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Post-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR DOCETAXEL WINTHROP

International Nonproprietary Name:
docetaxel

Procedure No. EMEA/H/C/808/II/05

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application, with all information of a commercially confidential nature deleted. It may not include all available information on the product in the event that the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application. It should therefore be read in conjunction with the "Questions and Answers" document on the withdrawal of the application, which provides an overview of all available information at the time of the Applicant's withdrawal.

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SCIENTIFIC DISCUSSION

Introduction

Docetaxel Winthrop 20 and 80 mg concentrate and solvent for solution for infusion (INN: docetaxel) was granted a Marketing Authorisation (MA) in April 2007.

Docetaxel Winthrop is an antineoplastic agent (ATC code: L01CD02) that blocks cells in the M phase of the cell cycle by interfering with microtubule structure and function. Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly, which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

Docetaxel Winthrop is indicated for the treatment of:

Breast cancer
- in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node- positive breast cancer.
- in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.
- in monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.
- in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.
- in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer
- in monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
- in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.

Prostate cancer
- in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric adenocarcinoma
- in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Head and neck cancer
- in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

Scope of the variation

This variation concerns an extension of indication for Docetaxel Winthrop (docetaxel) in adjuvant treatment of early stage breast cancer. The Applicant has proposed to add the following new indications to section 4.1 of the SPC:

- Doxorubicin and cyclophosphamide followed by DOCETAXEL WINTHROP in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2.

- DOCETAXEL WINTHROP in combination with trastuzumab, and carboplatin (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2.

This claim is based on the results of the Breast Cancer International Research Group (BCIRG) 006 phase III study **TAXGMA302**. The study compared:

- **AC→T** (= Doxorubicin 60 mg/m² with cyclophosphamide 600 mg/m² on an every 3 weeks basis for 4 cycles followed by docetaxel 100 mg/m² on an every 3 weeks basis for 4 cycles) **(control arm)**;

to

- **AC→TH** (= same as AC→T plus trastuzumab starting at the same time as docetaxel at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration) **(tested arm)**;

and

- **TCH** (= 6 cycles of docetaxel 75 mg/m2 with carboplatin AUC = 6 mg/mL/min, with trastuzumab starting at the same time as docetaxel and carboplatin at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration) **(tested arm)**.

Further, the MAH applied also to amend sections 4.2, 4.4, 4.8 and 5.1 of the SPC and to update the Package Leaflet accordingly. In addition, the MAH proposed to take the opportunity to amend the statement regarding breast feeding in section 4.3 of the SPC and section 2 of the Package Leaflet**.**

Breast cancer

Breast cancer is the most common malignant disease in women, occurring more frequently in developed countries but showing a rising incidence in developing countries. Breast cancer is a public health issue on a global scale. According to estimates in 2002, there were 1 152 161 new cases of breast cancer diagnosed, 411 093 deaths caused by breast cancer and more than 4.4 million women living with breast cancer worldwide (1,2). In Europe, 371 000 estimated new cases of breast cancer were diagnosed and 129 900 breast-cancer-related deaths were reported in 2004 (3).

Surgery is the main modality of treatment in patients with early stage breast cancer. Surgery and/or radiotherapy can control local-regional disease in the majority of patients. Several randomized trials and meta-analyses have demonstrated that both chemotherapy and hormonal therapy, given postoperatively, significantly reduce the risk of relapse and mortality in patients with node-positive or negative operable breast cancer (4,5).

The development of adjuvant chemotherapy began in the 1970s, first with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil [5-FU]) which was then followed by anthracycline-containing regimens, including FAC (5-FU, doxorubicin, cyclophosphamide), FEC (5-FU, epirubicin, cyclophosphamide) and AC (doxorubicin, cyclophosphamide). These regimens produced additional reductions in the risk of relapse and death (6,7,8,9,10,11).
The taxanes (paclitaxel and docetaxel) were then incorporated into these classical regimens either:
- in combination with anthracyclines (docetaxel in combination with doxorubicin and cyclophosphamide – [TAC regimen] /TAX) and sequentially (AC followed by docetaxel / NSABP-27 study) (12,24,25),
- or sequentially (paclitaxel following anthracycline and cyclophosphamide [AC] therapy / CALGB9344 and NSABP-B28 studies) (22,23).

Preclinical data have demonstrated a synergistic effect of the combination of docetaxel and trastuzumab, whereas the combination of trastuzumab and other agents such as paclitaxel was shown to be additive (18). Trastuzumab has been identified as the treatment of choice for patients with HER2-positive breast cancer, and its combination with docetaxel has demonstrated an increase in OS

of 8.5 months compared with single-agent docetaxel (study M77001) in metastatic breast cancer patients (19).

The synergistic effect and the promising results of docetaxel combined with trastuzumab in HER2-positive metastatic breast cancer justified its development in the adjuvant setting (BCIRG006/TAXGMA302 study submitted in the current variation).

Of note, in 2006 Herceptin (trastuzumab) was approved for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable), based on the HERA trial results where Herceptin was initiated after completions of standard chemotherapy (most commonly, anthracycline-containing regimens or anthracyclines plus a taxane).

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Non clinical aspects

Non clinical toxicology studies

Docetaxel Winthrop (docetaxel) was previously found to have a large spectrum of antitumour activity in the preclinical models of murine and human origin, representing a variety of tissue types and behaviour patterns. These previous findings have been used to support the previous indications. Of interest, complete regressions and tumour free survivors were obtained against advanced human MX-1 (mammary tumour xenograft). And for the mammary tumours MA13/C and MA16/C, there were complete regressions of advanced stage tumours. In addition, preclinical studies have demonstrated a synergistic interaction, between docetaxel and trastuzumab in HER2-overexpressing breast cancer cell lines.

No additional specific non clinical toxicology studies have been performed with Docetaxel Winthrop (docetaxel) for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2. All the non clinical toxicology studies already performed and previously submitted, support the present submission, especially the 10-cycle toxicity and toxicokinetic studies in rats and dogs (one cycle consisting of a single intravenous administration every 3 weeks) which were conducted with the same regimen of administration as in the claimed indication.

Environmental risk assessment

The environmental risk assessment (ERA) is submitted on the basis of available information, including results from studies conducted several years ago in compliance with local chemical manufacturing requirements, to ensure that no other environmental concerns were apparent from use of docetaxel.
The present type II variation of Docetaxel Winthrop which concerns the use of Docetaxel Winthrop in combination with trastuzumab for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2, should be exempted from ERA testing requirements because of the non significant increase of environmental exposure related to this new application. The amount predicted for all indications in the next five years in the EU is evaluated at a maximum of 450 kg/year, and the penetration factor is calculated to be 0.044% for a maximal dose of 7 mg/day and 400,000,000 inhabitants in the EU. Under these conditions, the refined PEC surface water is 0.0015 µg/L. The calculated PEC is well overestimated if we consider the short duration of treatment by parenteral route, the compound's high biotransformation, and its limited persistence in the environment as shown by hydrolysis and biodegradation data.

Furthermore, although the octanol/water partition coefficient is elevated, docetaxel was only weakly bound to soil. Finally, although the compound is a potent neoplastic agent and shows marked toxicity to mammals (aneuploidy, hematotoxicity and effect on the reproductive function), there is a threshold dose-response relationship, and a concentration has been determined below which effects are unlikely to occur. In addition, docetaxel shows lower toxicity to bacteria and daphniae which are 105 and 103 times less sensitive than mammalian cells, respectively. For all of the above reasons, the Applicant concluded that there is no major risk for the environment due to the small quantity of docetaxel marketed and in particular no special concerns have been identified. In addition, docetaxel is used in small quantity in major pathologies (cancer) under strict medical supervision in hospitals which ensures confinement of the product and prevents contamination of the environment.

Discussion on Non clinical aspects

- No additional specific non clinical toxicology studies have been performed with Docetaxel Winthrop (docetaxel) for the adjuvant treatment of breast cancer. The absence of non clinical toxicology studies is justified.

- The applicant has presented an ERA study for Docetaxel Winthrop (docetaxel) in which results and methods are acceptable.

Clinical aspects

GCP compliance

According to the applicant, the pivotal trial carried outside the European Union met the ethical requirements of the Declaration of Helsinki, Good Clinical Practice (GCP), applicable national laws and regulations and the ethical principles of Directive 2001/20/EC.

Clinical Pharmacology

The pharmacokinetic profile of Herceptin (trastuzumab) is well known and is based on interaction with HER2 on the tumour, forming complexes with shed HER2 antigen and non-specific disposition similar to that for endogenous IgG. It can be described by a two-compartment model and is characterised by non-linearity at low doses whilst at therapeutic doses (4mg/kg loading dose followed by 2 mg/kg weekly) the kinetic is linear with a half-life of approximately 4 weeks. To date, no clear relationship has been demonstrated between the pharmacokinetics of Herceptin and either safety or efficacy. So far there is no evidence for a PK interaction between Herceptin and other chemotherapies.

The pharmacokinetics of Docetaxel Winthrop (docetaxel) is dose proportional (up to doses of 115 mg/m^2 with infusion times of 1 to 2 hours) and can be described by a three-compartmental model with a terminal half-life of approximately 11 hours. Besides a predominating faecal elimination, docetaxel is eliminated in the urine. Docetaxel is approximately 94% protein bound and is metabolized by the CYP3A4 isoenzyme. Due to the differences in clearance mechanisms and protein binding of trastuzumab and docetaxel a pharmacokinetic interaction is very unlikely. However, as docetaxel might be an independent predictor of both safety and efficacy, it is important to clarify whether concomitant administration of Herceptin might have a significant influence on the PK of docetaxel.
Thus, one formal PK drug-to-drug interaction study was performed in Japan to investigate possible interactions between Herceptin and docetaxel. This was an open-label single arm study enrolling 16 patients with HER2-positive metastatic breast cancer. After a 2 week monotherapy with docetaxel the combination period started.

The treatment schedule was as follows:

Docetaxel: $60mg/m^2$ over 60 min infusion on day 1 followed by a second cycle at 3 weeks and subsequent cycles at 3- to 4-weekly intervals thereafter up to six cycles. One cycle was defined as the time from one administration of docetaxel to the next.
Herceptin: the loading dose was given on day 15 of cycle 1(4mg/kg over 90 min) and thereafter weekly (2mg/kg over 90 or 30 min).

Blood samples for docetaxel determinations were taken on day 1 of the first cycle (monotherapy) and on day 1 of the second cycle (concomitant Herceptin). Samples for Herceptin (concomitant docetaxel) determinations were taken on day 1 of the second cycle. Patients were followed for safety until discontinuation of therapy. The timing of sampling was as follows:
Docetaxel: 0, 0.5, 1, 1.25, 2, 4, 6, 8 and 24 hours post-dose,
Herceptin: 0, 0.75, 1.5, 6, 10, 26, 48, 72 and 168 hours post-dose.

A total of 14 patients were evaluable for PK, and for the comparison of docetaxel monotherapy and concomitant docetaxel and Herceptin therapy data from 10 patients were available. The concentration-time profiles with a 2-phase elimination (Figure 1) and PK parameters (Table 1) were similar for docetaxel alone and for the combination with Herceptin.

FIGURE 1: MEAN PLASMA DOCETAXEL CONCENTRATIONS OVER TIME WITH AND WITHOUT CONCOMITANT HERCEPTIN (N=10)

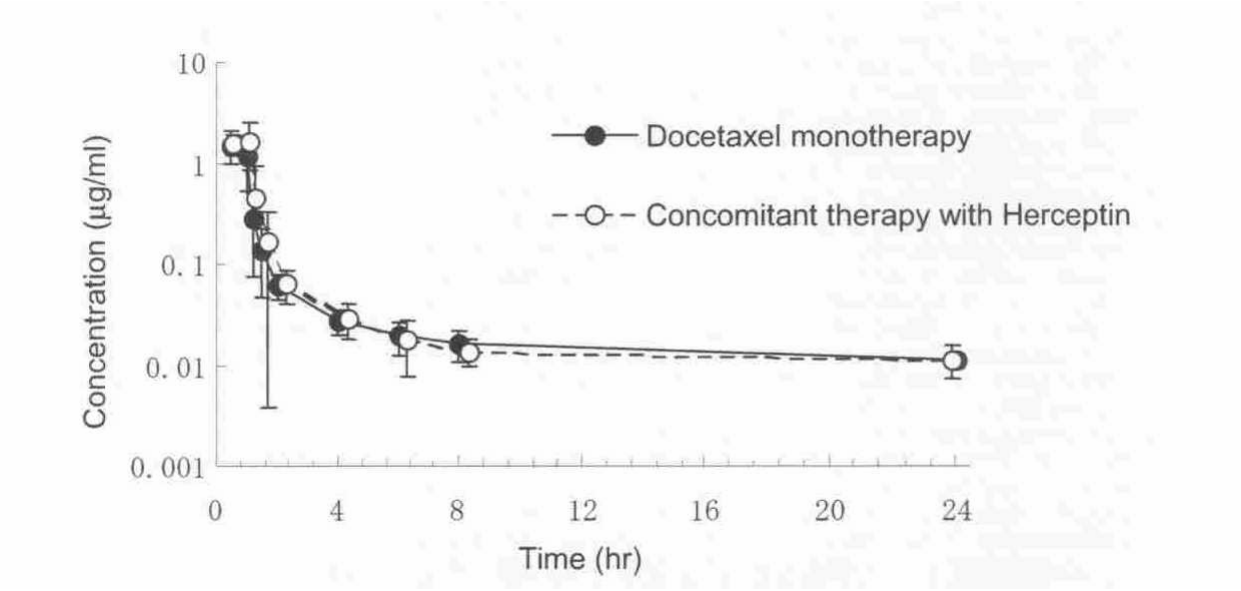

TABLE 1 : MEAN (±SD) PHARMACOKINETIC PARAMETERS OF DOCETAXEL AS MONOTHERAPY AND WITH CONCOMITANT HERCEPTIN

	Docetaxel	Docetaxel + Herceptin
N	10	10
Cmax (μg/mL)	1.65±0.55	1.84±0.69
AUC (μg.hr/mL)	1.89±0.57	2.05±0.5
CL (L/hr/m2)	34.8±12.1	31.4±9.3
Vss (L/m2)	188±133	138±116
t½ (hr)	13.4±8.5	11.6±9.0

The ratio of geometric means (95% CI) were for AUC 1.10 (0.88, 1.36) and Cmax 1.11 (0.85, 1.45). While these point estimates for AUC and Cmax were close to 1.0 the confidence intervals remain quite broad, thus no final conclusion with regard to a possible alteration of the combined administration with Herceptin on the PK of docetaxel can be drawn from this data.
The effect of docetaxel administration on the PK of Herceptin was evaluated retrospectively, because Herceptin was not given as monotherapy. An analysis was made between simulated parameters obtained by population PK analysis of the results of the Japanese Phase I study (MKC454) and the mean serum concentrations from this study.
The obtained data showed that the serum concentration of Herceptin after concomitant administration with docetaxel does not significantly change.

Clinical Efficacy

Pivotal study BCIRG006/TAXGMA302

- **Methods**

Objectives

Primary
To compare disease-free survival (DFS) in 3 groups of subjects treated by:
– doxorubicin and cyclophosphamide followed by docetaxel (AC→T, control group)

- doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH, test group)
- docetaxel in combination with carboplatin and trastuzumab (TCH, test group) in the adjuvant treatment of node positive and high risk node negative patients with operable breast cancer containing the HER2 alteration.

Secondary
- To compare overall survival (OS) between the 3 above mentioned arms.
- To compare cardiac and non-cardiac toxicity between the 3 above mentioned arms.
- To compare toxicity and quality of life between the 3 above mentioned arms.
- To evaluate pathologic and molecular markers which may be considered predictors of response in these patient groups. These markers include: p53, members of the bcl family (Bcl-2, bax, Bcl-X and Bag-1), and MUC1.
- In addition, an independent socio-economic study would be conducted in parallel with the clinical study.

Study Design

BCIRG006 is a multicentre, non-blinded, randomized, stratified, phase III study comparing 3 therapy regimens as adjuvant therapy for women with **HER2-positive**, **early-stage**, **node-positive** and **high-risk** (at least one of the following: tumour size >2 cm, oestrogen receptor or progesterone receptor [ER/PR]-negative, age <35 years, histologic and/or nuclear Grade 2 or 3) **node-negative operable** breast cancer.

High-risk node-negative patients were defined as patients having invasive adenocarcinoma with either no axillary lymph nodes showing evidence of tumour among a minimum of six resected lymph nodes, or a negative sentinel node biopsy and at least one of the following factors: tumour size >2 cm, ER and PR negative, histologic and/or nuclear Grade of 2 or 3, or age <35 years.

Randomization was based on a dynamic minimization procedure, taking into account the following stratification factors: centre, number of axillary lymph nodes involved, and hormonal receptor status.
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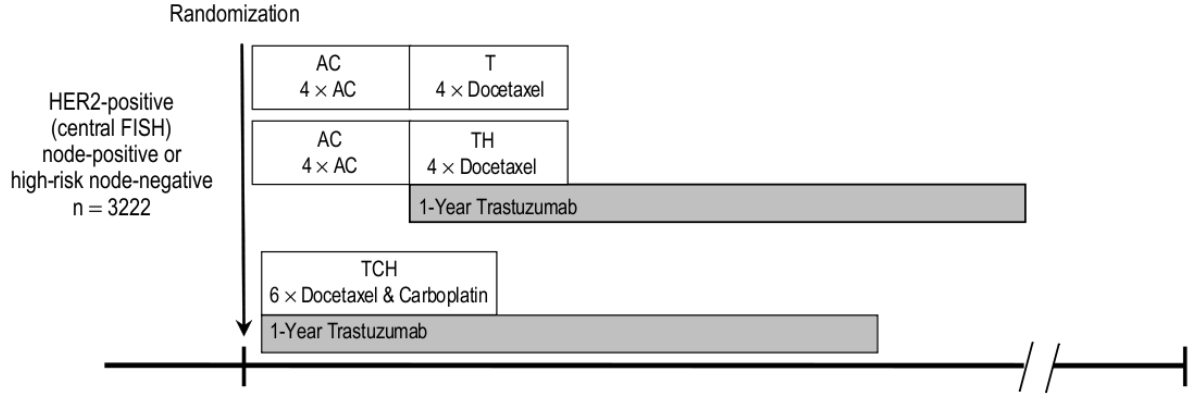


AC = doxorubicin plus cyclophosphamide; AC→T = four cycles of AC followed by four cycles of docetaxel every 3 weeks; AC→TH = same chemotherapy regimen with the addition of 52 weeks of trastuzumab starting concurrently with docetaxel and continuing as monotherapy; FISH = fluorescence in situ hybridization; T = docetaxel; TCH = docetaxel plus carboplatin every 3 weeks concurrently with trastuzumab, followed by trastuzumab monotherapy.

Patients were assessed every 3 weeks during chemotherapy, at the end of chemotherapy, every 3 months for the first 2 years, every 6 months for the next 3 years, and then every year for the final 5 years (10 years of follow-up after the end of chemotherapy).
During the follow-up period, LVEF (echocardiography or MUGA scan) was assessed 3 months, 1 year and 3 years after chemotherapy, mammogram every year during 10 years, and chest x-ray every year during 5 years.

An independent monitoring committee (IDMC) was responsible for ongoing monitoring of safety data and the review of scheduled efficacy and cardiac safety analyses. The IDMC requested that an independent cardiac review panel (ICRP) be constituted to review all cardiac adverse events in a blinded manner.

Study Participants

The main inclusion criteria were:
- age between 18 and 70 years old.
- performance status ≥ 80 %.
- histologically proven breast cancer treated by surgery (margins of resected specimen from definitive surgery had to be histologically free of invasive adenocarcinoma and/or ductal carcinoma in situ) with axillary lymph node involvement assessment.
- lymph node positive or high risk node negative (invasive adenocarcinoma with either 0 (pN0) among a minimum of 6 resected lymph nodes or negative sentinel node biopsy (pN0) AND at least one of the following factors: tumour size >2 cm, ER and PR status is negative, histologic and/or nuclear Grade 2-3, or age <35 years.)
- presence of HER2 gene amplification (FISH analysis).
- Estrogen and progesterone receptor analysis performed on the primary tumour prior to randomization.
- Normal cardiac function had to be confirmed by LVEF (echocardiography or MUGA scan) and ECG within 3 months prior to registration.
- Adequate renal, liver, and haematological function.

The main exclusion criteria were:
- Any T4 or N2 or known N3 or M1 breast cancer.
- Cardiac disease that would preclude the use of doxorubicin, docetaxel, and trastuzumab.
- No previous anticancer therapy for breast cancer, no prior treatment with anthracycline therapy, taxoids or platinium salts.

Treatment

Surgery
Definitive surgical treatment had to be either mastectomy with axillary lymph node involvement assessment, or breast conserving surgery with axillary lymph node involvement assessment.

Chemotherapy

AC→T
Every 3 weeks for 4 cycles, Doxorubicin 60 mg/m^2 as a 5- to 15-minute intravenous (IV) bolus injection followed by cyclophosphamide 600 mg/m^2 as a 5- to 60-minute IV bolus injection.
Beginning 3 weeks after the last cycle of AC, patients received 100 mg/m2 docetaxel as a 1-hour IV infusion every 3 weeks for four cycles. **Control arm.**

AC→TH
Every 3 weeks for four cycles, patients in the AC→TH arm received 60 mg/m2 doxorubicin as a 5- to 15-minute IV bolus injection followed by 600 mg/m2 IV cyclophosphamide as a 5- to 60-minute IV bolus injection. Three weeks after the last treatment with AC (ie, on Day 1 of Cycle 5), a 4-mg/kg trastuzumab loading dose was administered as a 90-minute IV infusion. Beginning on Day 8 of Cycle 5, 2 mg/kg trastuzumab was administered as a 30-minute IV infusion every week. Docetaxel 100 mg/m2 was administered as a 1-hour IV infusion every 3 weeks for four cycles, beginning on Day 2 of Cycle 5 and then on Day 1 of all subsequent cycles. Beginning 3 weeks after the last treatment with docetaxel, 6 mg/kg trastuzumab was administered as a 30-minute IV infusion every 3 weeks.

Trastuzumab treatment was to continue for 1 year from the date of first administration, regardless of the number of doses received or missed. For days on which docetaxel and trastuzumab were both due to be administered, docetaxel was administered first. **Tested arm.**

TCH

Patients in the TCH arm received a 4-mg/kg trastuzumab loading dose as a 90-minute IV infusion on Day 1 of Cycle 1. Beginning on Day 8 of Cycle 1, 2 mg/kg trastuzumab was administered as a 30-minute IV infusion every week. Every 3 weeks for six cycles, beginning on Day 2 of Cycle and then on Day 1 of all subsequent cycles, 75 mg/m2 docetaxel was administered as a 1-hour IV infusion, followed by carboplatin at a target AUC of 6 mg/mL/min as a 30- to 60-minute IV infusion (the dose of carboplatin was calculated using a modified Calvert formula). Beginning 3 weeks after the last treatment with chemotherapy, 6 mg/kg trastuzumab was administered as a 30 minute IV infusion every 3 weeks. Trastuzumab treatment was to continue for 1 year from the date of first administration, regardless of the number of doses received or missed. For days on which docetaxel, carboplatin, and trastuzumab were all scheduled to be administered, docetaxel was administered first, followed by carboplatin and then trastuzumab. **Tested arm.**

Dosing Modification

- Chemotherapy modifications

Chemotherapy discontinuation, dose reductions, or dosing delays were planned for each of the treatment arms in case of severe toxicity. Once a dose had been reduced for toxicity, it was not to be re-escalated, except in the case of resolution of liver enzyme abnormalities.

- Trastuzumab modifications

No dose reductions were planned for trastuzumab. For patients who experienced trastuzumab related Grade 3 or 4 non-haematologic toxicities other than those related to cardiac dysfunction, trastuzumab was held until recovery to Grade 1 or 2.

If recovery to Grade 1 or 2 did not occur, continuation of trastuzumab was left to the discretion of the investigator. If the same Grade 3 or 4 non-haematologic toxicity recurred, trastuzumab was permanently discontinued. Trastuzumab was not held for haematologic toxicity.

Other Protocol-Specified Anti-Tumour Therapy

Hormonal therapy

Patients with positive estrogen and/or progesterone receptors were allowed to have hormonal therapy with tamoxifen or anastrozole, for a total duration not exceeding 5 years.

Radiation therapy

Radiation therapy was to begin 3–8 weeks after completion of chemotherapy. Radiotherapy was mandatory in case of breast-conserving surgery. It was allowed, but not mandatory, in case of mastectomy. Radiation therapy to the internal mammary chain was prohibited for patients if they had developed CHF during study chemotherapy and/or for patients who had trastuzumab administration held at least once for an asymptomatic decrease in LVEF or for a symptomatic cardiac event.

Endpoints

Primary: Disease-Free Survival (DFS) (time from the date of randomization to the date of local, regional, or distant relapse, the date of second primary cancer, or the date death from any cause, whichever occurred first).

Secondary: Overall Survival (OS) (time from the date of randomization to the date of death). Quality of life and evaluation of pathologic and molecular markers for predicting efficacy were not analyzed in this study report.

Statistical methods

Population
DFS and OS were analysed in the Intent-to-treat population. Safety analyses included patients who received any amount of study treatment according to actual treatment regimen received.

Primary and secondary endpoints
1- to 5-year DFS and OS and their 95% CI were estimated using Kaplan-Meier product limit methodology.
Comparisons between treatment arms used logrank-test stratified for nodal status (0 vs. 1–3 vs. ≥4) and hormone receptor status (ER and/or PR positive versus negative).

Multiple comparison
There were two primary comparisons of interest: AC→T versus AC→TH, and AC→T versus TCH. A "step-down" testing procedure was used to compare the control arm AC→T to each trastuzumab containing arm, AC→TH and TCH, using the log-rank test stratified for nodal status (0 vs. 1–3 vs. ≥4) and hormone receptor status (ER and/or PR positive versus negative), at a level α/2 to account for multiple testing. If both of the previous were statistically significant, then comparison of the two trastuzumab-containing regimens could be conducted at the alpha level of significance. All tests of hypotheses were two sided.

Interim analyses
Three interim analyses were to be conducted, when 300, 450, and 650 DFS events had been observed, and a main analysis was to be conducted when 900 DFS events had been observed. A pragmatic group sequential design, as suggested by O'Brien and Fleming, was to be used with overall significance levels alpha of 0.0002, 0.0030, and 0.0111, respectively, for the interim analyses, and an overall significance level of 0.0461 for the main analysis.

The alpha level for each planned interim analyses was determined according to O'Brien and Fleming approach, to ensure an overall alpha-level < 5 % at the end of the study.

- The first interim analysis was performed at 322 events (planned : 300 events), 224 events in the AC→T + AC→TH arms, and 245 in the AC→T + TCH arm. The overall alpha-level for the first interim analysis is 0.00036. The significance-level is 0.00036*224/322 = 0.000172 for AC→T/AC→TH comparison, and 0.00036*245/322 = 0.000188 for the AC→T/TCH comparison.

- The second interim analysis was performed at 474 events (planned : 450 events), 329 events in the AC→T + AC→TH arms, and 340 in the AC→T + TCH arm, leading to an overall alpha-level for the second interim analysis of 0.003916, a significance-level of 0.001926 for the AC→T/AC→TH comparison, and 0.001990 for the AC→T/TCH comparison.

Sample size
To detect a 7% absolute improvement in 5-year DFS (ie, an increase from 55% in AC→T arm to 62% in other arms), with a 2-sided 5% significance level and a 80% power 3150 patients (1050 in each arm) were to be recruited, in order to observe 1308 DFS events. Three pairewise comparisons were of equal interest in the final analysis (AC→T/AC→TH, AC→T/TCH and AC→TH/TCH), the error rate for each comparison was set at 0.017. An interim analysis was planned at 654 DFS events, with an overall alpha-level of 0.001, allowing the use of an unadjusted level of 0.05 for the final analysis.

Safety analysis
The primary population for the analysis of safety was all patients treated with any amount of study drug. Patients were evaluated according to the treatment received.

Interim cardiac analyses
Four cardiac toxicity analyses were to be conducted: after 100 patients per arm, 300 patients per arm, 500 patients per arm, and when all patients randomized in the study had been recruited and evaluated up to and including the fifth LVEF measurement, at nine months from randomization.

The following cardiac events were considered significant: cardiac deaths, CHF events (Grade 3 or 4 CLVF), Grade 3 or 4 arrhythmias, Grade 3 or 4 cardiac ischemia/infarction events. A difference of >4% between the AC→T arm and either of the trastuzumab-containing arms (AC→TH or TCH) would be considered unacceptable, and the concerned treatment arm was to be discontinued.

Subgroup analyses
Several subgroup analyses were performed for DFS and OS, especially according to node-status.
Several sensitivity analyses were planned on the primary and secondary endpoints.

Follow-up
All patients were to be followed in the study until 10 years of follow up.

Efficacy results

Disposition of patients
There were 3222 patients randomized in the study (1073 in AC→T arm, 1074 in AC→TH arm and 1075 in TCH arm), in 43 countries with a total of 433 active centres.
Disposition of patients is summarized in Table 11.

Table 11 – Patient populations

	Number of Patients			
	AC→T	AC→TH	TCH	All
Efficacy population [a]	1073	1074	1075	3222
Safety population [b]	1050	1068	1056	3174
Treatment received				
AC→T [c]	1044	6	0	1050
AC→TH [d]	1	1066	1	1068
TCH [e]	0	0	1056	1056
Untreated	28	2	18	48

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel plus platinum salt plus trastuzumab.
[a]The efficacy population consists of all randomized patients, and all analyses were conducted according to the ITT principle.
[b]The safety population consists of all treated patients and all analyses were conducted on an "as-treated" basis.
[c]Patients 30857, 31363, 31579, 32022, 32376, and 33197 were randomized to receive AC→TH but did not receive trastuzumab.
[d]Patient 31682 was randomized to AC→T but received her first dose of trastuzumab during the monotherapy phase of the study. One patient (30344) was randomized to receive TCH but received AC→TH.
[e]Patients 32533 and 32816 received trastuzumab but no chemotherapy.
Source: Table 14.1/3.

Protocol deviations
There are few major protocol deviations (2.4%), well reparted in the three arms (2.3% in AC→T arm, 2.2% in AC→TH arm, and 2.6% in TCH arm). Twelve patients with HER2-negative by FISH were included in the study. Eighteen (18) patients from the control arm crossed over and received trastuzumab.

Baseline data
Study Demographic and tumour characteristics at baseline are shown in Table 14 and Table 15.

Table 14 – Demographic and baseline characteristics: Randomized patients

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
Age (yr)			
n	1073	1074	1075
Mean (SD)	48.8 (9.7)	48.7 (9.7)	48.6 (9.9)
Median	49.0	49.0	49.0
Range	23–74	22–74	23–73
≤ 50	608 (56.7%)	596 (55.5%)	620 (57.7%)
> 50	465 (43.3%)	478 (44.5%)	455 (42.3%)
< 65	1009 (94%)	1015 (94.5%)	1004 (93.4%)
≥ 65	64 (6.0%)	59 (5.5%)	71 (6.6%)
Weight (kg)			
n	1072	1074	1075
Mean (SD)	69.5 (15.2)	70.5 (16)	69.6 (15.1)
Median	66.0	68.0	66.4
BSA (m^2)			
n	1072	1074	1074
Mean (SD)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)
Median	1.7	1.7	1.7
Karnofsky PS			
n	1073	1074	1075
100%	856 (79.8%)	853 (79.4%)	862 (80.2%)
<100%	217 (20.2%)	221 (20.6%)	213 (19.8%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; BSA=body surface area; PR=progesterone receptor; PS=performance status; SD=standard deviation; TCH=docetaxel plus platinum salt plus trastuzumab.

Source: Table 14.1/18.

Table 15 – Tumor and surgery history: All randomized patients

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
HER2 status per central laboratory			
n	1072[a]	1074	1075
Positive	1066 (99.4%)	1070 (99.6%)	1073 (99.8%)
Negative	6 (0.6%)	4 (0.4%)	2 (0.2%)
Primary surgery type			
n	1073	1074	1075
Mastectomy	638 (59.5%)	674 (62.8%)	642 (59.7%)
Quadrantectomy	270 (25.2%)	255 (23.7%)	268 (24.9%)
Lumpectomy	165 (15.4%)	145 (13.5%)	165 (15.3%)
Detection type			
n	869	864	871
Sentinel node	113 (13.0%)	112 (13.0%)	115 (13.2%)
Axillary dissection	757 (87.1%)	753 (87.2%)	757 (86.9%)
Both	1 (0.1%)	1 (0.1%)	1 (0.1%)
Number of positive nodes			
n	1073	1074	1075
0	309 (28.8%)	306 (28.5%)	307 (28.6%)
1–3	413 (38.5%)	410 (38.2%)	415 (38.6%)
4–9	207 (19.3%)	236 (22.0%)	232 (21.6%)
10+	144 (13.4%)	122 (11.4%)	121 (11.3%)
Hormone receptor	1073	1074	1075
ER-positive and/or PR-positive	577 (53.8%)	578 (53.8%)	579 (53.9%)
ER-negative and PR-negative	496 (46.2%)	496 (46.2%)	496 (46.1%)
Tumor size (cm)			
n	1073	1074	1074
≤2	437 (40.7%)	413 (38.5%)	433 (40.3%)
>2	636 (59.3%)	661 (61.5%)	641 (59.7%)
Margin involvement			
n	1073	1074	1074
Yes	2 (0.2%)	3 (0.3%)	3 (0.3%)
No	1071 (99.8%)	1071 (99.7%)	1071 (99.7%)
Nuclear grade			
n	1073	1074	1075
GX: grade not assessable	44 (4.1%)	52 (4.8%)	45 (4.2%)
G1: well differentiated	24 (2.2%)	12 (1.1%)	18 (1.7%)
G2: moderately differentiated	301 (28.1%)	321 (29.9%)	300 (27.9%)
G3: poorly differentiated	701 (65.3%)	688 (64.1%)	709 (66.0%)
G4: undifferentiated	3 (0.3%)	1 (0.1%)	3 (0.3%)
Histologic type			
n	1073	1074	1075
Infiltrating ductal carcinoma	966 (90.0%)	981 (91.3%)	986 (91.7%)
Infiltrating lobular carcinoma	38 (3.5%)	31 (2.9%)	30 (2.8%)
Other	69 (6.4%)	62 (5.8%)	59 (5.5%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI=confidence interval; TCH=docetaxel plus platinum salt plus trastuzumab.
[a]Patient 30839 was found to be HER2-positive based upon local test results but could not be assessed by central laboratory.
Source: Table 14.1/18.

Concomitant treatment

Use of treatments for the cardiovascular system during the study is comparable in the AC→TH and TCH arms (23.7% and 22.2%, respectively), and is lower in the AC→T arm (17.3%).

Treatments with anti-infectives for systemic use were administered to 55.3% of patients in the AC→T arm, 60.2% in AC→TH arm, and 52.4% in TCH arm.

Forty-three percent (43%) of patients received anti-estrogen, 44% received cytokines and this was well balanced between treatment arms.

Radiation therapy was given to 62% of all patients, most often on the breast/chest wall region, and supraventricular region (especially for node-positive patients).

Primary efficacy endpoint

The primary efficacy analysis was the comparison of DFS between treatment arms in the ITT population.

- First interim analysis

The median duration of follow-up at data cut-off date was 23 months. 322 DFS events were observed. The p-value for the AC→T versus AC→TH comparison was 0.0000005 (alpha level : 0.000172, HR : 0.49; 95% CI: 0.37, 0.65). the p-value for the AC→T versus TCH comparison was 0.000153 (alpha level : 0.000188, HR: 0.61; 95% CI: 0.47, 0.79).

- Second interim analysis

The median duration of follow-up at data cut-off date was 36 months. 474 DFS events were observed. The p-value for the AC→T versus AC→TH comparison was <0.0001 (alpha level : 0.001926, HR : 0.61; 95% CI: 0.49, 0.77). the p-value for the AC→T versus TCH comparison was 0.0003 (alpha level: 0.001990, HR: 0.67; 95% CI: 0.54, 0.83).

195 events were observed in AC→T arm, 134 in AC→TH arm, and 145 in TCH arm. In AC→T arm, 85.6% of events are relapse of breast cancer, in AC→TH arm 80.6%, and in TCH arm 84.8%. Most of relapses were distant recurrence.

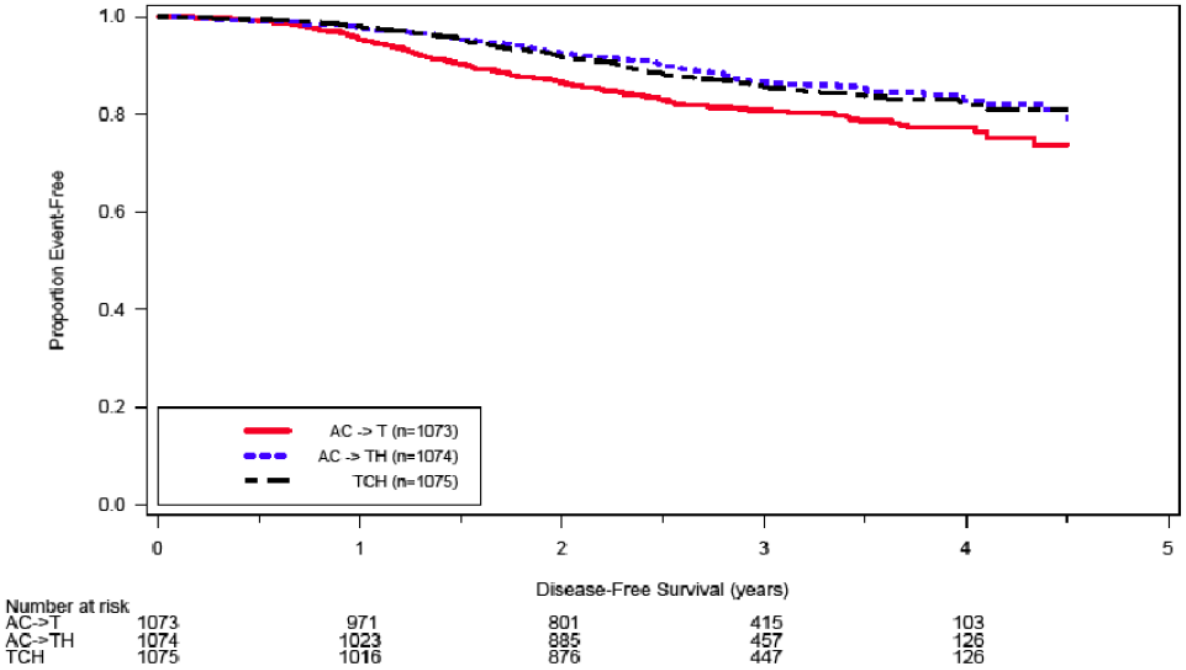
There was no difference between the AC→TH and the TCH arms (p :0.46, HR: 1.09 ; 95% CI: 0.86; 1.38).
Three-year survival rate was 80.9% in AC→T arm, 86.7% in AC→TH arm, and 85.5% in TCH arm.

Table 18 – Disease-free survival: All randomized patients

	AC→T (n = 1073)	AC→TH (n = 1074)	TCH (n = 1075)
Patients with an event [a]	195 (18.2%)	134 (12.5%)	145 (13.5%)
Breast Cancer Relapse [b]	167	108	123
- Distant recurrence	142	89	97
- Local/regional recurrence	40	28	37
Second primary cancer	23	21	15
Death NED	5	5	7
Patients without an event	878 (81.8%)	940 (87.5%)	930 (86.5%)
Stratified analysis			
Hazard ratio [c]	NA	0.61	0.67
95% CI	NA	(0.49, 0.77)	(0.54, 0.83)
p-value [d]	NA	<0.0001	0.0003
Percent event free at: (95% CI); **absolute benefit** [e]			
Year 1	95.2% (93.9%, 96.5%)	97.8%; **2.6%** (96.9%, 98.7%)	98.0%; **2.8%** (97.1%, 98.8%)
Year 2	86.6% (84.5%, 88.7%)	92.6%; **6.0%** (91.0%, 94.2%)	91.8%; **5.2%** (90.1%, 93.5%)
Year 3	80.9% (78.3%, 83.5%)	86.7%; **5.8%** (84.4%, 89.0%)	85.5%; **4.6%** (83.2%, 87.9%)
Year 4	77.3% (74.1%, 80.5%)	82.9%; **5.6%** (79.6%, 86.1%)	82.0%; **4.7%** (78.8%, 85.1%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI = confidence interval; NA = not applicable; NED = no evidence of disease; TCH = docetaxel plus platinum salt plus trastuzumab.
[a] Earliest contributing event.
[b] A patient could be included in more than one event category; thus, the sum across rows may not equal the value in the "Major" row.
[c] Relative to AC→T. Estimated using Cox regression stratified by node and hormonal receptor status.
[d] Stratified log-rank p-value.
[e] Numbers are based on Kaplan-Meier estimate. Absolute benefit in percent event free compared with AC→T.
Source: Tables 14.2/4, 14.2/5, and 14.2/6.

Figure 2 – Disease-free survival: ITT population



Number at risk					
AC->T	1073	971	801	415	103
AC->TH	1074	1023	885	457	126
TCH	1075	1016	876	447	126

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; n = population size; TCH = docetaxel plus carboplatin plus trastuzumab.
Source: CSR Appendices [Table 14.2/1]

Secondary efficacy endpoints

DFS by nodal status

Results in high risk node negative patients (n = 922) and in node positive patients (n = 2300) are still in favour of experimental arms. In node negative patients, difference between AC→T and AC→TH and between AC→T and TCH arms are statistically significant (respectively: HR: 0.36; 95% CI: 0.19, 0.68 and HR: 0.52; 95% CI: 0.30, 0.92), and are slightly larger than in node positive patients (respectively: HR: 0.67; 95% CI: 0.53, 0.85 and HR: 0.70; 95% CI: 0.56, 0.89).

Overall Survival

At the cut off date, 185 patients had died (80, 49 and 56 in the AC→T, AC→TH and TCH treatment groups, respectively). The proportion of patients lost to follow-up was similar in the 3 treatment groups (1.5% overall).

Table 24 – Overall survival: All randomized patients

	AC→T (n=1073)	AC→TH (n=1074)	TCH (n=1075)
Patients who died	80 (7.5%)	49 (4.6%)	56 (5.2%)
Patients alive	993 (92.5%)	1025 (95.4%)	1019 (94.8%)
Stratified analysis			
Hazard ratio [a]	NA	0.58	0.66
95% CI	NA	(0.40, 0.83)	(0.47, 0.93)
p-value [b]	NA	0.0024	0.0182
Percent event free at: (95% CI); **absolute benefit** [c]			
Year 1	99.3% (98.8%, 99.8%)	99.6%; **0.3%** (99.2%, 100%)	99.5%; **0.2%** (99.1%, 99.9%)
Year 2	96.8% (95.7%, 97.9%)	98.5%; **1.8%** (97.8%, 99.3%)	97.8%; **1.1%** (96.9%, 98.7%)
Year 3	93.0% (91.2%, 94.8%)	95.5%; **2.5%** (94.0%, 96.9%)	95.2%; **2.2%** (93.7%, 96.6%)
Year 4	86.6% (83.2%, 90.1%)	92.2%; **5.5%** (89.5%, 94.8%)	91.1%; **4.4%** (88.4%, 93.8%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; NA = not applicable; TCH = docetaxel plus platinum salt plus trastuzumab.

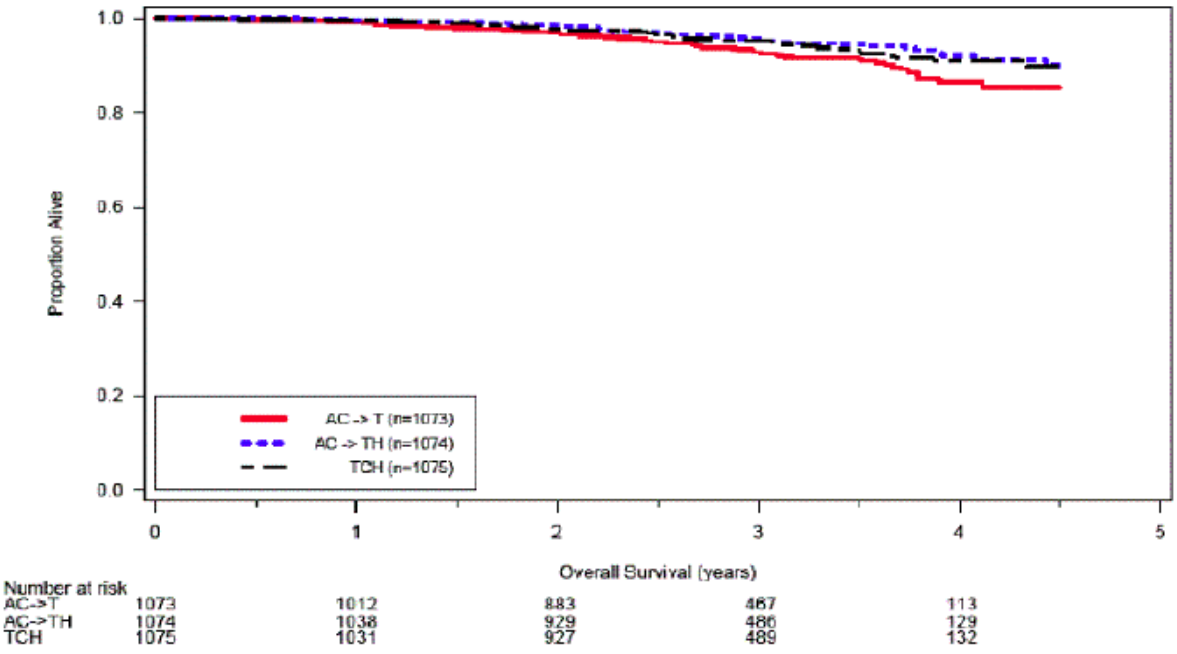
[a] Relative to AC→T. Estimated using Cox regression stratified by the node and hormonal receptor status.

[b] Stratified log-rank p-value.

[c] Numbers are based on Kaplan-Meier estimate. Absolute benefit in percent event free compared with AC→T.

Source: Tables 14.2/17, 14.2/18 and 14.2/19

Figure 4 – Overall survival: ITT population



AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; ITT = intent-to-treat; n = population size; TCH = docetaxel plus carboplatin plus trastuzumab.

Source: CSR Appendices [Table14.2/3].

The difference between AC→T and AC→TH treatment groups was statistically significant (HR 0.58, 95% CI: 0.40-0.83; p = 0.0024). The difference between AC→T and TCH treatment groups was statistically significant (HR 0.66, 95% CI: 0.47-0.93; p = 0.0182).

There was no difference between the AC→TH and TCH arms for OS (HR: 1.16; 95% CI: 0.79-1.70; p=0.45).
The 3-years survival rate estimate was 93% in AC→T arm, 95.5% in AC→TH arm, and 95.2% in TCH arm.

Discussion on Clinical Efficacy

BCIRG006/TAXGMA302 is a multicentre, non-blinded, randomized, stratified, phase III study comparing 3 therapy regimens as adjuvant therapy in women with HER2-positive, early-stage, node-positive and high-risk (at least one of the following: tumour size >2 cm, estrogen receptor or progesterone receptor [ER/PR]-negative, age <35 years, histologic and/or nuclear Grade 2 or 3) node-negative operable breast cancer.
The study treatments are:
-AC→T (= Doxorubicin 60 mg/m² with cyclophosphamide 600 mg/m² on an every 3 weeks basis for 4 cycles followed by docetaxel 100 mg/m² on an every 3 weeks basis for 4 cycles). **Control arm.**
-AC→TH (= same as AC→T plus trastuzumab starting at the same time as docetaxel at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration). **Tested arm.**
-**TCH** (= 6 cycles of docetaxel 75 mg/m2 with carboplatin AUC = 6 mg/mL/min, with trastuzumab starting at the same time as docetaxel and carboplatin at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration). **Tested arm.**

The randomization is stratified for the participating centre, number of axillary lymph nodes involved, and hormonal receptor status.

The control arm, AC→T, may have been acceptable at study initiation and would have been a logical one for answering the question of whether Herceptin (trastuzumab) could add a benefit to a sequential combination without Herceptin. However, in the context of the current application, the question of interest is "does docetaxel add any benefit when used in a modified sequential combination with Herceptin (i.e., AC followed by TH) as compared to currently approved regimens (e.g., AC followed by T followed by H)?"

Study BCIRG006 was not designed to isolate the effect of docetaxel but to define the effect of the combination of Docetaxel Winthrop (docetaxel) and Herceptin (trastuzumab). Thus, based on the submitted data, it is not possible to establish from direct comparison that the effect of AC→TH is at least comparable to any approved and currently used optimal adjuvant regimen (i.e., including Herceptin, specifically TAC followed by Herceptin).. This constitutes a major concern.

Another major concern comes from the fact that a strong rationale for the addition of carboplatin to Docetaxel Winthrop (docetaxel) and Herceptin (TCH arm) is missing. Although the early introduction of trastuzumab without doxorubicin and cyclophosphamide in the treatment strategy for adjuvant breast cancer could be of interest mainly from the viewpoint of achieving lower cardiotoxicity, the MAH has provided only pre-clinical justifications to support the use of the TCH arm. In this regard, a trial comparing TC vs T would have helped to assess the added value of carboplatin.
This concern is strengthened by the fact that study BCIRGOO7 (TCH vs TH) remains negative.

Clinical efficacy results of study BCIRG006/TAXGMA302 would only be convincing with reference to Herceptin (trastuzumab) (added to docetaxel +/- carboplatin) in terms of significantly decreasing the risk of disease relapse (disease free survival (DFS), primary endpoint) and a benefit in Overall Survival (OS) (secondary endpoint). The primary efficacy analysis reached statistical significance in favour of both experimental arms AC→TH and TCH, compared to AC→T (HR: 0.61; 95% CI: 0.49-0.77, p value < 0.0001 and HR: 0.67; 95% CI: 0.54-0.8, p value 0.0003, respectively).
The 3-year survival rate was 80.9% in the AC→T arm, 86.7% in the AC→TH arm, and 85.5% in the TCH arm.

Secondary analyses of OS supported the conclusion of the primary ones.
The difference between the AC→T and AC→TH treatment groups was statistically significant (HR 0.58, 95% CI: 0.40-0.83 p value 0.0024).
The difference between the AC→T and TCH treatment groups was statistically significant (HR 0.66, 95% CI: 0.47-0.93, p value 0.0182). The 3-year survival rate was 93% in the AC→T arm, 95.5% in the AC→TH arm, and 95.2% in the TCH arm.

No statistically significant difference between the AC→TH and TCH arms was observed with reference to DFS and OS.

Several secondary endpoints of interest related to quality of life (QoL) and molecular markers were planned for analysis. The results of the QoL analyses showed:
- comparable scores at baseline across the 3 arms;
- a transient deterioration for all 3 arms during treatment period;
- and a return to baseline values or better during the follow up period for all 3 arms.
These analyses also show that the fact that the TCH arm showed a better score at the end of the treatment in comparison with the AC-T and AC-TH arms is not a demonstration of a better safety profile during treatment but suggest that patients treated with TCH recovered more rapidly from toxicities.

Regarding analyses of molecular markers, the MAH provided information on one aspect only (TOPOIIa amplification). Several other markers (as p53, members of the bcl family, and MUC1) were planned but were not discussed by the Applicant in the documentation provided.

Furthermore, the benefit of adjuvant Docetaxel Winthrop (docetaxel) treatment has been demonstrated only in node positive patients. BCIRG006/TAXGMA302 does not provide proof of efficacy of chemotherapy in general, and of docetaxel in particular, in node negative patients. Rather, the result implies that Herceptin alone may be efficacious in the treatment of node negative patients, although a definitive conclusion cannot be made. Thus, evidence of efficacy of Docetaxel Winthrop containing adjuvant chemotherapy in node-negative patients has not been provided by the Applicant due to the design of the single pivotal trial submitted.

Despite the fact that study BCIRG006 is a positive trial demonstrating that both experimental arms AC→TH and TCH significantly decrease the risk of disease relapse compared to the control arm AC→T, the benefit of the proposed regimens (AC-TH and TCH) must be compared to what is currently known about the value of adding Herceptin (trastuzumab) only to any regimen. Considering this, and keeping the limitations of inter-studies comparisons in mind, a demonstration of the advantage is missing for both tested arms (the HR for the AC-TH and TCH arms are 0.61 and 0.67, respectively, and the HR was 0.54 when Herceptin was added to any regimen in the HERA study). In this context, it should be noted that the HERA trial (being the basis of the adjuvant indication for Herceptin) investigated Herceptin vs. observation after chemotherapy, which means that potential benefits of concomitant use of Herceptin and chemotherapy are still open to discussion.

Thus, the well conducted and analysed trial BCIRG006/TAXGMA302 allows the conclusion that Herceptin (trastuzumab) has adjuvant efficacy in HER2+ positive, node negative and positive, patients after surgery in early breast cancer. However, the contribution of Docetaxel Winthrop (docetaxel) to the overall outcome can not be established due to the study design of the single pivotal study submitted.

Clinical Safety

Safety was assessed by evaluating treatment exposure, adverse events, deaths, significant overdoses, and specific safety issues including cardiac events, laboratory results, and analyses by age. The safety population included all patients who received at least one dose of study treatment (AC→T = 1050; AC→TH = 1068; and TCH = 1056).

The median duration of follow-up among safety-evaluable patients was 36 months for each treatment arm, with a relative majority of patients in all three study arms having at least a 2-year follow-up.
More than 98% of patients treated with AC→T and AC→TH received the protocol-specified four cycles of doxorubicin, and the protocol-specified four cycles of cyclophosphamide.
A total of 90.9% and 92.5% of patients in the AC→T and AC→TH arms received the protocol-specified four cycles of docetaxel, respectively.
Of the patients treated with TCH, 95.3% received the protocol-specified six cycles of docetaxel.

- **Discontinuation of chemotherapy**

Table 44 – Reasons for chemotherapy discontinuation: Safety population

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Began chemotherapy treatment	1050 (100.0%)	1068 (100.0%)	1054 (99.8%)
Completed chemotherapy	958 (91.2%)	987 (92.4%)	1010 (95.6%)
Discontinued chemotherapy	92 (8.8%)	81 (7.6%)	44 (4.2%)
Reason for discontinuation:			
breast cancer relapse	5 (0.5%)	4 (0.4%)	1 (0.1%)
second primary malignancy	0 (0.0%)	1 (0.1%)	0 (0.0%)
cardiac adverse event	4 (0.4%)	2 (0.2%)	7 (0.7%)
non-cardiac adverse event	41 (3.9%)	40 (3.7%)	22 (2.1%)
withdrawal of consent/refusal	40 (3.8%)	30 (2.8%)	10 (0.9%)
death	1 (0.1%)	0 (0.0%)	2 (0.2%)
other [a]	0 (0.0%)	3 (0.3%)	1 (0.1%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel plus platinum salt plus trastuzumab.
aOther included "other" and "other deviation from protocol" categories.

Patients in the TCH arm were more likely to complete chemotherapy administration, compared with those in the AC→T and AC→TH arms (AC→T: 91.2%; AC→TH: 92.4%; and TCH: 95.6%). The most frequent causes of discontinuation were the occurrence of a non-cardiac adverse event, followed by patient withdrawal of consent or refusal of further treatment. Causes of premature discontinuation of chemotherapy in the AC→T and AC→TH arms were comparable. Early discontinuation of chemotherapy for a cardiac adverse event was uncommon and occurred more often in the TCH arm, compared with the AC→T and AC→TH arms (AC→T: 0.4%; AC→TH: 0.2%; and TCH: 0.7%). Beside adverse events, withdrawal of consent was the most frequent reported cause of discontinuation (AC→T: 3.8%; AC→TH: 2.8%; and TCH: 0.9%). Other causes were death (AC→T: 0.1%; AC→TH: 0; and TCH: 0.2%), protocol deviation (AC→T: 0; AC→TH: 0.2%; and TCH: 0), and "other" (AC→T: 0; AC→TH: 0.1%; and TCH: 0.1%).

Of the patients in the AC→TH and TCH arms, 75.3% and 86.5%, respectively, received trastuzumab therapy for more than 11 months without reporting discontinuation.
The majority of patients (90.9% and 95.4%) in the AC→TH and TCH arms completed planned trastuzumab treatment administered concurrently with chemotherapy. Relatively few patients discontinued trastuzumab prior to the end of chemotherapy (respectively, 6.7% in the AC→TH arm and 4.6% in the TCH arm). The most frequent cause of discontinuation prior to the end of chemotherapy was trastuzumab toxicity, which was reported in 35 patients (3.3%) in the AC→TH arm and 13 patients (1.2%) in the TCH arm.

Table 47 – Reasons for discontinuation of trastuzumab during monotherapy: Safety population

	AC→TH (n=1068)	TCH (n=1056)
Started trastuzumab monotherapy	975[a] (91.3%)	1008[b] (95.5%)
Trastuzumab treatment completed	804 (75.3%)	913 (86.5%)
Trastuzumab treatment incomplete but not discontinued	64 (6.0%)	38 (3.6%)
Trastuzumab treatment discontinued	107 (10%)	57 (5.4%)
Reason for discontinuation:		
breast cancer relapse	8 (0.7%)	7 (0.7%)
second primary malignancy	1 (0.1%)	2 (0.2%)
significant cardiac disease	42 (3.9%)	12 (1.1%)
death	0 (0.0%)	1 (0.1%)
lost to follow-up	0 (0.0%)	1 (0.1%)
significant concomitant therapy other than anti-tumor therapy	1 (0.1%)	0 (0.0%)
patient refusal to continue trastuzumab	24 (2.2%)	12 (1.1%)
other	30 (2.8%)	21 (2.0%)
missing	1 (0.1%)	1 (0.1%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; NA = not applicable; TCH = docetaxel plus platinum salt plus trastuzumab.

[a]In the AC→TH arm, 971 patients completed trastuzumab treatment during chemotherapy ; a total of 975 patients were treated during monotherapy, 2 of these patients (31894 and 32745) had trastuzumab discontinued during chemotherapy but went on to receive trastuzumab during monotherapy and an additional 2 patients (31624 and 33030) never received chemotherapy but went on to receive trastuzumab monotherapy.

[b]In the TCH arm, 1007 patients completed trastuzumab treatment during chemotherapy; a total of 1008 patients were treated during monotherapy, an additional patient (32659) was noted to have discontinued trastuzumab during chemotherapy but went on to receive trastuzumab monotherapy.

During trastuzumab monotherapy, a higher proportion of patients, 10% in the AC→TH treatment arm, discontinued trastuzumab compared with 5.4% in the TCH arm. The most frequent cause of discontinuation of trastuzumab during monotherapy was “significant cardiac disease” for 42 (3.9%) and 12 patients (1.1%) in the AC→TH and TCH arms, respectively.

- **Adverse events**

All Adverse Events

Table 49 – Key safety outcomes at any time during the study: Safety population

Safety Outcome	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Deaths	78 (7.4%)	48 (4.5%)	55 (5.2%)
Related to study treatment (all within 30 days after last infusion of chemotherapy)	1 (0.1%)	0 (0.0%)	2 (0.2%)
Within 30 days after last infusion (chemotherapy or trastuzumab monotherapy)	1 (0.1%)	1 (0.1%)	3 (0.3%)
on chemotherapy [a]	1 (0.1%)	0 (0.0%)	2 (0.2%)
during trastuzumab monotherapy, within 30 days after last infusion	0 (0.0%)	1 (0.1%)	1 (0.1%)
>30 days after last infusion of study treatment	77 (7.3%)	47 (4.4%)	52 (4.9%)
Adverse Events [b]			
NON-CARDIAC			
Any grade	1049 (99.9%)	1068 (100.0%)	1053 (99.7%)
Grade 3/4	704 (67.0%)	709 (66.4%)	670 (63.4%)
Any grade related	1049 (99.9%)	1068 (100.0%)	1053 (99.7%)
Grade 3/4 related	603 (57.4%)	593 (55.5%)	552 (52.3%)
CARDIAC			
Any grade	366 (34.9%)	486 (45.5%)	448 (42.4%)
Grade 3/4	41 (3.9%)	70 (6.6%)	76 (7.2%)
Any grade related	86 (8.2%)	127 (11.9%)	111 (10.5%)
Grade 3/4	13 (1.2%)	14 (1.3%)	19 (1.8%)
3-year cumulative incidence of CHF following T, TH, TCH per the ICRP [c]	3 (0.3%)	20 (1.9%)	4 (0.4%)
Overall incidence of symptomatic cardiac events per the ICRP [d]	6 (0.6%)	23 (2.2%)	12 (1.1%)
Asymptomatic decline in LVEF of >15% below the LLN	43 (4.1%)	109 (10.2%)	36 (3.4%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; ICRP = independent cardiac review panel; LLN = lower limit of normal; T = docetaxel; TCH = docetaxel plus platinum salt plus trastuzumab; TH = docetaxel and trastuzumab.

[a] The "on-chemotherapy" period was defined as the period from the date of randomization until 30 days following the last IV of study chemotherapy.

[b] Adverse events are classified according to NCI-CTC.

[c] Congestive heart failure (CHF) was confirmed by the ICRP and defined as a NCI-CTC, v2, Grade 3/4 cardiac left ventricular function (CLVF) adverse event.

[d] Symptomatic cardiac events included cardiac death, Grade 3/4 CLVF, Grade 3/4 cardiac arrhythmia, Grade 3/4 cardiac ischemia/infarction as confirmed by the ICRP.

Grade 3/4 non-cardiac AEs related to study treatment were less frequent (by 3%) in the TCH arm, compared to the other two arms. Any-grade cardiac AEs related to study treatment were less frequent in the AC→T arm, compared to the other two arms; Grade 3/4 cardiac AEs related to study treatment, however, showed a similar incidence across all treatment arms. The incidence of protocol-defined CHF at the 3-year follow-up, overall incidence of symptomatic cardiac AEs, and asymptomatic >15% LVEF decline was higher in the AC→TH arm, compared to the other two arms.

The ten most common related adverse events reported in all three treatment arms were as follows:

Table 53 – The 10 most common related AEs (all grades): Safety population

Adverse event (NCI-CTC term)	AC→T (n = 1050) %	AC→TH (n = 1068) %	TCH (n = 1056) %
Alopecia	98.0	98.0	95.8
Hemoglobin[a]	91.1	97.0	96.3
Nausea	87.2	87.2	80.8
Leukocyte[a]	83.6	87.0	83.0
Neutrophils[a]	81.7	86.3	81.3
Fatigue	80.4	81.3	80.4
Stomatitis/pharyngitis	63.1	65.0	51.8
SGPT[a]	48.4	54.4	53.2
Vomiting	54.4	55.3	39.4
Diarrhea	37.6	45.3	55.8

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel, platinum salt, and trastuzumab.

[a]Regardless of causality

The ten most common Grade ¾ related adverse events were the following :

Table 54 – The 10 most common related AEs with severity Grades 3/4: Safety population

Adverse event (NCI-CTC term)	AC→T (n = 1050) %	AC→TH (n = 1068) %	TCH (n = 1056) %
Neutrophils[a]	63.2	71.3	65.9
Leukocytes[a]	51.4	60.2	48.0
Irregular menses	23.6	19.9	21.4
Febrile neutropenia	9.0	10.9	9.8
Infection with neutropenia	7.9	9.2	7.7
Infection with unknown ANC	7.0	5.5	3.6
Fatigue	6.8	6.6	6.9
Nausea	5.8	5.3	4.6
Vomiting	5.8	6.4	3.0
Diarrhea	3.0	5.1	4.9

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel, platinum salt, and trastuzumab.

aRegardless of causality

- Adverse events by age

The majority of patients in the safety population were <65 years old (AC→T: 93.9%; AC→TH: 94.6%; and TCH: 93.3%). 64 patients in the AC→T arm (6.1%), 58 patients in the AC→TH arm (5.4%), and 71 patients in the TCH arm (6.7%) were ≥65 years old.

Among the cardiac events, cardiac left ventricular function was reported more frequently (by ≥10%) in elderly patients within the AC→TH treatment arm, compared to non-elderly patients
(AC→T: 1.6%; AC→TH: 17.2%; and TCH: 1.4%, compared to AC→T: 2.2%; AC→TH: 7.0%; and TCH: 2.2%, respectively).
In all treatment arms, hypertension was reported more frequently (by ≥10%) in elderly patients compared to non-elderly patients (AC→T: 35.9%; AC→TH: 39.7%; and TCH: 47.9%, compared to AC→T: 15.1%; AC→TH: 18.0%; and TCH: 18.1%, respectively).

Table 57 – Cardiac adverse events by age (<65, ≥65) occurring at any time during the study in >1% of patients, regardless of relationship to study treatment: Safety population

Adverse Event (NCI-CTC term)	Age < 65			Age ≥ 65		
	AC→T n = 986 n (%)	AC→TH n = 1010 n (%)	TCH n = 985 n (%)	AC→T n = 64 n (%)	AC→TH n = 58 n (%)	TCH n = 71 n (%)
Cardiac left ventricular function	22 (2.2)	71 (7.0)	22 (2.2)	1 (1.6)	10 (17.2)	1 (1.4)
Cardiac– ischemia/infarction	7 (0.7)	11 (1.1)	10 (1.0)	0 (0.0)	2 (3.4)	1 (1.4)
Conduction abnormality/ atrioventricular heart block	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.4)
Hypertension	149 (15.1)	182 (18.0)	178 (18.1)	23 (35.9)	23 (39.7)	34 (47.9)
Hypotension	18 (1.8)	28 (2.8)	20 (2.0)	4 (6.3)	3 (5.2)	1 (1.4)
Palpitations	71 (7.2)	92 (9.1)	89 (9.0)	7 (10.9	0 (0.0)	6 (8.5)
Pericardial effusion/pericarditis	17 (1.7)	19 (1.9)	15 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus bradycardia	6 (0.6)	10 (1.0)	4 (0.4)	0 (0.0)	1 (1.7)	0 (0.0)
Sinus tachycardia	43 (4.4)	42 (4.2)	51 (5.2)	4 (6.3)	2 (3.4)	6 (8.5)
Supraventricular arrhythmias	9 (0.9)	5 (0.5)	7 (0.7)	2 (3.1)	2 (3.4)	3 (4.2)
Thrombosis/embolism	17 (1.7)	19 (1.9)	26 (2.6)	0 (0.0)	3 (5.2)	3 (4.2)
Vasovagal episode	1 (0.1)	4 (0.4)	7 (0.7)	0 (0.0)	0 (0.0)	1 (1.4)
Ventricular arrhythmia	4 (0.4)	6 (0.6)	6 (0.6)	2 (3.1)	0 (0.0)	0 (0.0)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel plus platinum salt plus trastuzumab

Deaths

A total of 181 deaths were reported among the 3174 treated patients. The overall incidence of death was highest in the AC→T arm (7.4% of 1050 patients), followed by the TCH arm (5.2%of 1056 patients) and the AC→TH arm (4.5% of the 1068 patients). The majority of deaths (overall 5.5%) occurred during the post-treatment period, and was the result of breast cancer (in 5.0% of all patients).
Three toxic deaths occurred on chemotherapy within 30 days following the last IV of study treatment: one case of pneumonia with Grade 4 neutropenia in the AC→T arm; one case of MOF with renal insuficiency in a patient with diabetes mellitus in the TCH arm, and one death at home related to bronchopneumonia in the TCH arm.
Two additional deaths (one of unknown cause in the AC→TH arm, and one Grade 4 cranial trauma with acute subdural haematoma in the TCH arm) occurred within 30 days after last infusion of trastuzumab monotherapy, and were both not related to protocol treatment.

Table 60 – Deaths: Safety population

	AC→T (n=1050) n (%)	AC→TH (n=1068) n (%)	TCH (n=1056) n (%)	All Patients (n=3174) n (%)
Deaths	78 (7.4%)	48 (4.5%)	55 (5.2%)	181 (5.7%)
on chemotherapy [a]	1 (0.1%)	0 (0.0%)	2 (0.2%)	3 (0.1%)
during trastuzumab monotherapy, within 30 days	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
>30 days after last infusion of study treatment	77 (7.3%)	47 (4.4%)	52 (4.9%)	176 (5.5%)
Cause of death:				
n	78	48	55	181
Septic toxicity due to study chemotherapy	1 (0.1%)	0 (0.0%)	2 (0.2%)	3 (0.1%)
Breast cancer	68 (6.5%)	43 (4.0%)	47 (4.5%)	158 (5.0%)
Malignant disease, other than breast cancer	5 (0.5%)	1 (0.1%)	2 (0.2%)	8 (0.3%)
Other:	4 (0.4%)	4 (0.4%)	4 (0.4%)	12 (0.4%)
cerebral stroke	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
complications of hypercalcaemia	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
cranial trauma with acute subdural hematoma	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
pneumonia	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
pulmonary consolidation	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
septic shock	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
sudden death	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
truck rollover accident	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
unknown	0 (0.0%)	3 (0.3%)	1 (0.1%)	4 (0.1%)

AC→T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH = doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH = docetaxel, platinum salt, and trastuzumab.

[a] The "on-chemotherapy" period was defined as the period from the date of randomization until 30 days following the last IV of study chemotherapy.

Eight patients died from malignant disease other than breast cancer. Among these eight patients, five patients died of the following second primary malignancies: gastic adenocarcinoma and intestinal adenocarcinoma both in the AC→T arm; ovarian carcinoma in the AC→TH arm; and glioblastoma and pancreatic carcinoma both in the TCH arm. Three additional patients, all in AC→T arm, died from leukemia reported as not related to study therapy.

Serious adverse events

A total of 216 SAEs were reported in the AC→T arm; 283 in the AC→TH arm; and 253 in the TCH arm. The most common non-cardiac SAEs were (in descending order of frequency): febrile neutropenia (6.9%; 8.4%; 7.5%), neutropenic infection (4.5%; 4.8%; 4.5%), infection, neutropenia, vomiting, fever, and diarrhoea. Their incidence was uniform across all three treatment arms.
The most common cardiac SAEs were: thrombosis/embolism, and cardiac left ventricular function. The incidence of serious cardiac left ventricular function was higher in the AC→TH arm (2.2%), compared to the other two arms (0.3% AC/T arm ; 0.1% TCH arm).

Adverse events leading to withdrawal

Common non-cardiac adverse events leading to withdrawal of study chemotherapy were higher in the AC/T arm compared to AC/TH and TCH (4.3%; 2.15%; 1.42%).
Cardiac adverse events leading to withdrawal of study chemotherapy were higher in the TCH arm compared to the AC/T and the AC/TH arms (0.57% ; 0.38% ; 0.19%)
Regarding trastuzumab monotherapy, common non-cardiac adverse events leading to withdrawal were higher in the THC arm compared to the AC/TH arm (1.14% ; 0.37%) ; the percentage of cardiac

adverse events leading to withdrawal was the same between the AC/TH and the TCH arms (1.5% ; 1.23%).

Other significant adverse events

- **Cardiac safety**

- Symptomatic and Asymptomatic LVEF events

The most frequently occurring symptomatic cardiac event across all treatment arms was Grade 3/4 CLVF (Cardiac Left Ventricular Function), which corresponds to symptomatic CHF (Congestive Heart Failure). The incidence was highest in the AC→TH arm (1.9%) compared to both the AC→T (0.3%) and TCH arms (0.4%).

Table 69 – Symptomatic cardiac events per the ICRP occurring at any time during the study: Safety population

Event Type	AC→T (n=1050) n (%)	AC→TH (n=1068) n (%)	TCH (n=1056) n (%)
CHF (Grade 3/4 CLVF)	3 (0.3%)	20 (1.9%)	4 (0.4%)
Grade 3/4 cardiac ischemia/infarction	0 (0.0%)	2 (0.2%)	2 (0.2%)
Grade 3/4 arrhythmia	3 (0.3%)	2 (0.2%)	6 (0.6%)
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any symptomatic cardiac event [a]	6 (0.6%)	23 (2.2%)	12 (1.1%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CHF=congestive heart failure; CLVF=cardiac left ventricular function; TCH=docetaxel, platinum salt, and trastuzumab.
[a]A patient could be included in more than one event type category; therefore, the "any symptomatic cardiac event row" is less the sum of number of events in a given column.

The incidence of symptomatic and asymptomatic LVEF (Left Ventricular Ejection Fraction) events was similar in the AC→T and TCH arms and was higher by ≥5% in the AC→TH arm relative to both the AC→T and TCH arms.
At 3 years, the rate of symptomatic cardiac events was 0.5%, 2.4%, and 1.16% in the AC→T, AC→TH, and TCH arms, respectively. For symptomatic CHF (Grade 3/4 CLVF), the 3-year rate was 0.3%, 1.9%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.

- Cardiac adverse events (Recorded on adverse events CRF)

The overall incidence of cardiac adverse events was higher by 10.6% in the AC→TH arm compared to the AC→T arm. The overall incidence of cardiac adverse events was higher by 3.1% in the AC→TH arm compared to the TCH arm; however, the incidence of Grade 3/4 cardiac adverse events was the highest in the TCH arm (7.2%), and the AC→TH arm (6.6%), compared to the AC→T arm (3.9%). No fatal outcomes were reported as a consequence of these cardiac AEs.

Table 75 – Cardiac adverse events occurring at any time during the study: Safety population

Type of Cardiac Adverse Event	AC→T (n=1050) n (%)	AC→TH (n=1068) n (%)	TCH (n=1056) n (%)
Any cardiac adverse event	366 (34.9%)	486 (45.5%)	448 (42.4%)
Grade 3/4	41 (3.9%)	70 (6.6%)	76 (7.2%)
Characterized as serious	17 (1.6%)	46 (4.3%)	32 (3.0%)
Deemed possibly or probably related to study treatment			
Related to chemotherapy	95 (9.0%)	132 (12.4%)	104 (9.8%)
Related to trastuzumab	2 (0.2%)	98 (9.2%)	94 (8.9%)
Resulting in study treatment discontinuation			
Discontinuation of chemotherapy	4 (0.4%)	2 (0.2%)	7 (0.7%)
Discontinuation of trastuzumab	(0.0%)	16 (1.5%)	16 (1.5%)
With hospitalization as a significant consequence	15 (1.4%)	36 (3.4%)	34 (3.2%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH=docetaxel, platinum salt, and trastuzumab.

The most frequently reported (in ≥4% of all patients in all treatment arms) cardiac adverse events included hypertension (18.6%), palpitations (8.3%), sinus tachycardia (4.7%), and CLVF (4.0%).
The overall incidence of CLVF adverse events was increased in the AC→TH arm (7.6%) compared to both the AC→T and TCH arms (2.2% each). In the same way, Grade ¾ CLVF was increased in the AC/TH arm (2%) compared to AC/T and TCH arm (0.3% and 0.1%).

All patients were required to undergo LVEF measurements at baseline, and at 3, 4½, 6, 9, and 18 months following randomization: The mean decline in LVEF from baseline to Month 3 was similar in all the treatment arms (AC→T: -1.3%; AC→TH: -1.8%; and TCH: -1.5%). Subsequently, and until Month 42, the 221 patients in the TCH arm are showing the closest recovery to their mean baseline LVEF value (respectively, 65.7% LVEF at Month 42, compared to 65.5% LVEF at baseline).
The degree of decline in LVEF was greater, beginning at Month 6 and continuing during the subsequent time points, in the AC→TH arm, compared to both the AC→T and TCH arms. The mean absolute decline in LVEF from baseline until the end of chemotherapy was -1.8%, -4.1%, and -1.7% in the AC→T, AC→TH, and TCH arms, respectively.

Patients in the AC→TH arm had an estimated 3.75-fold higher risk (p=0.0039; 95% CI: 1.5, 9.2) of a cardiac event compared with those in the AC→T arm.
Patients >50 years old had a 2.44-fold increase in the risk (p=0.0222; 95% CI: 1.1, 5.3) of developing a cardiac event compared with those ≤50 years old.
The incidence of cardiac events was increased in patients >50 years old in both the AC→T and AC→TH arms. Overall, cardiac events seemed to be more frequent in the AC→TH compared to the AC→T treatment arm, independent of prior or current use of cardiovascular medications at baseline.
Further, the risk of a cardiac event in patients treated with AC→TH was increased (≥2%) relative to patients treated with AC→T in the presence of ongoing hypertension at baseline.

- **Neutropenic complications and infection**

Grade 4 neutropenia occurred in 505 (48.1%) of patients in the AC→T arm, 566 (53.0%) of patients in the AC→TH arm, and 522 (49.4%) of patients in the TCH arm.
Similar rates of neutropenic infection and febrile neutropenia were observed in the three treatment arms.

Table 83 – Number of patients with neutropenic infection and febrile neutropenia

	No. of Patients		
	AC→T (n=1050) n (%)	AC→TH (n=1068) n (%)	TCH (n=1056) n (%)
Neutropenic infection (any relationship)	128 (12.2%)	139 (13.0%)	123 (11.6%)
Neutropenic infection (related to treatment)	93 (8.9%)	107 (10.0%)	89 (8.4%)
Febrile neutropenia (any relationship)	99 (9.4%)	120 (11.2%)	106 (10.0%)
Febrile neutropenia (related to treatment)	98 (9.3%)	117 (11.0%)	105 (9.9%)

AC→T= doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH= doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH= docetaxel, platinum salt, and trastuzumab.

In the AC→T and AC→TH, the incidence of febrile neutropenia was greatest during Cycles 5 and 6, following initiation of T or TH. In the TCH arm, the incidence was greatest during Cycle 1, when more than half of the patients (57.5%) experienced febrile neutropenia.

Clinical laboratory evaluations

Anaemia
The overall incidence of anaemia was higher by >5% in each of the trastuzumab-containing arms, compared with the AC→T arm. Grade 3/4 anaemia was highest in the TCH arm (>2.5% higher, compared with the incidence of Grade 3/4 anaemia in both the AC→T and AC→TH arms).

Neutropenia / leucopenia
The overall incidence of neutropenia and leucopenia were higher in the AC→TH arm, compared to the incidence in both the AC→T and TCH arms. Similarly, the incidence of Grade 3/4 neutropenia and leucopenia were highest in the AC→TH arm compared to the incidence of Grade ¾ neutropenia and leucopenia in both the AC→T and TCH arms.

Table 89 – Hematologic laboratory abnormalities: Safety population

	AC→T (n=1050)	AC→TH (n=1068)	TCH (n=1056)
Anemia [a]	957 (91.1%)	1036 (97.0%)	1017 (96.3%)
Grade 3/4	25 (2.4%)	34 (3.2%)	61 (5.8%)
Neutropenia [b]	859 (81.8%)	922 (86.3%)	859 (81.3%)
Grade 3/4	664 (63.2%)	761 (71.3%)	696 (65.9%)
Thrombocytopenia	296 (28.2%)	350 (32.8%)	667 (63.2%)
Grade 3/4	10 (1.0%)	13 (1.2%)	57 (5.4%)
Leukopenia	878 (83.6%)	929 (87.0%)	877 (83.0%)
Grade 3/4	540 (51.4%)	643 (60.1%)	507 (48.0%)

AC→T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC→TH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; TCH=docetaxel, platinum salt, and trastuzumab.
[a]Anemia is defined as hemoglobin level < 12 g/dL.
[b]Neutropenia is defined as absolute neutrophil count < 1.0×10^9/L.

Thrombocytopenia
The overall incidence of thrombocytopenia was higher by >30% in the TCH arm, compared to the incidence in both the AC→T and AC→TH arms. Similarly, the incidence of Grade ¾ thrombocytopenia was highest in the TCH arm (by >4% in the TCH arm compared to the incidence of Grade 3/4 thrombocytopenia in both the AC→T or AC→TH arms.

Discussion on Clinical Safety

From the point of view of clinical safety, the reported adverse events are in accordance with the safety profile of the single substances.

The most common related adverse events showed similar frequencies across all treatment arms.

The overall frequency of serious adverse events in ≥ 1% of patients is higher in the AC/TH arm (22%) compared to the AC/T arm (17%) and the TCH arm (18.5%).

Regarding Grade ¾ related adverse events, neutropenia and leucopenia were more frequent (by ≥ 5%) in the AC/TH arm compared to both other arms. Febrile neutropenia and infection with neutropenia were also slightly higher in the AC/TH arm. However, the three toxic deaths due to sepsis were reported in both the AC/T and TCH arms.

The AC/TH regimen presented a higher cardiac toxicity including the long term cardiac toxicity (3-year cumulative incidence of congestive heart failure (CHF) compared to the two other regimens.
The overall frequency of serious cardiac adverse events was higher in the AC/TH arm (4.2%) compared to AC/T arm (1.42%) and TCH arm (2.5%). Among the 4.2% of cardiac adverse events reported in the AC/TH arm, 2.2% concerned cardiac left ventricular function.
No fatal outcome was reported as a consequence of cardiac adverse events, although one case in the AC/TH arm reported as death of unknown cause concerned a patient with decreased LEFV of 50% three weeks after the last dose of trastuzumab.
At 3 years, the rate of symptomatic cardiac events was higher in the AC/TH arm (2.4%) compared to the other arms (0.5%, 1.16%). For symptomatic CHF (Grade 3/4 CLVF), the 3-year rate was 0.3%, 1.9%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.
Age over 50 years old is a risk factor for cardiac events in both AC/T and AC/TH arms. The risk of a cardiac event in patients treated with AC→TH was increased (≥2%) relative to patients treated with AC→T in the presence of ongoing hypertension at baseline.

Three cases of secondary leukaemia leading to death were reported in the AC/T arm and one case of leukaemia (outcome unknown) was also reported in the AC/TH arm. No case was reported in the TCH arm.

Benefit/Risk assessment

This variation concerns an extension of indication for Docetaxel Winthrop (docetaxel) in adjuvant treatment of early stage breast cancer. On the basis of the results of the 2nd interim analysis of the phase III trial, BCIRG006/TAXGMA302, conducted after 474 disease free survival (DFS) events had been recorded at a median follow up of 36 months (for the final analysis 900 DFS events are required), the MAH has proposed the following new indications for Docetaxel Winthrop (docetaxel):
- Doxorubicin and cyclophosphamide followed by DOCETAXEL WINTHROP (docetaxel) in combination with trastuzumab (AC→TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours over express HER2.
- DOCETAXEL WINTHROP (docetaxel) in combination with trastuzumab and carboplatin (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours over express HER2.

BCIRG006/TAXGMA302 is a multicentre, non-blinded, randomized, stratified, phase III study comparing 3 therapy regimens as adjuvant therapy in women with HER2-positive, early-stage, node-positive and high-risk (at least one of the following: tumour size >2 cm, estrogen receptor or progesterone receptor [ER/PR]-negative, age <35 years, histologic and/or nuclear Grade 2 or 3) node-negative operable breast cancer.
The study treatments are:
-AC→T (= Doxorubicin 60 mg/m² with cyclophosphamide 600 mg/m² on an every 3 weeks basis for 4 cycles followed by docetaxel 100 mg/m² on an every 3 weeks basis for 4 cycles). **Control arm.**
-AC→TH (= same as AC→T plus trastuzumab starting at the same time as docetaxel at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration). **Tested arm.**
-TCH (= 6 cycles of docetaxel 75 mg/m2 with carboplatin AUC = 6 mg/mL/min, with trastuzumab starting at the same time as docetaxel and carboplatin at the dose of 4 mg/kg for the first administration, then at 2 mg/kg weekly during chemotherapy; starting 3 weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg every 3 weeks for a total duration of 1 year from first administration). **Tested arm.**

The randomization is stratified for the participating centre, number of axillary lymph nodes involved, and hormonal receptor status.

The two major efficacy objections of the CHMP concern:
- The control arm, AC→T, does not answer the question of possible added benefit of Docetaxel Winthrop (docetaxel). It may have been acceptable at study initiation and would have been a logical one for answering the question of whether Herceptin (trastuzumab) could add a benefit to a sequential combination without Herceptin. However, in the context of the current application, the question of interest is "does docetaxel add any benefit when used in a modified sequential combination with Herceptin (i.e., AC followed by TH) as compared to currently approved regimens (e.g., AC followed by T followed by H)?"

Study BCIRG006 was not designed to isolate the effect of docetaxel but to define the effect of the combination of Docetaxel Winthrop (docetaxel) and Herceptin (trastuzumab). Thus, based on the submitted data, it is not possible to establish from direct comparison that the effect of AC→TH is at least comparable to any approved and currently used optimal adjuvant regimen (i.e., including Herceptin, specifically TAC followed by Herceptin). This constitutes a major concern.

- Another major concern comes from the fact that a strong rationale for the addition of carboplatin to Docetaxel Winthrop (docetaxel) and Herceptin (TCH arm) is missing. Although the

early introduction of trastuzumab without doxorubicin and cyclophosphamide in the treatment strategy for adjuvant breast cancer could be of interest mainly from the viewpoint of achieving lower cardiotoxicity, the MAH has provided only pre-clinical justifications to support the use of the TCH arm. In this regard, a trial comparing TC vs T would have helped to assess the added value of carboplatin.
This concern is strengthened by the fact that study BCIRGOO7 (TCH vs TH) remains negative.

Clinical efficacy results of study BCIRG006/TAXGMA302 would only be convincing if Herceptin (trastuzumab) were the main investigated medicinal product (added to docetaxel +/- carboplatin) in terms of demonstrating a significant decrease in the risk of disease relapse (disease free survival (DFS), primary endpoint) and a benefit in Overall Survival (OS) (secondary endpoint). The primary efficacy analysis reached statistical significance in favour of both experimental arms AC→TH and TCH, compared to AC→T (HR: 0.61; 95% CI: 0.49-0.77, p value < 0.0001 and HR: 0.67; 95% CI: 0.54-0.8, p value 0.0003, respectively).
The 3-year survival rate was 80.9% in the AC→T arm, 86.7% in the AC→TH arm, and 85.5% in the TCH arm.

Secondary analyses of OS supported the conclusion of the primary ones.
The difference between the AC→T and AC→TH treatment groups was statistically significant (HR 0.58, 95% CI: 0.40-0.83 p value 0.0024).
The difference between the AC→T and TCH treatment groups was statistically significant (HR 0.66, 95% CI: 0.47-0.93, p value 0.0182). The 3-year survival rate was 93% in the AC→T arm, 95.5% in the AC→TH arm, and 95.2% in the TCH arm.

No statistically significant difference between the AC→TH and TCH arms was observed with reference to DFS and OS.

Several secondary endpoints of interest related to quality of life (QoL) and molecular markers were planned for analysis. The results of the QoL analyses showed:
- comparable scores at baseline across the 3 arms;
- a transient deterioration for all 3 arms during treatment period;
- and a return to baseline values or better during the follow up period for all 3 arms.
These analyses also show that the fact that the TCH arm showed a better score at the end of the treatment in comparison with the AC-T and AC-TH arms is not a demonstration of a better safety profile during treatment but suggest that patients treated with TCH recovered more rapidly from toxicities.

Regarding analyses of molecular markers, the MAH provided information on one aspect only (TOPOIIa amplification). Several other markers (as p53, members of the bcl family, and MUC1) were planned but were not discussed by the Applicant in the documentation provided.

Furthermore, the benefit of adjuvant Docetaxel Winthrop (docetaxel) treatment has been demonstrated only in node positive patients. BCIRG006/TAXGMA302 does not provide proof of efficacy of chemotherapy in general, and of docetaxel in particular, in node negative patients. Rather, the result implies that Herceptin alone may be efficacious in the treatment of node negative patients, although a definitive conclusion cannot be made. Thus, evidence of efficacy of Docetaxel Winthrop containing adjuvant chemotherapy in node-negative patients has not been provided by the Applicant due to the design of the single pivotal trial submitted.

Despite the fact that study BCIRG006 is a positive trial demonstrating that both experimental arms AC→TH and TCH significantly decrease the risk of disease relapse compared to the control arm AC→T, the benefit of the proposed regimens (AC-TH and TCH) must be compared to what is currently known about the value of adding Herceptin (trastuzumab) only to any regimen. Considering this, and keeping the limitations of inter-study comparisons in mind, a demonstration of the advantage is missing for both tested arms (the HR for the AC-TH and TCH arms are 0.61 and 0.67, respectively, and the HR was 0.54 when Herceptin was added to any regimen in the HERA study). In this context, it should be noted that the HERA trial (being the basis of the adjuvant indication for Herceptin)

investigated Herceptin vs. observation after chemotherapy, which means that potential benefits of concomitant use of Herceptin and chemotherapy are still open to discussion.

Thus, the well conducted and analysed trial BCIRG006/TAXGMA302 can only allow the conclusion that Herceptin (trastuzumab) has adjuvant efficacy in HER2+ positive, node negative and positive, patients after surgery in early breast cancer. However, the contribution of Docetaxel Winthrop (docetaxel) to the overall outcome can not be established due to the study design of the single pivotal study submitted.

From the point of view of clinical safety, the reported adverse events are in accordance with the safety profile of the single substances. The most common related adverse events showed similar frequencies across all treatment arms.

The overall frequency of serious adverse events in ≥ 1% of patients is higher in the AC/TH arm (22%) compared to the AC/T arm (17%) and the TCH arm (18.5%).

Regarding Grade 3/4 related adverse events, neutropenia and leucopenia were more frequent (by ≥ 5%) in the AC/TH arm compared to both other arms. Febrile neutropenia and infection with neutropenia were also slightly higher in the AC/TH arm. However, the three toxic deaths due to sepsis were reported in both AC/T and TCH arms.

The AC/TH regimen presented a higher cardiac toxicity including the long term cardiac toxicity (3-year cumulative incidence of congestive heart failure (CHF) compared to the two other regimens.
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No fatal outcome was reported as a consequence of cardiac adverse events, although one case in the AC/TH arm reported as death of unknown cause concerned a patient with decreased LEFV of 50% three weeks after the last dose of trastuzumab.
At 3 years, the rate of symptomatic cardiac events was higher in the AC/TH arm (2.4%) compared to the other arms (0.5%, 1.16%). For symptomatic CHF (Grade 3/4 CLVF), the 3-year rate was 0.3%, 1.9%, and 0.4% in the AC→T, AC→TH, and TCH arms, respectively.
Age over 50 years old is a risk factor for cardiac events in both the AC/T and the AC/TH arms. The risk of a cardiac event in patients treated with AC→TH was increased (≥2%) relative to patients treated with AC→T in the presence of ongoing hypertension at baseline.

Regarding long term cardiac toxicity, only one patient presented Grade 4 CHF (all the other cases were Grade 3 CHF). Moreover, most of the cases presented a favourable outcome.
Cardiac toxicity is mentioned in the SPC of Docetaxel Winthrop (docetaxel) in section 4.4 with a statement regarding cardiac monitoring during treatment. A cross reference to trastuzumab appears sufficient in this regard.

Three cases of secondary leukaemia leading to death were reported in the AC/T arm and one case of leukaemia (outcome unknown) was also reported in the AC/TH arm. No case was reported in the TCH arm.

Conclusion of the Benefit/Risk assessment

The CHMP considered that the Benefit/Risk ratio for the addition of Docetaxel Winthrop (docetaxel) in both combinations AC→TH (doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab) and TCH (docetaxel, carboplatin and trastuzumab) is negative since no benefit has been clearly established.
In addition, the TCH regimen is currently not approvable due to the lack of a clear clinical rationale for its use.

CONCLUSION

On 24 July 2008 the CHMP considered this Type II variation and agreed that the changes to the terms of the Marketing Authorisation should be refused on the following grounds:

- It is not possible to establish, based on the design of the single pivotal study submitted, the Benefit/Risk of including Docetaxel Winthrop (docetaxel) in the proposed adjuvant regimens.

- No sufficient clinical evidence has been provided to justify the use of the combination of Docetaxel Winthrop (docetaxel), carboplatin and trastuzumab.