, one recovering, and two single episode events reported as not recovered) and one patient with ejection fraction decreased and left ventricular dysfunction (outcome: resolved for both events) in the L+T+AI arm;

- Two patients had ejection fraction decreased in the L+AI arm (two occurrences of the same event in both subjects), all events were reported as recovered;

- Two patients had ejection fraction decreased (outcome recovered) and one subject presented with cardiac failure (two occurrences: one recovered and one intermittent event reported as not resolved) in the T+AI arm.

Regular monitoring of left ventricular ejection fraction (LVEF) every 12 weeks showed a decrease of any degree in 59%, 65%, and 65% of the subjects in the L+T+AI arm, L+AI arm, and T+AI arm, respectively.

● Interstitial lung disease event occurred in one patient in the L+AI arm and one patient in T+AI arm, for a total of two events. Both events were grade 2 events of pneumonitis, lasting 15 and 38 days. The events led to study treatment discontinuation in both cases.

2.5.1. Discussion on clinical safety

At the time of the cut-off date of the primary analysis (11-Mar-2016), a total of 355 patients were enrolled in the study. The safety population included however 353 patients (two patients randomized to trastuzumab were excluded from the safety population as they did not receive any study treatment).

The same proportion of patients experienced AEs in the L+T+AI arm (92%) and the L+AI arm (92%) with notably less in the T+AI group (74%). In the L+T+AI arm and the L+AI arm there were higher proportions of patients with AEs suspected to be related to study treatment compared to the T+AI arm (83% and 74% vs. 42%).

It is recognised that the safety characteristics of lapatinib is consistent with the known safety and tolerability profiles of lapatinib and trastuzumab. SOCs with a more than 10% difference between arms (L+T+AI and L+AI vs. T+AI) were GI disorders (75% and 64% vs. 31%); Skin and subcutaneous tissue disorders (66% and 59% vs. 12%); Infections and infestations (49% and 37% vs. 24%); Metabolism and nutrition disorders (33% and 23% vs. 13%); Investigations (33% and 33% vs. 22%).

Diarrhoea, rash, paronychia, and nausea were amongst the most common occurring AEs (all grades) in the L+T+AI (69%, 36%, 30% and 22%, respectively) and the L+AI arm (51%, 28%, 15% and 22%, respectively). As expected these events occurred less frequently in the T+AI arm (9%, 2%, 0%, and 9%, respectively).

SAEs whilst on therapy occurred in 14% of the patients in the L+T+AI arm, in 17% in the L+AI arm and in 10% in the T+AI arm.

The proportion of treatment discontinuation due to AEs in the respective arms is considered low and does not raise any concerns (3% of the patients in the L+T+AI arm, 9% in the L+AI arm and 6% in the T+AI arm).

AEs requiring study drug interruption of lapatinib and/or AI occurred in a higher proportion of patients in the L+T+AI arm and L+AI arm as compared to the T+AI arm (25% and 27% vs. 3%). The most frequently reported AEs were diarrhoea (13% and 8% vs. 0%), vomiting (3% and 2% vs. 0%) and paronychia (2% and 3% vs. 0%). Thirteen patients (11%) in the L+T+AI arm experienced AEs requiring dose delays of trastuzumab infusion mainly due to diarrhoea (4%) and respiratory tract infection (2%). Two patients (single events) in the T+AI arm had AEs requiring dose delays.

A total of 14 on-treatment deaths (defined as on treatment and up to 30 days after discontinuation of study treatment) were reported: three patients in the L+T+AI arm, six patients in the L+AI, and five patients in the T+AI group. All deaths were due to disease progression with the exception of one death

due to cardiogenic shock and one death due to organ failure in the L+AI arm and one death due to cardiopulmonary arrest in the T+AI arm.

In terms of AEs of special interest, the following was reported:

● Diarrhoea occurred in 69% in the L+T+AI arm, 51% in the L+AI arm and in 9% in the T+AI arm. The majority experienced grade 1 or 2 events, with grade 3 diarrhoea in 19%, 11% and 0% of the patients, respectively. The median time to onset was 5, 8, and 75 days for the L+T+AI arm, L+AI arm, and T+AI arm and the median duration was 11, 15 days and 2 days, respectively.

● Rash events occurred in 54% in the L+T+AI arm, 44% in the L+AI arm, and in 5% in the T+AI arm. The majority were grade 1 or 2 except for four patients (8%) with rash in the L+AI arm that were grade 3. The median time to onset was 17, 18, and 91 days for the L+T+AI arm, L+AI arm, and T+AI arm and the median duration was 40, 56 and 15 days, respectively.

● Hepatobiliary events occurred in 16% in the L+T+AI arm, 21% in the L+AI arm, and 16% in the T+AI arm. The median time to onset was 85, 87, and 43 days for the L+T+AI arm, L+AI arm, and T+AI arm, respectively. In the L+T+AI arm the majority of patients experienced grade 1 or 2 events, and one patient out of 19 (5%) had a grade 3 event. In the L+AI arm, two of the events were serious (one grade 3 SAE of ALT increase related to study treatment, and one fatal SAE of hepatic failure). There were no cases of Hy's law.

● Cardiac events occurred in 7 % in the L+T+AI arm, 2 % in the L+AI arm, and 3 % in the T+AI arm, for a total of 16 cardiac events. Regular monitoring of LVEF every 12 weeks showed a decrease of any degree in 59%, 65%, and 65% of the patients in the L+T+AI arm, L+AI arm, and T+AI arm, respectively.

● Interstitial lung disease event occurred in one patient in the L+AI arm and one patient in T+AI arm, for a total of two events. Both events were grade 2 events of pneumonitis, lasting 15 and 38 days. The events led to study treatment discontinuation in both cases.

2.5.2. Conclusions on clinical safety

The safety profiles of the respective components i.e. lapatinib, trastuzumab and the aromatase infibitors are already sufficiently well characterized as monotherapies as well as in their respective approved combinations i.e. lapatinib+AI, lapatinib+trastuzumab and trastuzumab+AI. It is recognised that by adding lapatinib to that of the trastuzumab and AI combination, an increase in tolerability concerns may be expected. From the safety data provided however, this increase observed is deemed acceptable and considered manageable as evidenced by the low proportion of AE related treatment discontinuations. No new safety signal has been identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 35.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 35.1 with the following content:

Safety concerns

Important identified risks	Hepatobiliary events Decreased LVEF Pneumonitis/ILD Interactions with Other Drugs QTc prolongation Severe cutaneous reactions Food effect
Important potential risks	None
Missing information	Children Elderly Pregnant or lactating females Patients with moderate to severe hepatic disease Patients with severe renal disease Patients with low cardiac ejection fraction Patients of different racial and / or ethnic origin

No changes were proposed to the list of safety concerns as a result of this extension of indication which was found acceptable. However, the list of safety concerns was updated to include information from the RMP version 33 approved within Type II/50G:

- Removal of "rash" and "diarrhoea" as important identified risks
- Missing information updated as follows: "Patients with hepatic disease" to "Patients with moderate to severe hepatic disease" and "Patients with renal disease" to "Patients with severe renal disease".

Pharmacovigilance plan

Table of ongoing and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
EGF117165 (CLAP016A2206): Ongoing	To evaluate changes in the expression of biomarkers associated with immunomodulation.	Not applicable	Final Clinical Study Report submission	Q2-2019
Category 2 – Imposed mandatory additional pharmacovigilance activities.				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

No changes were made to the pharmacovigilance plan as a result of the new indication.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
Hepatobiliary Events	Section 4.2, Section 4.4, Section 4.8 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Decreased LVEF	Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Pneumonitis/ILD	Section 4.2, Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Interactions with other Drugs	Section 4.4 and Section 4.5 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
QTc Prolongation	Section 4.4, Section 4.8 and Section 5.1 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Severe Cutaneous Reactions	Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Food Effect	Section 4.2, Section 4.5, Section 5.1 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Children	Section 4.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Elderly	Section 4.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pregnant or Lactating Females	Section 4.6 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with moderate to severe Hepatic Disease	Section 4.2, Section 4.4, Section 4.8 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with severe Renal Disease	Section 4.2, Section 4.4 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with low cardiac ejection	Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
fraction		signal detection: None Additional pharmacovigilance activities: None
Patients of different racial and / or ethnic origin	Currently available data do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

No changes were proposed to the risk minimisations measures, which was found acceptable.

Routine risk minimisation activities remain sufficient to mitigate the safety concerns of Tyverb.

2.7. Update of the Product information

As a consequence of this new data from study EGF114299/LAP016A2307, sections 4.1, 4.4 and 5.1 of the SmPC have been updated. Particularly, any statement with regards to absence of data on the efficacy on patients previously treated with trastuzumab or an aromatase inhibitor has been removed in the product information.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH did not apply for a new indication or a change in the already approved indication, but proposed removal of the statement in 4.1 where the absence of trastuzumab comparative data and the fact that patients in the EGF30008 study were essentially trastuzumab naïve, is reflected.

3.1.1. Main clinical studies

Study EGF114299 (CLAP016A2307) is a Phase III, randomized (1: 1: 1), open-label, three-arm study of lapatinib (L)+trastuzumab (T)+aromatase inhibitor (AI), T+AI or L+AI to evaluate the efficacy and safety of these regimens as 1st or 2nd line therapy in postmenopausal patients with HR-positive, HER2-positive MBC who had received prior trastuzumab containing chemotherapy (CT) regimens and endocrine therapies.

Eligible patients were to have had received at least one prior regimen containing trastuzumab in combination with chemotherapy either only as (neo)adjuvant treatment (the vast majority, about 70 %) or had received one prior trastuzumab-containing regimen for metastatic disease (in total 30 %) and could (5 %) or could not (25 %) have received prior trastuzumab in combination with chemotherapy as neoadjuvant and/or adjuvant treatment.

- **Treatment group A (N=120)**: lapatinib (L) 1000 mg orally once daily plus trastuzumab (T) (loading dose of 8 mg/kg followed by the maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice).
- **Treatment group B (N=118)**: trastuzumab (T) (loading dose of 8 mg/kg followed by maintenance dose of 6 mg/kg IV q3weeks) plus an AI of Investigator's choice).
- **Treatment group C (N=117)**: lapatinib (L) 1500 mg orally once daily plus an AI of Investigator's choice).

The respective posologies of lapatinib when combined with trastuzumab and/ or AIs are in accordance with the EU approved label (Tyverb SmPC). The trastuzumab posology is in line with clinical practice.

The cut-off date of the primary analysis was 11-Mar-2016.

3.2. Favourable effects

The study met its primary objective demonstrating a 38% risk reduction in PFS in favour of treatment with L+T+AI in comparison with T+AI (HR 0.62, 95% CI: 0.45, 0.88, p=0.0064). About 5 months prolongation in median PFS was observed for the L+T+AI arm compared to T+AI (mPFS of 11 months and about 6 months respectively). The L+T+AI regimen, however, was not superior to the licensed L+AI regimen, but L+AI was borderline superior to T+AI (HR 0.71, 95% CI: 0.51, 0.98, p=0.0361) with median PFS of 8 months and 6 months respectively.

The median time to response was comparable in the treatment arms. The median duration of response was longer in the L+T+AI arm (14 months) than in the T+AI arm (8 months) and was 11 months in the L+AI arm.

Survival data are immature. In the ITT population, a total of 82 OS events were observed as of the cut-off date (21 events (18%) in the L+T+AI arm, 31 events (26%) in the L+AI arm, and 30 events (26%) in the T+AI arm).

The MAH is recommended to provide an update of PFS and OS, however mature survival data is not likely to be expected following the protocol amendment 5 where it was decided to no longer collect OS data. The submission is estimated to be approximately by Sep-2020.

3.3. Uncertainties and limitations about favourable effects

This was an open label study without IRC assessment of ORR and PFS.

3.4. Unfavourable effects

The same proportion of patients experienced AEs in the L+T+AI arm (92%) and the L+AI arm (92%) with notably less in the T+AI group (74%). In the L+T+AI arm and the L+AI arm there were higher proportions of patients with AEs suspected to be related to study treatment compared to the T+AI arm (83% and 74% vs. 42%).

SOCs with a more than 10% difference between arms (L+T+AI and L+AI vs. T+AI) were GI disorders (75% and 64% vs. 31%); Skin and subcutaneous tissue disorders (66% and 59% vs. 12%); Infections and infestations (49% and 37% vs. 24%); Metabolism and nutrition disorders (33% and 23% vs. 13%); Investigations (33% and 33% vs. 22%).

Diarrhoea, rash, paronychia, and nausea were amongst the most common occurring AEs (all grades) in the L+T+AI (69%, 36%, 30% and 22%, respectively) and the L+AI arm (51%, 28%, 15% and 22%, respectively). As expected these events occurred less frequently in the T+AI arm (9%, 2%, 0%, and 9%, respectively).

SAEs whilst on therapy occurred in 14% of the patients in the L+T+AI arm, in 17% in the L+AI arm and in 10% in the T+AI arm.

The proportion of treatment discontinuation due to AEs in the respective arms is considered low and does not raise any concerns (3% of the patients in the L+T+AI arm, 9% in the L+AI arm and 6% in the T+AI arm). The AEs leading to discontinuation occurring in more than one patient each were ALT increased (2%), AST increased (3%) and diarrhoea (2%) in the L+AI arm and ALT increased (2%), ejection fraction increased (2%), and dyspnoea (2%) in the T+AI arm.

AEs requiring study drug interruption of lapatinib and/or AI occurred in a higher proportion of patients in the L+T+AI arm and L+AI arm as compared to the T+AI arm (25% and 27% vs. 3%). The most frequently reported AEs were diarrhoea (13% and 8% vs. 0%), vomiting (3% and 2% vs. 0%) and paronychia (2% and 3% vs. 0%). Thirteen patients (11%) in the L+T+AI arm experienced AEs requiring dose delays of trastuzumab infusion mainly due to diarrhoea and respiratory tract infection). Two patients (single events) in the T+AI arm had AEs requiring dose delays.

A total of 14 on-treatment deaths (defined as on treatment and up to 30 days after discontinuation of study treatment) were reported: three patients in the L+T+AI arm, six patients in the L+AI, and five patients in the T+AI group. All deaths were due to disease progression with the exception of one death due to cardiogenic shock and one death due to organ failure in the L+AI arm and one death due to cardiopulmonary arrest in the T+AI arm.

In terms of AEs of special interest, occurrence of diarrhoea, rash and cardiac events was not unexpectedly somewhat higher in the L+T+AI arm as compared to in particular the T+AI arm. Hepatobiliary events occurred in 16% in the L+T+AI arm, 21% in the L+AI arm, and 16% in the T+AI arm. No cases of Hy's law were identified.

3.5. Uncertainties and limitations about unfavourable effects

Table 2. Effects Table for Tyverb (cut-off date of the primary analysis 11-Mar-2016)

Effect	Short Description	Unit	Lap+Tra+AI N=120	Tras+AI N=117	Lap+AI N=118	Uncertainties/ Strength of evidence
Favourable Effects						
Primary endpoint						
PFS INV L+T+AI vs. T+AI	Median	Mon	11.0 95% CI (8.3, 13.8)	5.7 95% CI (5.5, 8.4)		• HR 0.62 (95% CI; 0.45, 0.88) P=0.0064
	Event rate	N(%)	62 (52%)	75 (64%)		
Key Secondary endpoints						
PFS INV L+AI vs. T+AI	Median	Mon		5.7 (95% CI: 5.5, 8.4)	8.3 (95% CI: 5.8, 11.2)	• HR 0.71 (95% CI; 0.51, 0.98) P=0.036
PFS INV	Median	Mon	11.0 (95% CI: 8.3,		8.3 (95 % CI: 5.8,	• HR 0.76 (95 % CI: 0.54, 1.06)

Effect	Short Description	Unit	Lap+Tra+AI N=120	Tras+AI N=117	Lap+AI N=118	Uncertainties/ Strength of evidence
L+T+AI vs. L+AI			13.8)		11.2)	P= 0.104
ORR (CR+PR)		%	31.7	13.7	18.6	OR 2.83 for L+T+AI and T+AI comparison (p=0.0017)
CBR		%	40.8	30.8	33.1	
DoR	Months		13.9 months, (95% CI:5.7, 33.1)	8.3 months, (95% CI:2.8, NE)	11.1 months (95% CI:5.6, 22.0)	
OS	median	mon	46.0	45.1	40.0	Data immature (in the ITT population, a total of 82 OS events were observed as of the cut-off date (21 events (18%) in the L+T+AI arm, 31 events (26%) in the L+AI arm, and 30 events (26%) in the T+AI arm).
Unfavourable effects						
≥ 1 AE		%	92	74	92	
AE grade ≥3		%	35	25	35	
SAE		%	14	10	17	
AE leading to dose interruption		%	25	3	27	
AE leading to discontinuation		%	3	6	9	
Number of deaths		N	3	5	6	The majority was due to PD one death due to cardiogenic shock and one death due to organ failure in the L+AI arm and one death due to cardiopulmonary arrest in the T+AI arm.
Number of AE with fatal outcome		%	3	5		
Diarrhoea		%	69	9	51	
Rash		%	36	2	28	
Nausea		%	22	9	22	
Paronychia		%	30	0	15	
Arthralgia		%	13	10	14	
Fatigue		%	12	10	14	
Decreased appetite		%	18	3	13	
Stomatitis		%	17	3	15	
ASAT		%	6	9	17	
ALAT		%	7	15	6	
Vomiting		%	10	<1	14	

Abbreviations: CBR - clinical benefit rate (defined as the percentage of subjects with evidence of CR, PR, or SD for

at least 6 months)

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The EGF114299 (acronym ALTERNATIVE) study met its primary endpoint, demonstrating a 38% reduction in the risk of disease progression or death in favour of treatment with lapatinib+trastuzumab+AI (L+T+AI) compared to trastuzumab+AI (T+AI). This is supported by sensitivity- and subgroups analyses. A clinically meaningful 5 months prolongation in median PFS was observed (from 6 months for those receiving trastuzumab+AI to 11 months for patients receiving lapatinib+trastuzumab+AI).

Further exploratory ad hoc analyses confirm the superiority of L+T+AI over T+AI. This is observed regardless of time to progression from last (neo)adjuvant trastuzumab i.e early progressors (< 6 months and indicative of inhanced trastuzumab resistance) or late progressors (≥ 12 months indicative of trastuzumab sensitivity). Consistency with these findings are also observed regardless of whether patients had received prior trasuzumab in the (neo)adjuvant (70 % of the ITT population) or in the metastatic setting (30 %). Due to immature OS data no conclusion can be drawn but there might be at least numerically a favourable trend for the L+T+AI combination compared to the other two regimens.

The analyses further revealed that licensed L+AI combination compared favourably to the T+AI regimen whilst not inferior to the L+T+AI combination (p=0.1). Altogether available efficacy data are considered to support the benefit of the licensed L+AI regimen.

In addition, the response rate (CR+PR) was consistently at least numerically higher with the L+T+AI arm vs the other two treatment arms in all groups based on time to progression after (neo)adjuvant trastuzumab.

The current wording of the indication reads:

In combination with an aromatase inhibitor (AI) 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 AI (see sections 4.4. and 5.1). No data are available on the efficacy of this combination relative to trastuzumab in combination with an AI in this patient population*.**

Altogether available efficacy data are considered to support the benefit of the licensed regimen and the proposed deletion of the **part of the indication indicated in bold and italics above** is endorsed.

The safety profiles of the respective components i.e. lapatinib, trastuzumab and the utilized aromatase inhibitors are already sufficiently well characterized as monotherapies as well as in their respective approved combinations either lapatinib+AI, lapatinib+ The EGF114299 (acronym ALTERNATIVE) study met its primary endpoint, demonstrating a 38% reduction in the risk of disease progression or death in favour of treatment with lapatinib+trastuzumab+AI (L+T+AI) compared to trastuzumab+AI (T+AI). This is supported by sensitivity- and subgroups analyses. A clinically meaningful 5 months prolongation in median PFS was observed (from 6 months for those receiving trastuzumab+AI to 11 months for patients receiving lapatinib+trastuzumab+AI).

3.6.2. Balance of benefits and risks

The benefit risk balance of lapatinib in combination with an aromatase inhibitor in the already approved indication remains positive.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

Further support to the approved indication of lapatinib in combination with an AI has been provided. The proposed changes to Section 4.1, 4.4 and 5.1 of the SmPC are endorsed.

This variation concerning amendments to the SmPC, Annex II and to the RMP is approvable. ANX027.4 is considered fulfilled.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and II

Update of sections 4.1, 4.4 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 listed as a condition (ANX027.4) in the Annex II; a Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II has been updated accordingly. A revised RMP version 35.1 has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and Annex II and to the Risk Management Plan (RMP).

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

“To present data in patients with hormone receptor-positive metastatic breast cancer, not currently intended for chemotherapy, and previously treated with trastuzumab from:
A randomised and controlled clinical trial (EGF114299) in a patient population essentially identical to that of EGF30008 except that subjects must have received prior treatment with trastuzumab, with

aromatase inhibitor (AI) + trastuzumab included as the reference arm."

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.1, 4.4 and 5.1 of the SmPC based on results from study EGF114299/LAP016A2307 listed as a condition (ANX027.4) in the Annex II; a Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies. Annex II has been updated accordingly. A revised RMP version 35.1 has also been approved.

Summary

Please refer to the published Assessment Report: Tyverb H-0795-II-51-AR