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**ASSESSMENT REPORT**
**FOR**
**Docetaxel Winthrop**

**International non-proprietary name/Common name:**
**docetaxel**

**Procedure No. EMA/H/C/000808/II/0012**

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



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# 1. Scientific discussion

### *1.1. Introduction*

Docetaxel Winthrop 20 and 80 mg concentrate and solvent for solution for infusion (INN: docetaxel) was granted a Marketing Authorisation (MA) on 20 April 2007 as an informed consent application to the reference product Taxotere.

Docetaxel is a semisynthetic and important taxane which displays its cytotoxic/antineoplastic activity by promoting the assembly of free tubulin into stable microtubles thereby inhibiting mitosis.

On 30 November 2009 the Commission Decision for the additional strengths of 20 mg/1ml and 80 mg/4ml (concentrate for solution for infusion) was issued and on 5 May 2010 the Commission Decision was issued for a new presentation of 160 mg/8 ml of Docetaxel Winthrop concentrate for solution for infusion (one vial formulation).

The medicinal product is currently indicated for:

Breast cancer
- in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node- positive breast cancer.
- in combination with doxorubicin 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 for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease.
- in combination with capecitabine 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 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 for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric adenocarcinoma
- in combination with cisplatin and 5-fluorouracil 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 locally advanced squamous cell carcinoma of the head and neck.



The scope of this variation application is an extension of the breast cancer adjuvant treatment indication. The MAH initially proposed the new indication as follows:

> "DOCETAXEL WINTHROP in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-negative breast cancer (with one or more high risk factors [see section 5.1])."

This application is based on the results of The Grupo Espanol de Investigacion en Cancer de Mama (GEICAM) 9805 phase III study (TAX.ES1.301). Study GEICAM 9805 (TAX.ES1.301) compared:

TAC (docetaxel in combination with doxorubicin and cyclophosphamide) versus FAC (5-fluorouracil in combination with doxorubicin and cyclophosphamide) as a 6-cycle adjuvant treatment of high risk operable breast cancer patients with negative axillary lymph nodes.

Further to the assessment by CHMP the following final indication has been agreed:

"DOCETAXEL WINTHROP in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

- operable nodenegative breast cancer

For patients with operable nodenegative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer (see section 5.1)."

Consequently to the proposed new indication, SPC sections 4.2, 4.4, 4.8 and 5.1 as well as the Package Leaflet have been updated as well. In addition, the MAH took the opportunity to perform a correction in SPC section 6.6 and PL concerning the preparation guide for the 20mg/1ml, 80mg/4ml and 160mg/8ml concentrate for solution for infusion presentations.

### *1.2. Scientific Discussion*

#### *1.2.1 Non clinical aspects*

The MAH did not provide any new nonclinical data in this application which was considered acceptable by the CHMP.

**Ecotoxicity / Environmental Risk Assessment**

The MAH has predicted an environmental concentration in surface water of 3.9 10-4 µg/l and concluded that no further environmental risk assessment is necessary.

The MAH proposed to make a ratio of the maximal total quantity marketing forecast (estimated at 450 kg/year in 2011) to the total quantity of water consumption in Europe during the same period (i.e., 400 106 inhabitants x 200 L x 365 days) and use the usual dilution factor of 10. The exposure would therefore be the following:

$$\frac{450\ 10^{6}}{400\ 10^{6} \times 200 \times 365 \times 10} = 1.5 \times 10^{-6}\ \text{mg/L} = 0.0015\ \text{ug/L}$$

Concerning the present Type II variation for the combination of docetaxel with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with node-negative operable breast cancer eligible to chemotherapy, the number of patients concerned would be 7900 patients/year who receive 4 cycles of two 80 mg vials, i.e.:

$$7900 \times 4 \times 2 \times 80\ 10^{-3} = 5056\ \text{g}$$

The MAH stated that $\log_{KOW}$ of the active ingredient is 3.2 (calculated). In addition, the MAH referred to a literature review revealing other calculated or measured values as reported in table 1.

Table 1 - Various docetaxel log $K_{OW}$ values

| Source | Method | log $K_{OW}$ value |
|---|---|---|
| ChemIDplus | Calculated | 2.83 |
| Drug bank | Calculated | 2.59 |
| Drug bank | Measured | 2.40 |
| NDA | Calculated | 3.20 |

Furthermore, the MAH has provided information on fate (sorption, hydrolysis, aerobic biodegradation) and effects (acute toxicity test on Daphnia, minimal inhibiting concentration for micro-organisms) of docetaxel in the environment without submitting any study report.

**Discussion**

The CHMP considered that for the calculation of the exposure the number of inhabitants in Europe must be $497*10^6$(EU27, 2009): $450*10^6/(497*10^6*200*365*10)$ = 0.00124µg/L.
Concerning the present extension of indication, the potential market for docetaxel as chemotherapeutic agent should be considered. That means the increase of the quantity market will be 50.56 kg, based on this calculation: $79000*4*2*80*10\text{-}^6$ = 500.56 kg.

However, both exposure calculations lead to PECs beneath the trigger of 0.01 µg/L. A Fpen refinement would be accepted by the committee in Phase I, if the MAH provides the source of breast cancer incidences.

The $\log_{KOW}$ of the active ingredient is 3.2 (calculated). The MAH has further provided information on fate (sorption, hydrolysis, aerobic biodegradation) and effects (acute toxicity test on Daphnia, minimal inhibiting concentration for micro-organisms) of docetaxel in the environment without submitting any study report.

It was appreciated having received the data available on fate and effects of docetaxel in the environment. However, the data submitted are not in line with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/H/C/SWP/4447/00, June 2007). As the environment is continuously exposed to human medicinal products, short-term tests are not appropriate. Besides that, only one trophic level was tested. In any case, full test protocols which allow to check validity and plausibility of the results and to decide whether the use of non-OECD test guidelines would be acceptable need to be submitted.

The MAH argued that a phase I pbt assessment is not deemed to be necessary, because the estimated $\log_{KOW}$ is below 4.5. However, the MAH only calculated the $\log_{KOW}$ from the environmental assessment included in the NDA. In addition, the MAH referred to a literature review revealing other calculated or measured values as reported in table 1.

Because of lacking data the CHMP did not agree with the MAHs assumption that docetaxel does not present any risk of bioaccumulation. To assess the bioaccumulation potential ($\log_{KOW}$ >3) of the base docetaxel the mentioned $\log_{KOW}$ -study has to be described in more detail, at least the pH at which the study was conducted, has to be provided. If literature with more detailed parameters or a study report can not be submitted the MAH is asked to perform a KOW-study according to OECD 107 and to submit the final study report. However, if the log KOW > 3 was proven by a study, the MAH committed to perform a bioaccumulation study in line with OECD 305 in Phase II of the risk assessment.

During assessment the MAH was asked to provide medicines statistics or published epidemiological data on the prevalence of the indication which could be used to refine the market penetration factor in Phase I and to demonstrate that the extension of indication does not lead to an increased exposure of the environment to the active ingredient. However, the CHMP had difficulties to verify the internal data provided and to follow on the basis of the estimation of patients and market forecasts. If the source for medicines statistics or published epidemiological data on the prevalence of the indication which could be used to refine the market penetration factor in Phase I and to demonstrate that the new indication does not lead to an increased exposure of the environment to the active ingredient can not be provided by the MAH, the MAH committed to conduct a Phase II ERA.

### *1.2.2 Clinical Aspects*

#### *1.2.2.1 Introduction*

The submission comprised a single, pivotal phase III trial, TAX.ES1.301/GEICAM 9805. In the adjuvant treatment of operable node-positive and node-negative breast cancer, the recommended dose of docetaxel is 75 mg/m2 administered 1-hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 every 3 weeks for 6 cycles (TAC regimen) (see also Dose adjustments during treatment in section 4.2 of the SPC).

The European Medicines Agency has waived the obligation to submit the results of studies with Docetaxel Winthrop in all subsets of the paediatric population in breast cancer (see SPC section 5.1).

- **Tabular overview of clinical studies**

| Study | Design | Treatments | Primary | No. of patients | Reference |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | | | Endpoint | | |
| TAX.ES1.301/ GEICAM 9805 | Phase III, randomised, non-blinded | TAC *v.* FAC | Disease-free survival | randomised = 1060 | Martin, Lluch *et al*. Annals of Oncology 2006;17:1205-12 |

Abbreviations: docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC)

***GCP***

According to the MAH, the protocol of study GEICAM 9805 was designed in compliance with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments, with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted.

### *1.2.2.2 Clinical Pharmacology*

No pharmacokinetic and pharmacodynamic studies were submitted.

Discussion and conclusion

No pharmacokinetic interaction during the co-administration of doxorubicin cyclophosphamide, and docetaxel has been observed in the previously submitted study XRP6976D/1001 (a pharmacokinetic interaction study of docetaxel 75 mg/m2 i.v. on the combination therapy doxorubicin 50 mg/m2 i.v. and cyclophosphamide 500 mg/m2 i.v. in the treatment of advanced breast cancer, see variation application EMEA/H/C/073/II/54). No critical issues have been identified concerning clinical pharmacology.

The pharmacokinetic properties of docetaxel are adequately described SPC section 5.2.

### *1.2.2.3 Clinical efficacy*

#### *1.2.2.3.1 Dose response study(ies)*

No dose-response studies were submitted.

In the adjuvant treatment of operable node-positive and node-negative breast cancer, the recommended dose of docetaxel is 75 mg/m$^2$ administered 1-hour after doxorubicin 50 mg/m$^2$ and cyclophosphamide 500 mg/m$^2$ every 3 weeks for 6 cycles (TAC regimen). For the complete dosing recommendations, see SPC section 4.2. The initial dosing recommendation were based on a pilot phase II study of docetaxel in combination with doxorubicin and cyclophosphamide (Nabholtz et al., J Clin Oncol. 2001 Jan 15;19(2):314-21), see variation application EMEA/H/C/073/II/54.

#### *1.2.2.3.2 Main study – GEICAM 9805*

Title: A multicenter Phase 3 randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of high risk operable breast cancer patients with negative axillary lymph nodes.

**Methods**

**Study Participants**

The study participants had to satisfy the following inclusion and exclusion criteria:

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| - Written informed consent and expected cooperation of the subjects for the treatment and | - Prior immunotherapy, hormonotherapy, chemotherapy, or radiation therapy for breast |

| | |
|---|---|
| follow-up.<br>- Operable breast cancer patients, histologically proven, with negative axillary lymph nodes and high risk criteria according to St. Gallen consensus criteria (tumour size >2cm and/or negative ER and PR and/or histological/nuclear grade 2 to 3 and/or age <35 years)<br>- Patient without metastatic disease whom had undergone mastectomy or breast-conserving surgery within 60 days prior to enrolment.<br>- Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and ductal carcinoma in situ.<br>- Karnofsky Performance status index ≥80%.<br>- Basal electrocardiogram within 12 weeks prior to registration. In case of suspected cardiac dysfunction, normal cardiac function must be confirmed by assessment of LVEF or shortening fraction.<br>- Age ≥18 years and age ≤70 years.<br>- Estrogen and progesterone receptors performed on the primary tumour prior to randomization. Results must be known by the end of chemotherapy in order to decide whether hormonal therapy is indicated.<br>- Standard routine laboratory requirements and negative pregnancy test.<br>- Complete staging work-up within 12 weeks prior to registration. | cancer.<br>- Prior anthracycline therapy or taxoids for any malignancy.<br>- Male subjects<br>- Bilateral invasive breast cancer.<br>- Any T4 or N1 to N3 or M1 breast cancer.<br>- Past or current history of neoplasm other than breast carcinoma except for nonmelanomatous skin cancer, in situ carcinoma of the cervix, ipsilateral ductal carcinoma in situ and lobular carcinoma in situ of the breast.<br>- Pre-existing motor or sensory neurotoxicity of a severity ≥ grade 2 by NCI criteria and other serious illness or medical condition.<br>- Chronic treatment with corticosteroids<br>- Concurrent treatment with ovarian hormonal replacement, other experimental drugs, or any other anti-cancer therapy.<br>- Contraindications for the use of corticosteroids.<br>- Pregnant or lactating subjects. |



Investigators participating in the study were from institutions located in Spain, Germany and Poland.

**Treatments**

- **TAC**: Doxorubicin 50 mg/m² as 15-min IV infusion followed by Cyclophosphamide 500 mg/m², as 15-min IV infusion. There was a one-hour interval between the end of the IV infusion of doxorubicin and the beginning of the infusion of Docetaxel 75 mg/m² as 1-hour IV infusion. Prophylactic antibiotic therapy (Ciprofloxacin 500 mg orally twice daily for 10 days starting on Day 5 of each cycle) was compulsory for subjects treated with TAC. The following premedication regimen for fluid retention was compulsory for all subjects treated with TAC. Dexamethasone 8 mg orally for total of 6 doses.
- **FAC**: Doxorubicin 50 mg/m² as 15-min IV followed by 5-fluorouracil 500 mg/m² as 15-min IV and Cyclophosphamide 500 mg/m² as 15-min IV.

Patients were to receive a total of 6 cycles unless treatment was precluded by relapse, subject refusal, or unacceptable toxicities.
The chemotherapy doses were calculated according to baseline body surface area (BSA) for all cycles, and BSA was to be recalculated if there was a ≥10% decrease in body weight compared to baseline.
Dose reduction and/or treatment delay, supportive treatment adjustment, and treatment discontinuation were planned for the 2 treatment groups in cases of severe haematological and/or nonhaematological treatment-emergent adverse events (TEAEs) or laboratory abnormalities, including neutropenia.
In both treatment groups, the following additional therapies were administered:

- Tamoxifen 20 mg orally once daily for 5 years, starting 3 to 6 weeks after the last course of chemotherapy for patients with positive ER and/or PR, unless there was a contraindication for the use of tamoxifen therapy
- Patients treated with lumpectomy were to undergo postoperative radiotherapy after completion of chemotherapy and resolution of any side effect(s). Radiotherapy was allowed after mastectomy

and chemotherapy for node-negative tumours >5 cm, according to the guidelines at each institution.

A prophylactic antiemetic treatment was recommended for patients in both treatment groups, with the choice of antiemetic left to the discretion of the Investigator.
Subsequent to the initiation of the study, the protocol was amended to require primary granulocyte colony-stimulating factor (G-CSF) prophylaxis in all TAC patients (Protocol Amendment No. 3, 18 July 2000 was instituted after the first 230 patients were randomized). This was to be used as:

- primary prophylactic treatment in patients treated with TAC
- curative treatment in case of absolute neutrophil count (ANC) <0.5 X $10^9$/L lasting <7 days, febrile neutropenia, or infection
- prophylactic treatment in patients treated with FAC with a prior episode of febrile neutropenia in an earlier cycle
- treatment for delayed recovery of ANC at Day 21

Also in the TAC treatment group, antibiotic prophylaxis was to be administered to all patients from the first cycle of treatment. Ciprofloxacin was recommended at a dose of 500 mg orally twice daily for 10 days starting Day 5 of each cycle. If ciprofloxacin was not available or not tolerated, another oral antibiotic was required, the choice of which was at the discretion of the Investigator.
Patients were also required to receive prophylactic premedication for fluid retention (6 oral doses of dexamethasone 8 mg).

**Outcomes/endpoints**

The primary endpoint was disease-free survival (DFS). DFS was defined as the interval from the date of randomization to the date of local, regional, or metastatic relapse, or the date of second primary cancer, or death from any cause (whichever occurred first). If there was no event, the patient was censored at the last visit. Patients with only baseline data were censored 1 day after randomization.
The main secondary endpoints were:

- Overall survival (OS) defined as the time interval between the date of randomization and the date of death from any cause.
- Quality of life (QOL). QOL evaluation was based on EORTC QLQ-C30 and QLQ-BR23, self-administered by the patient.
- Pathologic and molecular markers for predicting efficacy.

Follow-up visits were to be every 12 weeks (3 months) for the first 2 years, every 6 months for years 3-5, and then annually for 10 years. Clinical follow-up could be more frequent according to the standard of practice at the participating center.

First 2 years:
- Every 12 weeks: physical examination
- Every 6 months: haematology and biochemistry in addition to a physical examination
- Every 12 months: mammography and chest X-ray in addition to a physical examination, haematology, and biochemistry

Years 3 to 5:
- Every 6 months: physical examination, haematology, biochemistry
- Every 12 months: mammography and chest X-ray in addition to a physical examination, haematology, and biochemistry

Years 6 to 10:
- Every 12 months: physical examination, haematology, biochemistry, and mammography
- Other diagnostic tests (ie, abdominal ultrasound and/or CT scan, bone scan) were to be performed only in the presence of signs and/or symptoms suggestive of cancer recurrence.
- A quality of life assessment was required 6 months, 12 months, and 24 months after the end of chemotherapy.

**Sample Size**

DFS in the control group was estimated to be around 80% at 5 years. The study was originally designed to detect a 7.5% increase in DFS for TAC compared to FAC (i.e. from 80% to 87.5%). To detect this difference at a 5% significance level with 90% power, 527 patients were calculated to be necessary in each arm (with an average follow-up period equal to 5 years). According to the MAH, this calculation took into account an expected 3% rate of ineligible patients. An interim analysis was planned in the initial protocol to take place 3 years after half of the expected recruitment had been completed using a group sequential design (Peto, 1976), with a significance level of 0.001 for the interim analysis.

**Randomisation**

The randomisation (1:1) was centralised and stratified according to the participating institution and menopausal status.

**Blinding (masking)**

The study was non-blinded.

**Statistical methods**

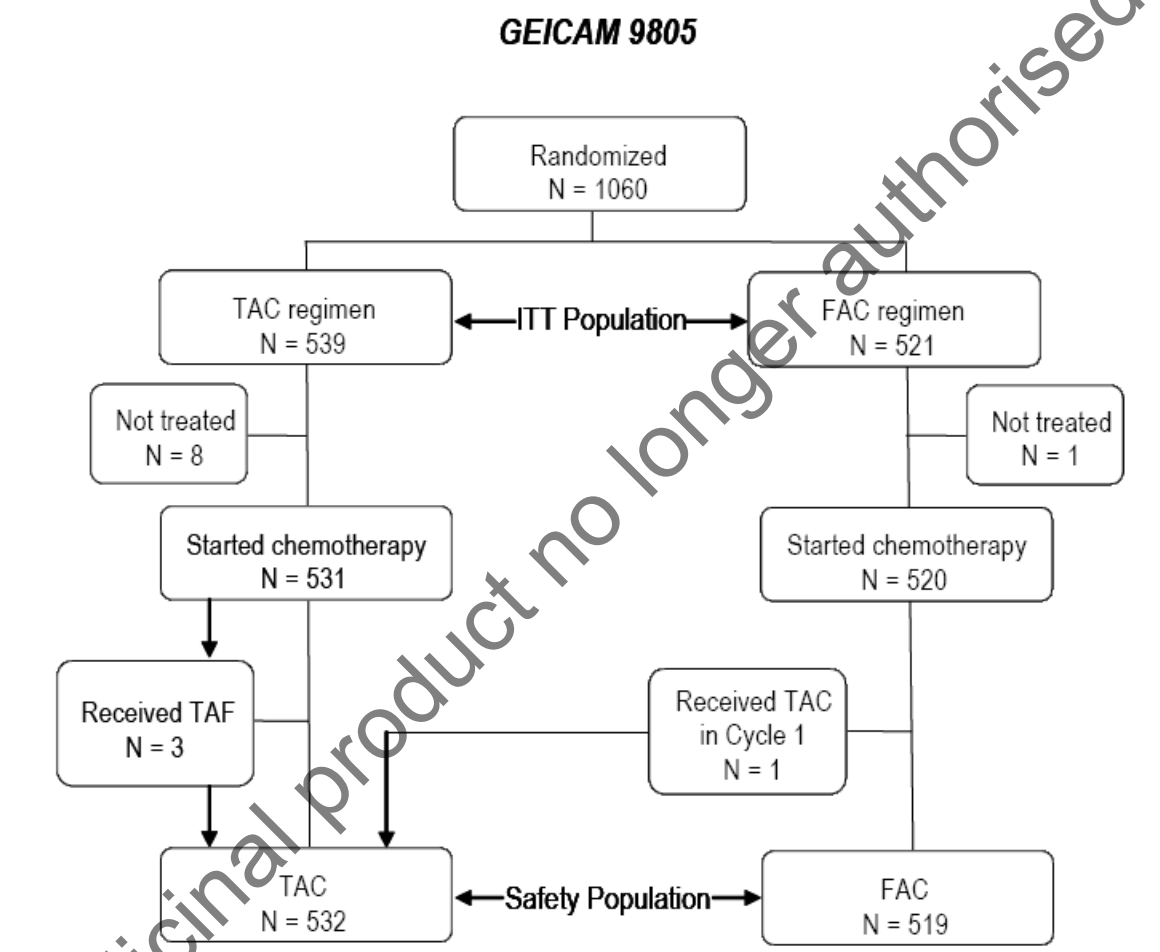
The unstratified log-rank test was used to compare the 2 treatment groups for DFS and OS. All tests of hypotheses were two-sided. The primary efficacy analysis population was the ITT population. The ITT population was defined as the population of all randomized patients, analyzed in the treatment group to which they were assigned. Randomized patients who did not receive chemotherapy according to randomization were analyzed in the treatment group of randomization.
The QoL population was defined as the population of all randomized patients who presented at least 1 baseline and post-baseline assessment of the QOL instruments. The GHS/QOL (Global Health Quality of Life) score was the primary endpoint of the QOL analysis. The GHS/QOL score was analyzed using a longitudinal mixed model with treatment and time as fixed effects and patient within the group as random effect.

## Results

### Participant flow

The cut-off date for data inclusion is 04 March 2009 (for clinical laboratory results, 05 May 2009), at which point all patients had completed at least 5 years of follow-up (median follow-up time of 6 years and 5 months [TAC: 76 months; FAC: 77 months]). A total of 1060 patients were randomized into the study. The first patient was randomized on 21 June 1999 and the last one on 10 March 2003. Fifty-five (55) centers actively recruited patients. The majority of patients were treated in Spain, with 962 of 1060 (90.8%) in Spain, 42 of 1060 (4.0%) in Germany, and 56 of 1060 (5.3%) in Poland. Details of overall patient disposition are provided in Figure 1.

Figure 1 – Participant Flow in GEICAM 9805




FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, TAC: docetaxel, doxorubicin, and cyclophosphamide, TAF: docetaxel, doxorubicin, and 5-fluorouracil.



There were 33 (6.1%) patients in the TAC treatment group and 13 (2.5%) patients in the FAC treatment group who discontinued chemotherapy treatment. Adverse events were the primary reason for treatment discontinuations in the TAC group (4.6% of patients), followed by withdrawal of consent (0.9% of patients).

### Recruitment

The first patient was enrolled on 21 June 1999; the last patient was enrolled on 10 March 2003. The statistical analysis plan (SAP), version 1.0 is dated on 11 February 2009. The Study cut-off date was 04 March 2009 with a median follow-up time of 77 months (presented as the final primary efficacy analysis).

**Conduct of the study**

The originally planned interim efficacy analysis after 3 years of follow-up was not performed because the number of events was too small for a meaningful analysis.

Two interim efficacy analyses were performed in December 2007 and April 2008; the latter one was an updated analysis. The purpose of these analyses was to present the 5 year follow-up analysis results at the 2008 American Society of Clinical Oncology (ASCO). Two other interim efficacy summaries were performed in May 2006 and May 2007 that were not intended for submission and were for internal data review only.

The following protocol amendments were performed:

| Amendment No. | Date | Major Changes |
|---|---|---|
| 1 | 24-Jun-1999 | • Incorporated an additional recommendation to inclusion criterion 6 (estrogen and progesterone receptor analysis)<br>• Explained inclusion criteria 9 (cardiac function) and 11 (complete staging work-up) in greater detail<br>• Increased the time window for the administration of cyclophosphamide<br>• Adapted the questionnaires of the quality of life to the most updated versions validated in Spain<br>• Added Appendix 11 (definition of menopausal status) |
| 2 | 24-Jan-2000 | • Extended the time period to perform the mammography prior to the patient's inclusion in the study<br>• Explained when the second CBC should be done in each cycle (Days 7-10) in greater detail |
| 3 | 18-Jul-2000 | • Added G-CSF systematically to the first treatment cycle and onwards for all patients included in the TAC treatment group in order to prevent the occurrence of febrile neutropenia, and added criteria for dose modification in case of thrombocytopenia on Day 1 of each cycle<br>• Adopted the new docetaxel F3 storage conditions in the European Union, Norway, and Switzerland |

CBC: complete blood count, G-CSF: granulocyte colony-stimulating factor, TAC: docetaxel, doxorubicin, and cyclophosphamide

**Baseline data**

The population enrolled in GEICAM 9805 included patients with operable node-negative breast cancer with 1 or more high-risk factors (tumour size >2 cm, age <35 years, ER and PR negative, histological or nuclear grade 2 or 3). Demographic data for the ITT population are presented in table 1.

Table 1 - Demographic data – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Age (years) | | | |
| Median | 50 | 49 | 50 |
| Min : Max | 23 : 74 | 23 : 73 | 23 : 74 |
| Age group | | | |
| <35 | 42 (7.8) | 33 (6.3) | 75 (7.1) |
| 35-49 | 218 (40.4) | 231 (44.3) | 449 (42.4) |
| 50-64 | 241 (44.7) | 224 (43.0) | 465 (43.9) |
| 65-74 | 38 (7.1) | 33 (6.3) | 71 (6.7) |
| ≥75 | 0 | 0 | 0 |
| Performance status group | | | |
| 80 | 3 (0.6) | 0 | 3 (0.3) |
| 90 | 87 (16.1) | 88 (16.9) | 175 (16.5) |
| 100 | 449 (83.3) | 433 (83.1) | 882 (83.2) |
| Menopausal status | | | |
| Premenopausal | 285 (52.9) | 272 (52.2) | 557 (52.5) |

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Postmenopausal | 254 (47.1) | 249 (47.8) | 503 (47.5) |
| Hormone receptor status | | | |
| Positive | 344 (63.8) | 349 (67.0) | 693 (65.4) |
| ER+/PR+ | 252 (46.8) | 268 (51.4) | 520 (49.1) |
| ER+/PR- | 63 (11.7) | 63 (12.1) | 126 (11.9) |
| ER-/PR+ | 26 (4.8) | 16 (3.1) | 42 (4.0) |
| ER+/PR unknown | 3 (0.6) | 1 (0.2) | 4 (0.4) |
| ER unknown/PR+ | 0 | 1 (0.2) | 1 (<0.1) |
| Negative | 195 (36.2) | 172 (33.0) | 367 (34.6) |
| ER-/PR- | 192 (35.6) | 170 (32.6) | 362 (34.2) |
| ER-/PR unknown | 0 | 1 (0.2) | 1 (<0.1) |
| ER unknown/PR- | 0 | 0 | 0 |
| ER unknown/PR unknown | 3 (0.6) | 1 (0.2) | 4 (0.4) |

Table 2: Breast cancer surgery at first diagnosis – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Patients with at least 1 type of surgery for breast cancer [a] | 538 (99.8) | 521 (100) | 1059 (>99.9) |
| Most recent surgery [b] | | | |
| Lumpectomy | 154 (28.6) | 159 (30.5) | 313 (29.5) |
| Quadrantectomy/segmental | 193 (35.8) | 152 (29.2) | 345 (32.5) |
| Mastectomy | 228 (42.3) | 250 (48.0) | 478 (45.1) |
| Other [c] | 52 (9.6) | 47 (9.0) | 99 (9.3) |
| Missing [d] | 1 (0.2) | 0 | 1 (<0.1) |

[a] If a patient had the same surgical procedure more than once, the patient is counted only once.

[b] A patient could have multiple choices that all applied.

[c] No further information is available.

[d] Patient No. 00662 in the TAC treatment group had surgery but the type was not specified.

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

About 97% of the receptor-positive subjects in each treatment arm received tamoxifen.

More than 50% of patients in each treatment group received adjuvant radiotherapy (TAC: 57.3%, FAC: 51.2%), consisting mostly of patients who had undergone breast-conserving surgery (TAC: 53.2%, FAC: 47.4%), but few who had undergone mastectomy (TAC: 4.1%, FAC: 3.8%).

Table 3: Breast cancer staging at first diagnosis – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Primary tumor site | | | |
| Left breast | 267 (49.5) | 258 (49.5) | 525 (49.5) |
| Right breast | 271 (50.3) | 263 (50.5) | 534 (50.4) |
| Missing [a] | 1 (0.2) | 0 | 1 (<0.1) |
| Primary tumor size | | | |
| pT1: ≤2 cm | 285 (52.9) | 249 (47.8) | 534 (50.4) |
| pT2: [2-5] cm | 241 (44.7) | 258 (49.5) | 499 (47.1) |
| pT3: >5 cm | 13 (2.4) | 13 (2.5) | 26 (2.5) |
| Missing [b] | 0 | 1 (0.2) | 1 (<0.1) |
| Regional lymph nodes | | | |
| pN0: no regional lymph nodes metastasis | 538 (99.8) | 520 (99.8) | 1058 (99.8) |
| pN1: metastasis to movable ipsilateral axillary nodes [c] | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Distant metastases | | | |
| M0: None | 539 (100) | 521 (100) | 1060 (100) |

[a] For Patient No. 00662 (TAC), information regarding tumor site was missing.

[b] For Patient No. 00604 (FAC), information regarding tumor size was missing.

[c] Patients No. 00041 (TAC) and 00066 (FAC) had metastasis to movable ipsilateral axillary lymph nodes.

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, M0: no distant metastasis, pN0: node-negative, pN1: node-positive, pT: primary tumor size, TAC: docetaxel, doxorubicin, and cyclophosphamide

Table 4: Histology at first diagnosis – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Histopathological type | | | |
| Infiltrating ductal | 462 (85.7) | 445 (85.4) | 907 (85.6) |
| Infiltrating lobular | 38 (7.1) | 45 (8.6) | 83 (7.8) |
| Other | 39 (7.2) | 31 (6.0) | 70 (6.6) |
| Histopathological grade (differentiation) | | | |
| Grade 1 (good) | 38 (7.1) | 34 (6.5) | 72 (6.8) |
| Grade 2 (moderate) | 216 (40.1) | 230 (44.1) | 446 (42.1) |
| Grade 3 (poor) | 259 (48.1) | 231 (44.3) | 490 (46.2) |
| Grade X (not assessed) | 25 (4.6) | 26 (5.0) | 51 (4.8) |
| Missing [a] | 1 (0.2) [a] | 0 | 1 (<0.1) [a] |
| Margins | | | |
| Free | 538 (99.8) | 521 (100) | 1059 (>99.9) |
| Missing [a] | 1 (0.2) | 0 | 1 (<0.1) |

[a] For Patient No. 00662 (TAC), information regarding histopathological grade and margins was missing.
FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

Table 5: Number of resected lymph nodes by randomization group – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Number of resected axillary lymph nodes | | | |
| Median | 16 | 16 | 16 |
| Min | 8 | 10 | 8 |
| Max | 58 | 49 | 58 |
| Number of resected lymph nodes | | | |
| [6-8] | 1 (0.2) | 0 | 1 (<0.1) |
| [9-10] | 43 (8.0) | 43 (8.3) | 86 (8.1) |
| [11-12] | 82 (15.2) | 72 (13.8) | 154 (14.5) |
| [13-15] | 134 (24.9) | 119 (22.8) | 253 (23.9) |
| [16-20] | 152 (28.2) | 153 (29.4) | 305 (28.8) |
| >20 | 126 (23.4) | 134 (25.7) | 260 (24.5) |
| Missing | 1 (0.2) | 0 | 1 (<0.1) |
| Number of positive axillary lymph nodes [a] | 1 (0.2) | 1 (0.2) | 2 (0.2) |

[a] Patients did not meet inclusion criteria.
FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

**Numbers analysed**

A total of 1060 patients were randomized per protocol. Seventeen (17) patients were subsequently found to be ineligible (TAC: 13; FAC: 4). Nine (9) patients were not treated (TAC: 8; FAC: 1) and 4 patients were not treated with study medication as randomized (TAC: 3; FAC: 1). Three (3) patients did not have baseline or postbaseline efficacy assessments, and 2 patients had at least 1 positive lymph node.

Table 6 - Patients randomized, treated, and eligible – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) | All (N=1060) n (%) |
|---|---|---|---|
| Randomized patients[a] | 539 (100) | 521 (100) | 1060 (100) |
| Per-protocol population[b] | 526 (97.6) | 517 (99.2) | 1043 (98.4) |
| Treated patients[c] | 531 (98.5) | 520 (99.8) | 1051 (99.2) |
| TAC[d] | 531 (98.5) | 1 (0.2) [d] | 532 (50.2) [d] |
| FAC | 0 | 519 (99.6) | 519 (49.0) |
| Not treated[e] | 8 (1.5) | 1 (0.2) | 9 (0.8) |

[a] All randomized patients were included in baseline characteristics and efficacy analysis (ITT population).

[b] Excluded patients who had major protocol deviations

[c] All patients who received study treatment (safety population)

[d] One patient randomized to FAC actually received TAC in the first cycle and is therefore analyzed in the TAC treatment group for safety analyses. Three patients randomized to TAC received TAF and were analyzed in the TAC treatment group, as randomized.

[e] Four TAC patients withdrew consent, 3 TAC patients withdrew for "other" reasons, 1 TAC patient withdrew due to a deviation from the protocol, and for 1 FAC patient the reason for no treatment was missing.

All 1060 randomized patients were included in the efficacy analysis (ITT population). However, 9 patients did not receive any study treatment, 8 (1.5%) in the TAC group and 1 (0.2%) in the FAC group. The reasons for not being treated were withdrawal of consent (4), deviation from the protocol (1), "other" (3), and missing (1). Three (3) patients randomized to the TAC group received TAF not according to the protocol, and 1 patient (Patient No. 00916) who was randomized to the FAC group received TAC in the first cycle and FAC in the remaining 5 cycles, not according to the protocol. This patient was analyzed for efficacy in the FAC group and for safety in the TAC group. The 3 TAF patients were analyzed in the TAC treatment group as randomized. Slightly more patients were treated with TAC compared with FAC. This was mainly due to chance because randomization was stratified by centers, and the large number (N = 55) of centers carried a chance of slight imbalances. For the purposes of efficacy analyses, patients in the ITT population were analyzed according to the randomization group to which they were assigned (TAC: 539; FAC: 521).

**Outcomes and estimation**

Disease-Free Survival (DFS)

The results of the primary endpoint are presented in Table 7 and Figure 2:

Table 4 - Disease-free survival analysis – ITT population

| **Time to event in months for DFS [a]** | **TAC (N=539)** | **FAC (N=521)** |
|---|---|---|
| Overall at a median 77 months follow-up: | | |
| Number assessed | 539 | 521 |
| Number censored, n (%) | 473 (87.8) | 426 (81.8) |
| Number of events, n (%) | 66 (12.2) | 95 (18.2) |
| Unstratified log-rank test p-value [b] | | |
| TAC versus FAC | 0.0141 | |
| Unadjusted hazard ratio (95% CI) [c] | | |
| TAC versus FAC | 0.676 (0.493, 0.926) | |
| Stratified log-rank test p-value [d] | | |
| TAC versus FAC | 0.0141 | |
| Adjusted hazard ratio (95% CI) [d] | | |
| TAC versus FAC | 0.68 (0.497 , 0.919) | |
| DFS rate at 5 year follow-up: | 0.901 | 0.853 |
| 95% CI | (0.875, 0.926) | (0.823, 0.884) |

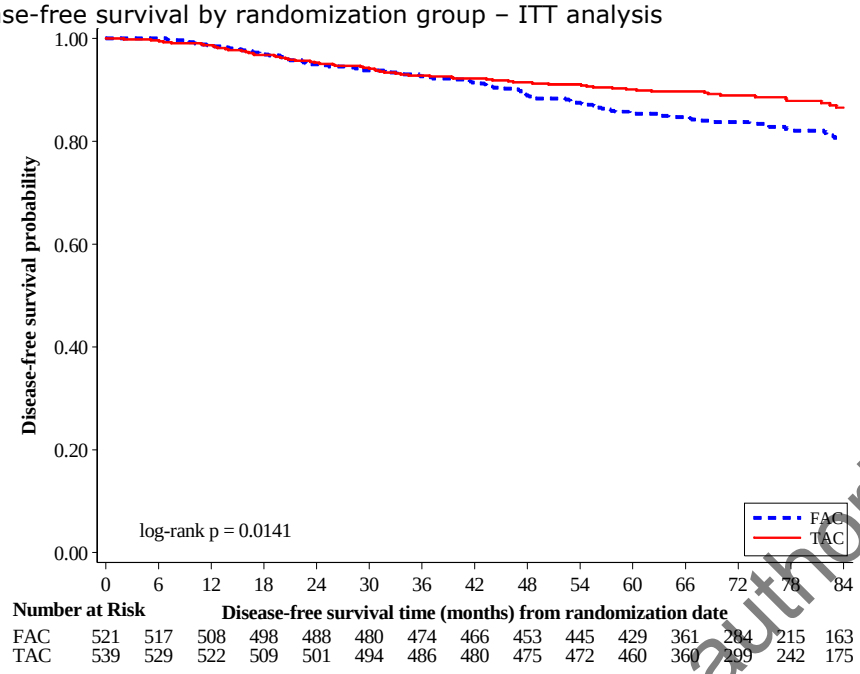
[a] Kaplan-Meier estimates

[b] Pairwise log-rank test of homogeneity between treatment groups

[c] Estimated using Cox proportional hazard model with treatment group as the factor

[d] Estimated using Cox proportional hazard model with treatment group as the factor, stratified by stratum of menopausal status

Figure 2 - Disease-free survival by randomization group – ITT analysis




FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide,
ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

The types of events for DFS analysis are described in Table 8.

Table 8 - Type of events for the disease-free survival analysis in all randomized patients, by randomization group – ITT population

| | TAC (N=539) n (%) | FAC (N=521) n (%) |
|---|---|---|
| Event-free patients | 473 (87.8) | 426 (81.8) |
| Patients with an event | 66 (12.2) | 95 (18.2) |
| Breast cancer relapse | 48 (8.9) | 66 (12.7) |
| Local | 4 (0.7) | 17 (3.3) |
| Regional | 3 (0.6) | 6 (1.2) |
| Regional alone | 0 | 4 (0.8) |
| Regional and local | 3 (0.6) | 2 (0.4) |
| Distant | 40 (7.4) | 43 (8.3) |
| Distant alone | 34 (6.3) | 38 (7.3) |
| Distant and local | 4(0.7) | 2 (0.4) |
| Distant and regional | 2 (0.4) | 3 (0.6) |
| Distant and regional and local | 0 | 0 |
| Missing | 1 (0.2) | 0 |
| Second type primary malignancy | 13 (2.4) | 26 (5.0) |
| Primary breast | 4 (0.7) | 10 (1.9) |
| Endometrium | 1 (0.2) | 4 (0.8) |
| Ovarian | 2 (0.4) | 1 (0.2) |
| Leukemia | 0 | 0 |
| Other | 6 (1.1) | 10 (1.9) |
| Missing | 0 | 1 (0.2) |
| Death (no evidence of disease) | 5 (0.9) | 3 (0.6) |
| Toxicity | | |
| Septic | 0 | 0 |
| Nonseptic | 0 | 0 |
| Toxicity due to chemotherapy given after relapse | 0 | 0 |
| Breast cancer | 1 (0.2) | 0 |
| Malignant disease, other than breast cancer | 0 | 0 |
| Other | 4 (0.7) | 3 (0.6) |

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide
PGM=XRP6976/IRF0414/NDA2009/BS/PGM_RPT/a6events.sas OUT=OUTPUT/a6events_x.rtf (14AUG2009 - 15:06)

Overall Survival (OS)

At the cut-off date of 04 March 2009, and with a greater than 5 year follow-up time (median follow-up time was 6 years and 5 months), 60 (5.7%) patients had died (TAC: 26 [4.8%]; FAC: 34 [6.5%]). No significant association was observed between treatment and OS (HR of TAC vs. FAC = 0.758, 95% CI = 0.454, 1.263; p=0.2853).

Table 9 and Figure 3 below summarize the result more comprehensively.

Table 9: Overall survival by randomization group – ITT population

| Time to event in months for OS [a] | TAC (N=539) | FAC (N=521) |
|---|---|---|
| Overall | | |
| Number assessed | 539 | 521 |
| Number censored, n (%) | 513 (95.2) | 487 (93.5) |
| Number of events, n (%) | 26 (4.8) | 34 (6.5) |
| Unstratified log-rank test p-value [b] | | |
| TAC versus FAC | 0.2853 | |
| Unadjusted hazard ratio (95% CI) [c] | | |
| TAC versus FAC | 0.758 (0.454, 1.263) | |
| Stratified log-rank test p-value [d] | | |
| TAC versus FAC | 0.2877 | |
| Adjusted HR (95% CI) [d] | | |
| TAC versus FAC | 0.758 (0.455, 1.263) | |

[a] Kaplan-Meier estimates

[b] Pairwise log-rank test of homogeneity between treatment groups

[c] Estimated using Cox proportional hazard model with treatment group as the factor

[d] Estimated using Cox proportional hazard model with treatment group as the factor, stratified by stratum of menopausal status

CI: confidence interval, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, HR: hazard ratio, ITT: intent-to-treat, OS: overall survival, TAC: docetaxel, doxorubicin, and cyclophosphamide



Figure 3: Overall survival – ITT analysis

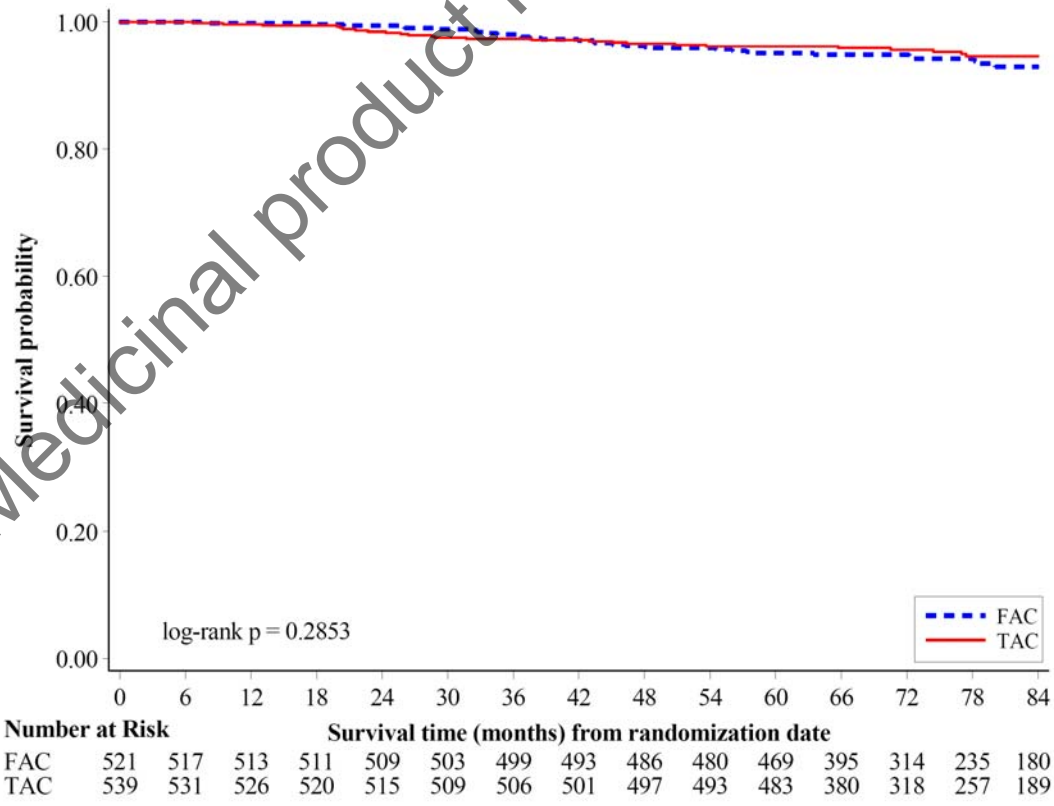



Table 10: Exposure to further anti-tumour therapy for breast cancer relapse – ITT population

| Types of therapy | TAC (N=539) n (%) | FAC (N=521) n (%) |
|---|---|---|
| No systemic anticancer therapy | 490 (90.9) | 450 (86.4) |
| Systemic anticancer therapy | | |
| Hormonal [a] | 13 (2.4) | 17 (3.3) |
| Immunotherapy | 2 (0.4) | 3 (0.6) |
| Chemotherapy | 35 (6.5) | 53 (10.2) |
| Other | 4 (0.7) | 5 (1.0) |
| No nonsystemic anticancer therapy | 500 (92.8) | 474 (91.0) |
| Nonsystemic anticancer therapy | | |
| Radiotherapy | 18 (3.3) | 22 (4.2) |
| Surgery | 27 (5.0) | 33 (6.3) |

Note: Patients may have had more than 1 type of antitumor therapy.

[a] Other than tamoxifen

FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

Quality of Life

A baseline evaluable QLQ-C30 questionnaire was available for 941 (88.8%) of the 1060 randomized patients. A baseline evaluable QLQ-BR23 questionnaire was available for 931 (87.8%) patients.

Compliance with the QLQ-C30 questionnaires was similar in both treatment groups, with a decline from baseline (TAC: 87.6%; FAC: 90.0%) to Cycle 6 (TAC: 71.1%; FAC: 74.1%) and to follow-up 8 (TAC: 25.4%; FAC: 26.3%).

Compliance with QLQ-BR23 questionnaires was similar in both treatment groups, with a decline from baseline (TAC: 86.1%; FAC: 89.6%) to Cycle 6 (TAC: 70.7%; FAC: 73.7%) and to follow-up 8 (TAC: 25.2%; FAC: 26.5%).

Baseline QOL score was 71 in both treatment groups (Table 11), and both groups reported a deterioration of QOL during treatment (i.e., until last cycle). The deterioration over time was statistically significant for TAC compared with FAC ($p = 0.0007$). The evolution over time was also statistically significant ($p < 0.0001$).

The reduction in QOL was transient. The GHS/QOL score reached a minimum at Cycle 6, with an estimated treatment difference of 5.83 points (TAC: 54.35; FAC: 60.18). The QOL scores in both treatment groups returned to the baseline value as of the second follow-up 2 visit. The GHS scores were comparable between the 2 treatment groups during follow-up visits.

Both groups reported a deterioration of QOL during treatment (i.e., until last cycle). The deterioration over time was statistically significant for TAC compared with FAC ($p = 0.0007$). The evolution over time was also statistically significant ($p < 0.0001$). There was no significant treatment by time interaction (interaction test $p=0.1762$).

The reduction in QOL was transient. The GHS/QOL score reached a minimum at Cycle 6, with an estimated treatment difference of 5.83 points (TAC: 54.35; FAC: 60.18). The QOL scores in both treatment groups returned to the baseline value as of the second follow-up 2 visit. The GHS scores were comparable between the 2 treatment groups during follow-up visits.

**Ancillary analyses**

Subgroup analyses of efficacy are presented in Table 11 and Figures 4-5.

Table 11 - Subgroup analyses for disease-free survival – ITT population

| Subgroups [a] | TAC (N=539) | FAC (N=521) | Hazard Ratio (TAC/FAC) (95% CI) |
|---|---|---|---|
| Overall | 539 | 521 | 0.676 (0.493, 0.926) |
| Hormonal receptor status | | | |
| Negative | 195 | 172 | 0.7 (0.447, 1.096) |
| Positive | 344 | 349 | 0.622 (0.398, 0.97) |
| HER2 status | | | |
| Missing | 188 | 196 | 0.85 (0.509, 1.422) |
| Negative | 307 | 275 | 0.563 (0.368, 0.862) |
| Positive | 44 | 50 | 0.849 (0.268, 2.691) |
| Menopausal status | | | |
| Premenopausal | 285 | 272 | 0.636 (0.403, 1.003) |
| Postmenopausal | 254 | 249 | 0.723 (0.468, 1.119) |
| Age category1 | | | |
| <50 years | 260 | 264 | 0.674 (0.434, 1.049) |
| ≥50 years | 279 | 257 | 0.667 (0.425, 1.045) |
| Age category2 | | | |
| <35 years | 42 | 33 | 0.307 (0.106, 0.886) |
| ≥35 years | 497 | 488 | 0.726 (0.522, 1.011) |
| Tumour size | | | |
| ≤2cm | 285 | 250 | 0.685 (0.428, 1.095) |
| >2cm | 254 | 271 | 0.681 (0.445, 1.043) |
| Karnofsky Index | | | |
| 100% | 449 | 433 | 0.696 (0.492, 0.985) |
| <100% | 90 | 88 | 0.593 (0.28, 1.255) |
| Surgery | | | |
| Breast-conserving surgery | 311 | 271 | 0.53 (0.328, 0.856) |
| Mastectomy | 228 | 250 | 0.861 (0.566, 1.309) |
| Radiotherapy | | | |
| Adjuvant | 309 | 267 | 0.528 (0.334, 0.833) |
| No adjuvant | 230 | 254 | 0.891 (0.576, 1.378) |
| Histological grade | | | |
| Grade 1 (includes grade not assessed) | 64 | 60 | 0.791 (0.241, 2.594) |
| Grade 2 | 216 | 230 | 0.771 (0.457, 1.3) |
| Grade 3 | 259 | 231 | 0.591 (0.389, 0.899) |
| Histological subtype | | | |
| Invasive ductal carcinoma | 462 | 445 | 0.72 (0.512, 1.012) |
| Other carcinoma | 77 | 76 | 0.466 (0.201, 1.081) |

[a] These subset analyses were prespecified in the statistical analysis plan.

Figure 4 - Forest chart for disease-free survival subgroup analysis – ITT population

| N | Subgroup | Category | TAC | FAC | HR (95% CI) |
|---|---|---|---|---|---|
| 1060 | Overall | Overall | 539 | 521 | 0.676 (0.493 to 0.926) |
| 367 | Hormonal receptor status | Negative | 195 | 172 | 0.7 (0.447 to 1.096) |
| 693 | | Positive | 344 | 349 | 0.622 (0.398 to 0.97) |
| 582 | HER2 status | Negative | 307 | 275 | 0.563 (0.368 to 0.862) |
| 94 | | Positive | 44 | 50 | 0.849 (0.268 to 2.691) |
| 49 | HR/HER2 | +/+ | 21 | 28 | 0.562 (0.057 to 5.584) |
| 399 | | +/- | 207 | 192 | 0.554 (0.309 to 0.995) |
| 45 | | -/+ | 23 | 22 | 0.872 (0.218 to 3.493) |
| 183 | | -/- | 100 | 83 | 0.546 (0.293 to 1.018) |
| 503 | Menopausal status | Post-Menopausal | 254 | 249 | 0.723 (0.468 to 1.119) |
| 557 | | Pre-Menopausal | 285 | 272 | 0.636 (0.403 to 1.003) |
| 75 | Age category2 | <35 years | 42 | 33 | 0.307 (0.106 to 0.886) |
| 985 | | >=35 years | 497 | 488 | 0.726 (0.522 to 1.011) |
| 535 | Tumor size | <=2cm | 285 | 250 | 0.685 (0.428 to 1.095) |
| 525 | | >2cm | 254 | 271 | 0.681 (0.445 to 1.043) |
| 124 | Histological grade | Grade 1 (includes grade not assessed) | 64 | 60 | 0.791 (0.241 to 2.594) |
| 446 | | Grade 2 | 216 | 230 | 0.771 (0.457 to 1.3) |
| 490 | | Grade 3 | 259 | 231 | 0.591 (0.389 to 0.899) |

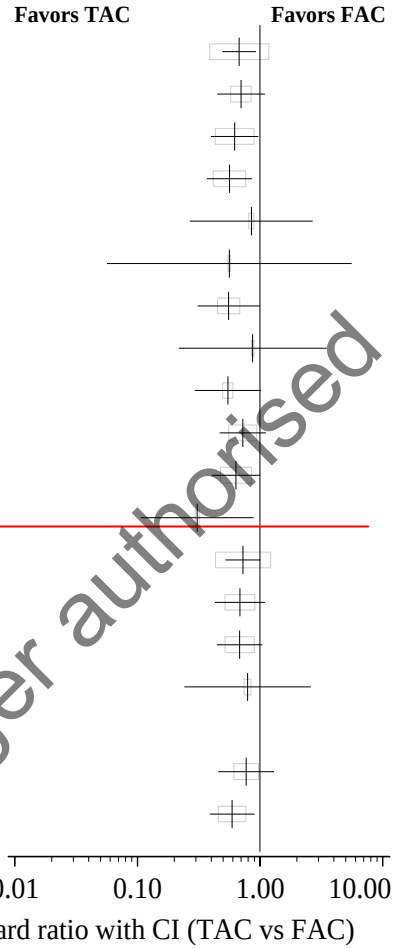
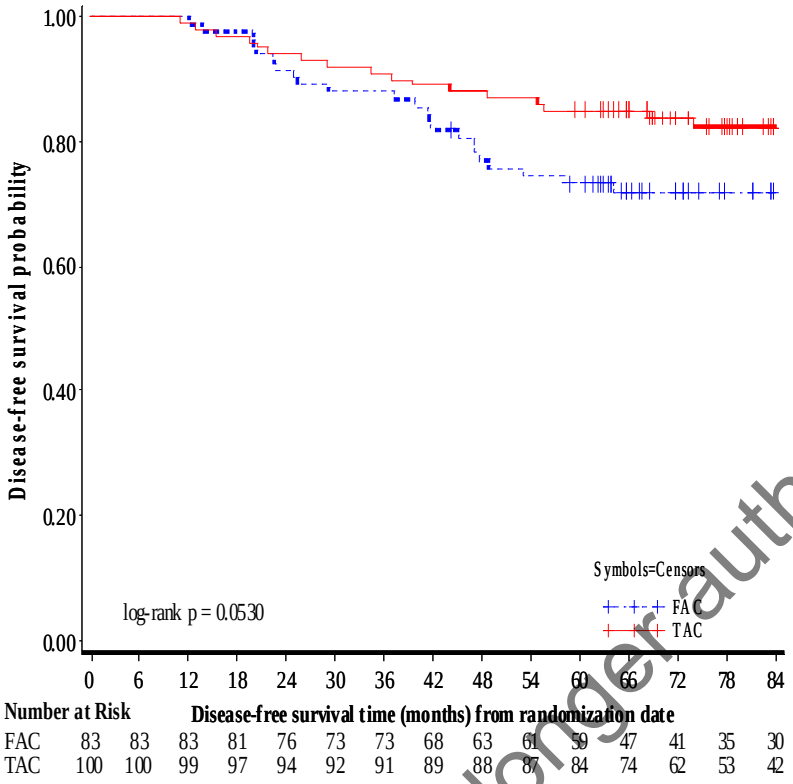


Figure 5 - Kaplan-Meier curves of disease-free survival for subgroups of HR-negative/HER2-negative status – ITT population




Abbreviations: DFS: disease-free survival, FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, ITT: intent-to-treat, TAC: docetaxel, doxorubicin, and cyclophosphamide

Further analyses have been performed with the ITT population considering the most recent clinical standards (St Gallen 2009 conference).

Table 12 - Number of patients who meet the 2009 St. Gallen chemotherapy criteria - ITT population

| Category | TAC (N=539) n (%) | FAC (N=521) n (%) |
|---|---|---|
| Patients who met relative indication for chemotherapy | 325 (60.3) | 294 (56.4) |
| ER and PR negative | 192 (35.6) | 170 (32.6) |
| Grade 3 | 259 (48.1) | 231 (44.3) |
| Tumour size >5 cm | 13 (2.4) | 13 (2.5) |
| Patients with criteria not useful for decision | 214 (39.7) | 227 (43.6) |
| Grade 2 | 172 (31.9) | 185 (35.5) |
| Tumour size (2-5 cm) | 105 (19.5) | 126 (24.2) |
| Grade 2 and tumour size (2-5 cm) | 67 (12.4) | 90 (17.3) |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; ER = estrogen receptor;
PR = progesterone receptor

Table 13 - Subgroup analyses for disease-free survival for patients who meet the 2009 St. Gallen chemotherapy criteria - ITT population

| Subgroups | TAC (N=539) | FAC (N=521) | Hazard Ratio (TAC/FAC) (95% CI) | p-value |
|---|---|---|---|---|
| Overall | 66 (12.2%) | 95 (18.2%) | 0.676 (0.493 , 0.926) | 0.0141 |
| Meeting relative indication for chemotherapy[a] | | | | |
| No | 18/214 (8.4%) | 26/227 (11.5%) | 0.796 (0.434 , 1.459) | 0.4593 |
| Yes | 48/325 (14.8%) | 69/294 (23.5%) | 0.606 (0.42 , 0.877) | 0.0072 |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; CI = confidence interval;
ER = estrogen receptor; PR = progesterone receptor
[a] ER/PR-negative or Grade 3 or tumour size >5 cm
The estimated hazard ratio was using Cox proportional hazard model with treatment group as the factor.

Table 14 - Subgroup analyses for overall survival for patients who meet the 2009 St. Gallen chemotherapy criteria - ITT population

| Subgroups | TAC (N=539) | FAC (N=521) | Hazard Ratio (TAC/FAC) (95% CI) | p-value |
|---|---|---|---|---|
| Overall | 26 (4.8%) | 34 (6.5%) | 0.758 (0.454 , 1.263) | 0.2853 |
| Meeting relative indication for chemotherapy[a] | | | | |
| No | 5/214 (2.3%) | 8/227 (3.5%) | 0.716 (0.234 , 2.193) | 0.5570 |
| Yes | 21/325 (6.5%) | 26/294 (8.8%) | 0.728 (0.409 , 1.294) | 0.2775 |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; CI = confidence interval;
ER = estrogen receptor; PR = progesterone receptor
[a] ER/PR-negative or Grade 3 or tumour size >5 cm
The estimated hazard ratio was using Cox proportional hazard model with treatment group as the factor.

Figure 6 - Disease-free survival for patients who met 2009 St. Gallen chemotherapy criteria

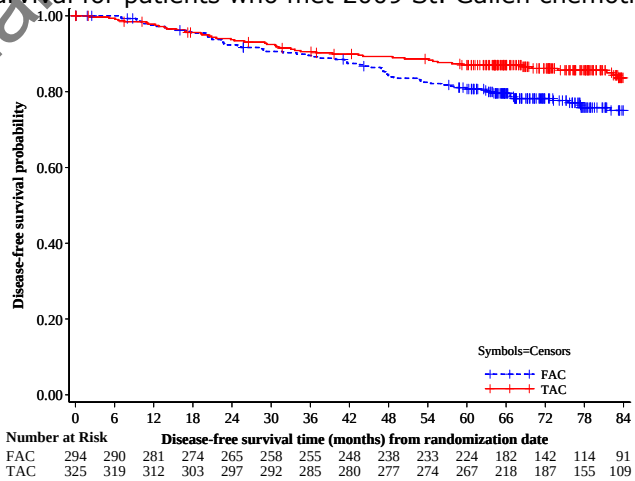
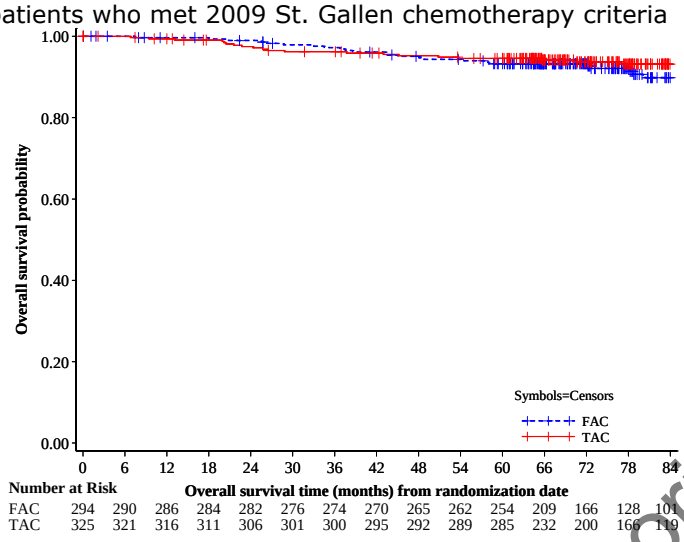


Figure 7 - Overall survival for patients who met 2009 St. Gallen chemotherapy criteria




The subgroup analyses for the triple-negative patients are provided in Table 19 for DFS and Table 20 for OS. The HR of DFS for triple-negative patients is 0.546 (0.293, 1.018). The HR of OS for triple-negative patients is 0.4 (0.15, 1.067). Both show benefit favourable toward the TAC arm.

Table 15 - Analysis of DFS for triple negative patients

| Subgroups | TAC (N=539) | FAC (N=521) | Hazard Ratio (TAC/FAC) (95% CI) | p-value |
|---|---|---|---|---|
| Overall | 66 (12.2%) | 95 (18.2%) | 0.676 (0.493 , 0.926) | 0.0141 |
| HR/HER2 | | | | |
| -/- | 17/100 (17.0%) | 24/83 (28.9%) | 0.546 (0.293 , 1.018) | 0.0530 |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; CI = confidence interval;
HR = hormone receptor; HER2 = Human Epidermal Growth Factor Receptor 2

Table 16 - Analysis of OS for triple negative patients

| Subgroups | TAC (N=539) | FAC (N=521) | Hazard Ratio (TAC/FAC) (95% CI) | p-value |
|---|---|---|---|---|
| Overall | 26 (4.0%) | 34 (6.5%) | 0.758 (0.454 , 1.263) | 0.2853 |
| HR/HER2 | | | | |
| -/- | 6/100 (6.0%) | 12/83 (14.5%) | 0.4 (0.15 , 1.067) | 0.0581 |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; CI = confidence interval;
HR = hormone receptor; HER2 = Human Epidermal Growth Factor Receptor 2

***Discussion on the Clinical Efficacy***

The international consensus panel meeting in St. Gallen in 1998 defined women with operable node-negative breast cancer to have a high risk of relapse if they met the following criteria:

- Tumour size greater than 2 cm and/or
- Negative ER and PR and/or
- Grade 2 to 3 (histological or nuclear, whichever is greatest) and/or
- Age less than 35 years.

Considering that, more than 25% of node-negative patients treated with FAC had recurrent disease at 10 years, in June 1999, the GEICAM 9805 trial was initiated to compare FAC with TAC in patients with high-risk, node-negative breast cancer as defined by the 1998 St. Gallen criteria. Tamoxifen therapy was indicated as a post-chemotherapy intervention for all patients with hormone-sensitive breast cancer.

Meanwhile, the adjuvant treatment selection algorithm for the management of early breast cancer radically changed during the last decade. As a consequence and according to the most recent concepts, the benefit of adjuvant chemotherapy is clear for triple negative patients and for HER2 positive disease. For the latter chemotherapy is given with or preceding Herceptin. While, for patients with ER positive, HER2 negative disease the decision for adjuvant chemotherapy is most difficult.

TAC dosage and schedule is similar to the one used for patient with node positive breast cancer (study TAX 316). Only the duration infusion for cyclophosphamide was lengthened from 5 to 15 minutes in order to improve tolerance. Anthracycline based regimens are viewed as standard therapies among several other regimens. Therefore, the comparator FAC was considered acceptable.

Based on the efficacy analyses presented, with a median follow-up time of 6 years and 5 months TAC was associated with a 32% relapse risk reduction compared with FAC (HR = 0.676, 95% CI = 0.493-0.926), p=0.014. When components of the composite DFS endpoint are taken into consideration, it appeared that a difference between TAC vs. FAC was observed in terms of secondary primary malignancies (2.4 % vs. 5.0%) and local breast cancer relapse (0.7% vs. 3.3%), but not in terms of distant metastases (7.4% vs. 8.3%).

To assess validity of the primary endpoint (DFS) and the consistency of the relapse assessments across treatment groups, a time to event analysis was performed, including presentation of Kaplan-Meier curves. The pattern of follow-up median time from randomization to physical examinations, mammogram, chest imaging, abdominal imaging, and bone imaging, respectively, was comparable between treatment groups (data not shown).

All subgroups analyses of DFS were consistent with the overall result. All estimated HR for subgroups consistently favoured TAC over FAC. The effect of TAC vs. FAC appeared to be more significant in patients having breast-conserving surgery (HR 0.53, 95%-CI 0.33-0.86) or patients receiving adjuvant radiotherapy (HR 0.53, 95%-CI 0.33-0.83). However, it is difficult to draw firm conclusions based on the subgroup analyses presented.

The pivotal trial included patients corresponding to the standard definition of high-risk for relapse (1998 St Gallen criteria) at the time where the trial was initiated (June 1999). Considering the most recent 2009 St Gallen consensus conference, adjuvant chemotherapy is the mainstay treatment of patients with triple negative early breast cancer. In study GEICAM this population is represented by 183 patients. However, in study GEICAM9805, the subgroup analysis on this population is underpowered to draw any firm conclusions.

No difference in OS was observed. The lack of a significant difference may be due to the small number of events 26 (4.82%) under TAC and 34 (6.53%) under FAC). The MAH committed to submit more mature OS data when available.

Due to the open design of the study, the importance of the observed results in terms of QOL data was considered to be limited.

A total of 4 unplanned interim efficacy analyses were performed. The CHMP was concerned that the single pivotal trial for this application may lack robustness and the final statistical significance of the proposed conclusion may not be convincing (see Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study, CPMP/EWP/2330/99). The MAH was requested to provide reassurance on the validity of the reported results. Although the methodological weaknesses were acknowledged, the CHMP concluded that in view of the supportive evidence and the overall coherent results, this did not constitute a major issue.

There are limited data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide. This is adequately reflected in section 4.4 of the SPC.

Essential prophylactic anti-emetic treatment was well planned in both arms. The oral dexamethasone premedication regimen is well specified in the protocol and is accordance with the proposed SPC. The protocol planned compulsory prophylactic antibiotic therapy for the TAC arm. However, no similar recommendation is specified in the SPC.

A primary prophylactic administration of G-CSF was introduced through protocol amendment and this is reflected in the SPC (see sections 4.2 and 5.1).

### *1.2.4 Clinical safety*

**Patient exposure**
Of the 1060 patients randomized, 1051 were evaluable for safety, according to the treatment actually received (TAC: 532; FAC: 519).

**Adverse events**
All the patients (100%) in both arm experienced at least 1 Treatment-emergent Adverse Event (TEAE).

There were more patients with Grade 3-4 TEAEs and SAEs in the TAC group as shown in Table 17 below. Treatment discontinuations due to TEAEs were also more frequently reported in the TAC group compared to the FAC group.

Table 17 Overview of TEAEs regardless of causal relationship, by study period

| | **TAC (N=532)** | | **FAC (N=519)** | |
|---|---|---|---|---|
| | **Chemotherapy n (%)** | **Follow-up n (%)** | **Chemotherapy n (%)** | **Follow-up n (%)** |
| Patients with at least | | | | |
| One TEAE | 532 (100.0) | 84 (15.8) | 519 (100.0) | 71 (13.7) |
| One Grade 3-4 TEAE [a] | 150 (28.2) | 11 (2.1) | 88 (17.0) | 13 (2.5) |
| One serious TEAE | **119 (22.4)** | 6 (1.1) | **22 (4.2)** | 9 (1.7) |
| One serious Grade 3-4 TEAE [a] | 55 (10.3) | 2 (0.4) | 10 (1.9) | 7 (1.3) |
| **Patients with TEAE(s) leading to treatment discontinuation** | 25 (4.7) | N/A | 4 (0.8) | N/A |
| **Patients with TEAE(s) leading to death** | 1 (0.2) [b] | 0 | 0 | 0 |

[a] Worst grade per patient, as reported by the Investigator
b Patient No. 00024

TEAEs regardless of causal relationship during chemotherapy are presented in table 18 below. For all grades of severity, the incidence rates of TEAEs were higher by ≥10% in the TAC treatment group compared with the FAC treatment group for: asthenia, diarrhoea, myalgia, arthralgia, peripheral edema, and febrile neutropenia. The incidence rate of peripheral sensory neuropathy was approximately double in TAC patients compared with FAC group.

The most common Grade 3 to 4 events in the TAC treatment group were: asthenia, neutropenia, nausea, stomatitis, and vomiting.

Table 18 TEAEs regardless of causal relationship during chemotherapy (3% or greater incidence in the TAC group)

| | **TAC (N=532)** | | **FAC (N=519)** | |
|---|---|---|---|---|
| | **All** | Grade 3-4 | **All** | Grade 3-4 |
| **MedDRA PT** | **n (%)** | n (%) | **n (%)** | n (%) |
| Alopecia | 514 (96.6) | 1 (0.2) | 508 (97.9) | 2 (0.4) |
| **Asthenia** | **387 (72.7)** | 46 (8.6) | **305 (58.8)** | 9 (1.7) |
| Nausea | 379 (71.2) | 27 (5.1) | 387 (74.6) | 19 (3.7) |
| Stomatitis | 292 (54.9) | 24 (4.5) | 265 (51.1) | 19 (3.7) |
| Vomiting | 292 (54.9) | 23 (4.3) | 294 (56.6) | 32 (6.2) |
| **Diarrhoea** | **147 (27.6)** | 19 (3.6) | **70 (13.5)** | 4 (0.8) |
| Infection | 143 (26.9) | 9 (1.7) | 128 (24.7) | 6 (1.2) |
| Constipation | 143 (26.9) | 6 (1.1) | 141 (27.2) | 3 (0.6) |
| **Myalgia** | **123 (23.1)** | 4 (0.8) | **15 (2.9)** | 0 |
| **Amenorrhoea** | **121 (22.7)** | N/A | **70 (13.5)** | N/A |
| Pain | 118 (22.2) | 3 (0.6) | 80 (15.4) | 0 |
| **Arthralgia** | **108 (20.3)** | 0 | **30 (5.8)** | 0 |
| Conjunctivitis | 108 (20.3) | 1 (0.2) | 104 (20.0) | 1 (0.2) |
| Menstruation irregular | 103 (19.4) | N/A | 90 (17.3) | N/A |
| Nail disorder | 102 (19.2) | 2 (0.4) | 77 (14.8) | 0 |
| **Oedema peripheral** | **101 (19.0)** | 0 | **20 (3.9)** | 0 |
| **Fever in absence of infection** | **97 (18.2)** | N/A | **23 (4.4)** | N/A |
| Skin disorder | 96 (18.0) | 3 (0.6) | 51 (9.8) | 0 |
| **Pyrexia** | **90 (16.9)** | 1 (0.2) | **46 (8.9)** | 0 |
| Dyspepsia | 87 (16.4) | 3 (0.6) | 65 (12.5) | 1 (0.2) |
| Anorexia | 85 (16.0) | 3 (0.6) | 67 (12.9) | 2 (0.4) |
| Dysgeusia | 85 (16.0) | 3 (0.6) | 71 (13.7) | 0 |
| **Peripheral sensory neuropathy** | **83 (15.6)** | 1 (0.2) | **38 (7.3)** | 1 (0.2) |
| Hot flush | 74 (13.9) | 0 | 54 (10.4) | 1 (0.2) |
| Abdominal pain upper | 59 (11.1) | 1 (0.2) | 52 (10.0) | 1 (0.2) |
| Headache | 53 (10.0) | 0 | 61 (11.8) | 1 (0.2) |
| **Neutropenia** | **33 (6.2)** | 30 (5.6) | **9 (1.7)** | 6 (1.2) |
| Weight increased | 29 (5.5) | 0 | 10 (1.9) | 0 |
| Insomnia | 27 (5.1) | 0 | 24 (4.6) | 0 |
| Cough | 26 (4.9) | 0 | 24 (4.6) | 0 |
| Affective disorder | 25 (4.7) | 1 (0.2) | 28 (5.4) | 1 (0.2) |
| Lacrimation increased | 24 (4.5) | 0 | 18 (3.5) | 0 |
| Hypersensitivity | 23 (4.3) | 1 (0.2) | 8 (1.5) | 1 (0.2) |
| Rhinitis | 21 (3.9) | 0 | 9 (1.7) | 0 |
| Bone pain | 19 (3.6) | 1 (0.2) | 1 (0.2) | 0 |
| Abdominal pain | 18 (3.4) | 0 | 6 (1.2) | 0 |
| **Peripheral motor neuropathy** | **18 (3.4)** | 0 | **2 (0.4)** | 0 |
| Back pain | 17 (3.2) | 0 | 6 (1.2) | 0 |
| Lung disorder | 17 (3.2) | 2 (0.4) | 14 (2.7) | 0 |
| Influenza | 16 (3.0) | 0 | 21 (4.0) | 0 |



Haematological TEAEs were more frequent in the TAC group (anaemia, thrombocytopenia and neutropenia, febrile neutropenia).

After 202 patients had been enrolled in the study, 33 patients had experienced serious haematological TEAEs, with 29.6% of TAC patients experiencing febrile neutropenia versus 0% of FAC patients.

Consequently, an amendment (Amendment No, 3, 18 July 2000) made primary prophylaxis with G-CSF mandatory for TAC patients. Before use of G-CSF became mandatory in the TAC patients, incidence of neutropenia, febrile neutropenia and neutropenic infection was very high (93.7%, 25.2% and 12.6% respectively). After protocol amendment and systematic administration of G-CSF, incidence of these events decreased to 32.1%, 5.5% and 5.0%.

Average incidence of neutropenia, febrile neutropenia and neutropenic infection remains higher in the TAC group compared to the FAC group (44.9% vs. 13.3%; 9.6% vs. 2.3% and 6.6% vs. 2.7% respectively).

Regarding TEAEs related to treatment during chemotherapy for all grades of severity, the incidence rates of the following related TEAEs were higher by ≥10% in the TAC treatment group compared to the FAC treatment group: asthenia (TAC: 71.4%; FAC: 57.8%), diarrhoea (TAC: 26.3%; FAC: 12.1%), myalgia (TAC: 19.4%; FAC: 2.1%), febrile neutropenia (TAC: 17.9%; FAC: 4.0%), arthralgia (TAC: 16.4%; FAC: 4.2%), and peripheral edema (TAC: 16.4%; FAC: 2.9%). The incidence rate of peripheral sensory neuropathy was more than double in TAC patients compared to FAC patients (TAC: 14.7%; FAC: 6.4%).

TEAEs into the follow-up period included TEAEs which occurred during the chemotherapy period and persisted into the follow-up period and TEAEs that started or worsened during the follow-up period. TEAEs were considered as they "did not resolve" if the last follow-up entry for that TEAE reported the outcome as "TEAE did not resolve". TEAEs were considered resolved only if resolution was documented. Absence of reporting a previously unresolved TEAE at a subsequent follow-up was not considered documentation of resolution. Patients were considered "lost to follow-up" when so identified on the CRF "end of chemotherapy" or "follow-up" pages.

In total, 33 patients in the FAC arm and 43 patients in the TAC arm had TEAEs that did not resolve in follow-up. TEAEs not resolved in multiple patients during follow-up, with a frequency at least two times greater in one treatment group compared to the other treatment group are summarized as follows:

- Prevalent in the TAC group: amenorrhea (13 patients in TAC, 5 patients in FAC), alopecia (7 patients in TAC, 1 patient in FAC), peripheral sensory neuropathy (6 patients in TAC, 2 patients in FAC), asthenia (4 patients in TAC, 2 patients in FAC), lymphoedema (4 patients in TAC, 1 patient in FAC), arrhythmia (3 patients in TAC, no patients in FAC), and hyperhydrosis (2 patients in TAC, no patients in FAC). One of the 3 TAC patients (patient 00923) who had arrhythmia at the follow up 3 visit was also diagnosed with grade 2 goiter since her follow up 2 visit; no other details were reported for the other two TAC patients (patients 00319 and 00650) with reported arrhythmia.
- Prevalent in the FAC group: menstruation irregular (6 patients in FAC, 1 patient in TAC), hot flush (5 patients in FAC, 2 patients in TAC), bone pain (3 patients in FAC, no patients in TAC), and nail disorder (2 patients in FAC, no patients in TAC).

Among TEAEs not resolved at follow-up, there was one serious adverse event (SAE) of Herpes zoster in the TAC group. In 4 additional cases, assessment of seriousness was not reported (lymphoedema and radiation skin injury in FAC group; amenorrhea and biopsy endometrium normal in TAC in TAC patients). All the other reported TEAEs persisting in follow-up were considered non serious.

All the persisting TEAEs had a severity Grade 1-2 (when reported), except for the following Grade 3 adverse events in TAC patients: arrhythmia, neutropenia, pain, and thrombocytopenia.

A total of 23 and 18 patients were considered lost to follow-up in the TAC and FAC groups respectively. The median duration of follow-up in these patients prior to being lost was greater than 2.5 years.

Table 19 - Summary of patients lost to follow-up - ITT population

| | Randomization Arm | | |
|---|---|---|---|
| **Study Phase** | **TAC (N=539)** | **FAC (N=521)** | **All (N=1060)** |
| During chemotherapy [a] | 0 | 1 (0.2%) | 1 (<0.1%) |
| During follow-up [b] | 23 (4.3%) | 17 (3.3%) | 40 (3.8%) |
| TOTAL | 23 (4.3%) | 18 (3.5%) | 41 (3.9%) |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide
[a] Data obtained from the "End of chemotherapy" page.
[b] Data obtained from the "Follow up" page.

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

Serious Adverse Events

There were significantly more SAEs in the TAC group compared to the FAC group during chemotherapy (22.4% vs. 4.2%). Study drug related SAEs were also more frequently reported in the TAC group compared to the FAC group (20.3 vs. 3.3).

Table 20 - Overview of serious TEAEs regardless of causal relationship, by study period

| | **TAC N=532 n (%)** | **FAC N=519 n (%)** |
|---|---|---|
| **During chemotherapy, at least** | | |
| **One serious TEAE** | **119 (22.4)** | **22 (4.2)** |
| **One serious TEAE related to study treatment** | **108 (20.3)** | **17 (3.3)** |
| One Grade 3-4 serious TEAE | 55 (10.3) | 10 (1.9) |
| One Grade 3-4 serious TEAE related to study treatment | 48 (9.0) | 6 (1.2) |
| **During follow-up, at least** | | |
| One serious TEAE | 6 (1.1) | 9 (1.7) |
| One serious TEAE related to study treatment | 2 (0.4) | 3 (0.6) |
| One Grade 3-4 serious TEAE | 2 (0.4) | 7 (1.3) |
| One Grade 3-4 serious TEAE related to study treatment | 2 (0.4) | 2 (0.4) |

The most frequent non haematological serious TEAEs reported during chemotherapy in both treatment groups were diarrhoea (1.7% vs. 0.6%), nausea, and vomiting (1.3% vs. 0.2% each).

Serious TEAEs of neutropenia and febrile neutropenia were approximately 7 fold more frequent in the TAC group (15.6% vs. 2.7% and 5.3% vs. 0.6% respectively).

After primary G-CSF prophylaxis became mandatory in the TAC group, incidence of serious TEAEs, decreased from 45% to 16.4% but remains higher than in the FAC group.

Table 21 - Serious TEAEs regardless of causal relationship during chemotherapy affecting more than 1 patient in either treatment group – safety population

| | TAC (N=532) | | FAC (N=519) | |
|---|---|---|---|---|
| **MedDRA PT** | **All n (%)** | **Grade 3-4** (a) **n (%)** | **All n (%)** | **Grade 3-4** (a) **n (%)** |
| **Fever in absence of infection (b)** | **80 (15.0)** | **N/A** | **14 (2.7)** | **N/A** |
| **Neutropenia (c)** | **28 (5.3)** | **27 (5.1)** | **3 (0.6)** | **3 (0.6)** |
| Diarrhoea | 9 (1.7) | 8 (1.5) | 1 (0.2) | 1 (0.2) |
| Nausea | 7 (1.3) | 4 (0.8) | 1 (0.2) | 1 (0.2) |
| Vomiting | 7 (1.3) | 4 (0.8) | 1 (0.2) | 1 (0.2) |
| Pyrexia | 4 (0.8) | 1 (0.2) | 0 | 0 |
| **Febrile neutropenia (d)** | **3 (0.6)** | **3 (0.6)** | **0** | **0** |
| Leucopenia (e) | 3 (0.6) | 1 (0.2) | 0 | 0 |
| Respiratory tract infection | 3 (0.6) | 1 0.2) | 0 | 0 |
| Skin infection | 3 (0.6) | 0 | 0 | 0 |
| Anaemia (f) | 2 (0.4) | 1 (0.2) | 1 (0.2) | 1 (0.2) |
| Asthenia | 2 (0.4) | 2 (0.4) | 0 | 0 |
| Cough | 2 (0.4) | 0 | 0 | 0 |
| Dyspepsia | 2 (0.4) | 1 (0.2) | 0 | 0 |
| General physical health deterioration | 2 (0.4) | 0 | 0 | 0 |
| Sinusitis | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Stomatitis | 2 (0.4) | 2 (0.4) | 0 | 0 |
| Tonsillitis | 2 (0.4) | 0 | 0 | 0 |

(a) Worst grade per patient, as reported by the Investigator
(b) Fever in the absence of infection (not a MedDRA PT) was reported on a CRF page for febrile neutropenia. Pyrexia was reported as a TEAE.
(c) Neutropenia reported by the Investigator as a TEAE.
(d) Febrile neutropenia reported by the Investigator as a TEAE.
(e)Leucopenia reported by the Investigator as a TEAE.
(f) Anaemia reported by the Investigator as a TEAE.



Deaths

As of 04 March 2009, 25 (4.7%) TAC patients and 34 (6.6%) FAC patients died, all during the follow-up period. No patient died within 30 days of the last study treatment.

Table 22 - Deaths occurring during chemotherapy and follow-up, by cause

| | TAC (N=532) n (%) | FAC (N=519) n (%) |
|---|---|---|
| **Death on study** | **25 (4.7)** | **34 (6.6)** |
| Death ≤30 days after last study treatment | 0 | 0 |
| Death >30 days after last study treatment | 25 (4.7) | 34 (6.6) |
| **Related to study treatment** | | |
| Septic | 0 | 0 |
| Nonseptic | 0 | 0 |
| TEAE due to chemotherapy given after relapse | 0 | 0 |
| **Breast cancer** | **19 (3.6)** | **22(4.2)** |
| **Malignant disease, other than breast cancer** | **1 (0.2)** | **8 (1.6)** |
| **Other** | **5 (0.9)** | **3 (0.6)** |
| **missing** | 0 | 1 (0.2) |

Among the 25 TAC patients who died, 19 died due to complications of breast cancer. Of the remaining 6 deaths, 1 patient died from second primary malignancy (colon cancer) and 1 patient with controlateral breast cancer died from massive pulmonary thromboembolism, 1additional patient died from thromboembolism, 2 died from myocardial infarction, and one 54-year-old patient with a medical history of arthrosis, hypertension and thrombosis of lower extremities (during study), died during sleeping 3 years and 10 months of the last study treatment.

In the FAC group 1 out of the 34 reported deaths was assessed as study drug related. In the TAC group, all the deaths were assessed as not related to study drug

It is to be noted that of the 6 TAC patients who died due to another cause than disease progression, 2 died from myocardial infarction and one 54-year-old patient without any significant cardiac medical history had a sudden death. In the last patient, cardiac death cannot be excluded. Overall, cardiac death can be suspected in 3 of the 6 TAC patients. However, given that cardiotoxicity has not been adequately monitored, no conclusion can be drawn from the provided data

Other significant TEAEs:

The following significant TEAEs were discussed by the MAH:

- **Neutropenic complications, infection and G-CSF use**

  After 202 patients had been enrolled in the study, 33 patients had experienced serious TEAEs, with 29.6% of TAC patients experiencing febrile neutropenia versus 0% of FAC patients.
  Consequently, an amendment (Amendment No, 3, 18 July 2000) made primary prophylaxis with G-CSF mandatory for TAC patients. Before use of G-CSF became mandatory in the TAC patients, incidence of neutropenia, febrile neutropenia and neutropenic infection was very high (93.7%, 25.2% and 12.6% respectively). After protocol amendment and systematic administration of G-CSF, incidence of these events decreased to 32.1%, 5.5% and 5.0%
  However, these events remains more frequent in the TAC group compared to the FAC group (44.9% vs. 13.3%; 9.6% vs. 2.3% and 6.6% vs. 2.7% respectively).

- **Cardiac TEAEs and hypertensive/hypotensive TEAEs**

  As a requirement of the protocol, LVEF was measured at baseline only in patients with suspected cardiac dysfunction, and during the study when considered clinically relevant by the Investigator. A total of 13 (2.4%) of patients in the TAC group and 2.7% in the FAC group had their LVEF assessed. Decrease in LVEF below lower normal limit was identified in 2 patients from the TAC group. Although, routine assessments were not performed, there were more cardiac events in the TAC group (3.8%) compared to the FAC group 12 (2.2%).

  In particular regarding cardiac TEAEs in total, all-grade cardiac failure, congestive heart failure (CHF), or cardiomyopathy were reported in 4 patients in the TAC arm and 5 patients in the FAC arm, while Grade 3-4 cardiac failure, CHF, or cardiomyopathy were reported in 1 patient in the TAC arm and 2 patients in the FAC arm.

  To further provide assessment of the long-term risk of cardiotoxicity in patients receiving the TAC regimen, data are presented below from TAX316, a study similar to GEICAM 9805 but in which the adjuvant TAC regimen was compared to FAC in node-positive breast cancer patients. Evaluation of the long term cardiac risk with the same TAC regimen is a post-marketing commitment for the protocol TAX 316. Interim results from the cardiac monitoring in study TAX 316 demonstrate the following data regarding cardiovascular toxicity: a total of 21 TAC-treated patients and 14 FAC-treated patients had developed Grade 3-4 CHF (Table 23).

Table 23 - Cardiac adverse events (TAX 316)

| **Cardiac event** | **TAC (N = 744)** | | **FAC (N = 736)** | |
|---|---|---|---|---|
| | **March 2005** | **March 2009** | **March 2005** | **March 2009** |
| **Congestive heart failure (cardiac function Grade 3-4):** | **17 (2.3%)** | **21 (2.8%)** | **7 (1.0%)** | **14 (1.9%)** |
| Grade 3 (mild, responsive to therapy) | 13 | 16 | 6 | 12 |
| Grade 4 (severe, refractory) | 4 | 5 | 1 | 2 |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide

As of the first Safety Update Report (SUR) of March 2005, there were 17 cumulative reports of CHF in the TAC arm, and 7 in the FAC arm, representing a relative increase of 0.6% and 0.5%, respectively, from the April 2003 safety cut off date for the CSR. Between March 2005 and March 2009, a modest increase in the incidence of CHF (0.5% in the TAC arm, and 0.9% in the FAC arm) was reported in both arms. Table 24 illustrates the time course of the cumulative reports of CHF, with 17 cases in the TAC arm in March 2005, and 4 additional TAC cases from March 2005 through March 2009. Comparatively, the reports of CHF in the FAC arm increased from 7 to 14 during the same interval.

Table 24 - Cumulative incidence of CHF (TAX 316)

| | **Congestive heart failure** | | | | | |
|---|---|---|---|---|---|---|
| | **April 2003 CSR** | **March 2005 1st SUR** | **March 2006 2nd SUR** | **March 2007 3rd SUR** | **March 2008 4th SUR** | **March 2009 5th SUR** |
| **TAC (n=744)** | **12 (1.6%)** | **17 (2.3%)** | **19 (2.5%)** | **19 (2.5%)** | **21 (2.8%)** | **21 (2.8%)** |
| **FAC (n=736)** | 4 (0.5%) | 7 (1.0%) | 11 (1.5%) | 13 (1.8%) | 14 (1.9%) | **14 (1.9%)** |

CSR = Clinical Study Report; SUR = Safety Update Report; TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide

By 2009, 542 patients in both treatment arms were evaluable for LVEF measurements (i.e., having at least 2 LVEF values recorded). The LVEF decreases among all the evaluable patients appear similar between both arms.

Table 25 - LVEF decrease comparison between arms - all evaluable patients (TAX 316)

| | **TAC** | | **FAC** | |
|---|---|---|---|---|
| | **All patients N = 309** | **CHF patients N = 13** | **All patients N = 233** | **CHF patients N = 7** |
| **No decrease** | **111 (35.9%)** | **--** | **70 (30.0%)** | **--** |
| **Relative decrease 0-10%** | **87 (28.2%)** | **2 (15.4%)** | **67 (28.8%)** | **--** |
| Decrease within normal limit | 84 (28.2%) | 1 (7.7%) | 63 (27.0%) | -- |
| Decrease below normal limit | 3 (0.9%) | 1 (7.7%) | 4 (1.7%) | -- |
| **Relative decrease [10-20]%** | **62 (20.1%)** | **2 (15.4%)** | **64 (27.5%)** | **2 (28.6%)** |
| Decrease within normal limit | 49 (15.9%) | -- | 56 (24.0%) | 2 (28.6%) |
| Decrease below normal limit | 23 (4.2%) | 2 (15.4%) | 8 (3.4%) | -- |
| **Relative decrease >20%** | **49 (15.9%)** | **9 (69.2%)** | **32 (13.7%)** | **5 (71.4%)** |
| Decrease within normal limit | 18 (5.8%) | 2 (15.3%) | 15 (6.4%) | -- |
| Decrease below normal limit | 31 (10.0%) | 7 (53.8%) | 17 (7.3%) | 5 (71.4%) |

TAC = docetaxel, doxorubicin, and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; CHF = congestive heart failure

- **Fluid retention**

  Despite of compulsory prophylactic premedication for fluid retention with corticosteroid in the TAC group, the incidence of fluid retention events was 4 fold higher in the TAC group (127/532) than in the FAC group (34/519).

- **Gastrointestinal TEAEs**

  Nausea, stomatitis, vomiting, diarrhoea, and constipation were the most common GI events reported for both TAC and FAC patients,
  The only gastrointestinal TEAE (all grades, regardless of causal relationship) to be reported ≥10% more frequently in the TAC treatment group compared with the FAC treatment group was diarrhoea. Serious gastrointestinal events occurring in more than 1 patient included diarrhoea (TAC: 1.7%; FAC: 0.2%), nausea (TAC: 1.3%; FAC: 0.2%), vomiting (TAC: 1.3%; FAC: 0.2%), stomatitis (TAC: 0.4%; FAC: 0), dyspepsia (TAC: 0.4%; FAC: 0), constipation (TAC: 0.2%; FAC: 0.2%), and abdominal pain (TAC: 0.2%; FAC: 0.2%). Intestinal obstruction was reported in 1 patient from the TAC group.

- **Neurological TEAEs**

There were more than double of peripheral neuropathy TEAEs (sensory and motor) in the TAC group (15.6% and 3.4%) compared to the FAC group (7.3% and 0.4%). Peripheral sensory neuropathy is listed as very common AE in the SPC.

- **Second Primary Malignancies**

  With respect to Second Primary Malignancies (SPM) the following listing of SPMs reported as efficacy endpoints has been provided:

Table 26 - Listing of SPMs reported as efficacy endpoints

| Treatment Arm | Patient Identifier | Diagnosis as Reported | Histopathological Procedure / Diagnosis | Interval between first chemotherapy dose and diagnosis of SPM (years) | Interval between last chemotherapy dose and diagnosis of SPM (years) |
|---|---|---|---|---|---|
| FAC | 00028 | Primary breast cancer-left | "PAAF" (fine-needle puncture aspiration) | 6.8 | 6.5 |
| | 00054 | Endocervix | Biopsy | 8.4 | 8.2 |
| | 00076 | Endometrium cancer | No histopathology reported | 6.4 | 6.1 |
| | 00097 | Colon cancer | Adenocarcinoma | 4.5 | 4.2 |
| | 00103 | Contralateral breast cancer | Ductal carcinoma in situ | 2.8 | 2.5 |
| | 00123 | Primary breast cancer-right | "BAG" | 4.8 | 4.5 |
| | 00168 | Primary breast cancer-right | Biopsy | 4.0 | 3.7 |
| | 00194 | GIST (gastro-intestinal stomal tumour) | Resection | 3.1 | 2.8 |
| | 00202 | Primary breast cancer-left | Biopsy | 7.0 | 6.7 |
| | 00229 | Pancreas | No histopathology reported | 5.2 | 4.9 |
| | 00298 | AML FAB M2 | Bone marrow biopsy | 4.6 | 4.3 |
| | 00318 | Endometrium cancer | Biopsy | 6.3 | 6.0 |
| | 00419 | Ovarian cancer | Ascitic fluid cytology | 0.9 | 0.6 |
| | 00477 | Primary breast cancer-left | Biopsy | 4.4 | 4.1 |
| | 00485 | Primary breast cancer-right | Infiltrating ductal carcinoma | 3.4 | 3.1 |
| | 00501 | Colon | No histopathology reported | 6.3 | 6.0 |
| | 00584 | Primary breast cancer-left | "PAAF" (fine-needle puncture aspiration) "Y B-CORE" | 1.1 | 0.9 |
| | 00615 | Primary breast cancer-left | Right breast biopsy[a] | 3.9 | 3.5 |
| | 00648 | Renal cancer | Kidney biopsy | 4.3 | 4.0 |
| | 00660 | Colorectal cancer | Colonoscopy | 1.5 | 1.2 |
| | 00672 | Primary breast cancer-left | Infiltrating ductal tumour | 4.1 | 3.8 |
| | 00732 | Primary breast cancer-right | Tumourectomy | 1.5 | 1.2 |
| | | Primary breast cancer-right | Biopsy | 3.8 | 3.5 |
| | 00739 | Rectum adenocarcinoma | Biopsy with colonoscopy | 2.8 | 2.5 |
| | 00817 | Endometrium cancer | Hysterectomy | 1.9 | 1.6 |
| | 00911 | Primary breast cancer-left | PAAF (fine-needle puncture aspiration) | 1.7 | 1.4 |
| | 00914 | Gastric cancer | No histopathology reported | 4.7 | 4.4 |

| Treatment Arm | Patient Identifier | Diagnosis as Reported | Histopathological Procedure / Diagnosis | Interval between first chemotherapy dose and diagnosis of SPM (years) | Interval between last chemotherapy dose and diagnosis of SPM (years) |
|---|---|---|---|---|---|
| | 00943 | Primary breast cancer-left | Unspecified infiltrating carcinoma | 3.7 | 3.4 |
| | 01004 | Endometrium cancer | No histopathology reported | 5.3 | 5.0 |
| TAC | 00018 | Melanoma | Breslow 0.5 mm Clark-II | 0.2 | -0.1[b] |
| | 00270 | Ovarian cancer | Hysterectomy and bilateral ovariectomy | 2.1 | 1.9 |
| | 00287 | Primary breast cancer-left | Infiltrating ductal carcinoma | 6.9 | 6.6 |
| | 00329 | Ovarian cancer | Serous carcinoma | 2.9 | 2.8 |
| | 00412 | Lung | Adenocarcinoma | 5.7 | 5.4 |
| | 00420 | Primary breast cancer-right | Biopsy | 1.6 | 1.3 |
| | 00442 | Colon cancer | Colonoscopy | 7.2 | 6.9 |
| | 00496 | Endometrium cancer | Biopsy | 3.7 | 3.4 |
| | 00794 | Primary breast cancer-left | Lobular carcinoma in situ | 1.8 | 1.5 |
| | 00871 | Cancer of gland thyroid | Papillary carcinoma | 1.3 | 1.0 |
| | 00937 | Melanoma | Melanoma 0.5 mm | 2.2 | 1.9 |
| | 00979 | Primary breast cancer-right | Biopsy | 4.9 | 4.7 |
| | 01011 | Hodgkin's lymphoma | Biopsy | 1.9 | 1.6 |
| | 01036 | Primary breast cancer-right | Right breast biopsy | 2.4 | 2.1 |

SPM = second primary malignancies; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide

[a] As reported by the investigator.

[b] Patient 00018 continued receiving TAC chemotherapy 49 days after she had been diagnosed with melanoma.

The malignant melanoma and acute leukaemia reported respectively in patients 00018 and 00740 were recorded as serious TEAEs. The melanoma in patient 00018 was also reported as an efficacy endpoint. Regarding the "*colon cancer*" reported in patient 00693, and assessed by the investigator as not related to chemotherapy, however, a laparotomy was performed to confirm a tentative diagnosis of colon cancer, which was reported as a TEAE ("*colon cancer*"). The tentative diagnosis was ultimately not confirmed, and thus the "*colon cancer*" was not reported as an efficacy endpoint in this patient.

Table 27 - List of SPMs reported as TEAEs

| Treatment Arm | Patient Identifier | MedDRA PT | Visit | Severity | SAE | Causality |
|---|---|---|---|---|---|---|
| TAC | 00018 | Malignant melanoma | Cycle 5 | Grade 4 | Y | None |
| TAC | 00693 | "*Colon cancer*"[a] | follow-up 7 | Grade 2 | N | Other (not related) |
| TAC | 00740 | Acute leukaemia | follow-up 10 | Grade 3 | Y | Study chemotherapy |

SPM = second primary malignancies; TEAEs = treatment-emergent adverse events; SAE = serious adverse event;
TAC = docetaxel, doxorubicin, and cyclophosphamide

[a] Patient 00693 underwent a laparotomy to confirm a tentative diagnosis of "colon cancer", reported as a TEAE and assessed by the investigator as not related to chemotherapy. The diagnosis was ultimately not confirmed.

- **Renal function**

  The incidence rate of renal and urinary TEAEs and laboratory abnormalities were comparable between the 2 treatment groups. No serious renal TEAEs or treatment discontinuations because of renal TEAEs were reported.

- **Hepatic function**

  The overall incidence of ALT and AST elevations was lower in the TAC group (45.3% and 34%) compared with the FAC group (54.1% and 44.9%); however, the incidence of Grade 3 to 4 ALT and AST elevations, was slightly higher in the TAC group (1.7 % vs. 1.3% and 1.1% vs. 0.2%).

  The overall incidence of total bilirubin elevation was higher in the TAC group (4.1%) compared with the FAC group (2.9%).

  There were 2 patients in the TAC treatment group who experienced serious liver/biliary toxicity.

Table 28: Hepatic TEAEs and laboratory abnormalities regardless of causal relationship during chemotherapy

| | **TAC (N=532)** | | **FAC (N=519)** | |
|---|---|---|---|---|
| **MedDRA PT [a]** | **All n (%)** | **Grade 3-4 n (%)** | **All n (%)** | **Grade 3-4 n (%)** |
| **ALT** | **241 (45.3)** | **9 (1.7)** | **281 (54.1)** | **7 (1.3)** |
| **AST** | **181 (34.0)** | **6 (1.1)** | **233 (44.9)** | **1 (0.2)** |
| ALP | 75 (14.1) | 2 (0.4) | 70 (13.5) | 4 (0.8) |
| Total bilirubin | 22 **(4.1)** | 1 (0.2) | 15 **(2.9)** | 2 (0.4) |
| Cholecystitis | 1 (0.2) | 1 (0.2) | 0 | 0 |
| Jaundice | 1 (0.2) | 0 | 0 | 0 |
| Hepatitis toxic | 1 (0.2) | 1 (0.2) | 0 | 0 |

a Includes all preferred terms mapped to SOC hepatobiliary disorders, and ALT, AST, ALP, and total bilirubin from laboratory data

**Discontinuation due to adverse events**

Twenty-five (4.7%) patients in the TAC group had study treatment discontinued because of 44 TEAEs versus 4 (0.8%) patients due to 7 TEAEs in the FAC group. Haematological TEAEs are the most frequently reported causes for treatment withdrawal (14 out of 25): febrile neutropenia (1.5% vs. 0% in the FAC group) and neutropenia/neutrophil count (1.1% vs. 0% in the FAC group). One patient from the TAC group was withdrawn because of cardiomyopathy.

Table 29 - TEAEs regardless of causal relationship leading to treatment discontinuation –safety population

| **MedDRA PT** (a) | **TAC (N=532) n (%)** | **FAC (N=519) n (%)** |
|---|---|---|
| **Patients with TEAEs leading to treatment discontinuation** (b) | **25 (4.7)** | **4 (0.8)** |
| Fever in absence of infection (c) | **8 (1.5)** | **0** |
| Neutropenia | **5 (0.9)** | **0** |
| Asthenia | 2 (0.4) | 0 |
| Diarrhoea | 2 (0.4) | 0 |
| Hypersensitivity | 2 (0.4) | 2 (0.4) |
| Lung disorder | 2 (0.4) | 0 |
| Abdominal pain upper | 1 (0.2) | 0 |
| Alexia | 0 | 1 (0.2) |
| Anorexia | 1 (0.2) | 0 |
| Aphasia | 0 | 1 (0.2) |
| Arrhythmia | 1 (0.2) | 0 |
| Bone pain | 1 (0.2) | 0 |
| Cardiomyopathy | 1 (0.2) | 0 |
| Catheter related infection | 1 (0.2) | 0 |
| Cerebral haemorrhage | 0 | 1 (0.2) |
| Cerebrovascular accident | 0 | 1 (0.2) |
| Disease progression | 1 (0.2) | 0 |
| Dyspnoea | 1 (0.2) | 0 |
| Eyelid infection | 1 (0.2) | 0 |
| Hepatitis toxic | 1 (0.2) | 0 |
| Injection site reaction | 1 (0.2) | 0 |
| Jaundice | 1 (0.2) | 0 |
| Nausea | 1 (0.2) | 0 |
| **Neutrophil count (d)** | **1 (0.2)** | **0** |
| Oedema peripheral | 1 (0.2) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 0 | 1 (0.2) |
| Peripheral sensory neuropathy | 1 (0.2) | 0 |
| Pyrexia (c) | 1 (0.2) | 0 |
| Skin disorder | 1 (0.2) | 0 |
| Skin infection | 1 (0.2) | 0 |
| Stomatitis | 1 (0.2) | 0 |
| Thrombocytopenia | 1 (0.2) | 0 |
| Thrombosis | 1 (0.2) | 0 |
| Vomiting | 1 (0.2) | 0 |

(a) Data are presented as number of patients with each event. More than 1 event may have occurred per patient.
(b) Six (6) patients in the TAC treatment group experienced TEAEs which Investigators indicated led to treatment discontinuation. In these patients, this indication was inconsistent with the reason given for the end of chemotherapy treatment ("consent withdrawn", "other deviation from protocol", and "received maximum number of cycles"
(c) Fever in the absence of infection (not a MedDRA PT) was reported on a CRF page for febrile neutropenia. Pyrexia was reported as a TEAE.
(d) Neutropenia reported by the Investigator as a TEAE.



**Safety meta-analysis of trials GEICAM 9805 and TAX 316**

During assessment the MAH was requested to present a safety meta-analysis as basis for the update of SPC section 4.8. The clinically important TEAEs from the two studies GEICAM 9805 and TAX 316 were grouped by body system, presented side-to-side and as integrated data in the Table 31 (Clinically important treatment-related TEAEs). The cut-off date for the data from the GEICAM 9805 study was 04 March 2009, and the cut off date for the data from the TAX 316 study was 02 June 2009. TEAEs were consistently coded using the MedDRA version 8.1.

The clinical importance of these TEAEs was determined with respect to the TAC regimen, based upon incidence (>10%), severity, or clinical impact of the TEAEs. The MAH outlined that apparent differences between the safety data from the study TAX 316 (adjuvant TAC in node-positive breast cancer) compared to GEICAM9805 (adjuvant TAC in node-negative breast cancer) should be

interpreted with caution, because the two studies were different regarding geographical regions, populations (e.g., overall post-menopausal status: 47.5% in GEICAM 9805 and 33.4% in TAX316; overall ER+/PR+ status: 49.1% in GEICAM 9805 and 60.6% in TAX316), and study conduct (e.g., primary prophylaxis with filgrastim –granulocyte colony-stimulating factor) [G-CSF] was required only in all TAC patients in GEICAM 9805 after the first 111 TAC patients, while it was not permitted in TAX316).

The integrated safety data describe the overall safety profile of the TAC regimen as adjuvant chemotherapy in breast cancer (node-positive and node-negative) and the information resulting from this integrated analysis has been translated in table "Adjuvant therapy with TAXOTERE 75 mg/m² in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316) and node-negative (GEICAM 9805) breast cancer - pooled data" in section 4.8 of the SPC.

Table 30 Clinically important treatment-related TEAEs regardless of causal relationship

| | GEICAM 9805 | | | | TAX 316 | | | | Integrated | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TAC (N=532) | | FAC (N=519) | | TAC (N=744) | | FAC (N=736) | | TAC (N=1276) | | FAC (N=1255) | |
| MedDRA PT | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) |
| Anemia [a] | 504 (94.7) | 7 (1.3) | 360 (69.4) | 4 (0.8) | 685 (92.1) | 31 (4.2) | 531 (72.1) | 12 (1.6) | 1189 (93.2) | 38 (3.0) | 891 (71.0) | 16 (1.3) |
| Neutropenia [a] | 378 (71.1) | 270 (50.8) | 417 (80.3) | 205 (39.5) | 534 (71.8) | 486 (65.3) | 601 (81.7) | 361 (49.0) | 912 (71.5) | 756 (59.2) | 1018 (81.1) | 566 (45.1) |
| Pyrexia [b] | 95 (17.9) | N/A | 21 (4.0) | N/A | 272 (36.6) | N/A | 63 (8.6) | N/A | 367 (28.8) | N/A | 84 (6.7) | N/A |
| Thrombocytopenia [a] | 64 (12.0) | 6 (1.1) | 26 (5.0) | 3 (0.6) | 294 (39.5) | 15 (2.0) | 207 (28.1) | 9 (1.2) | 358 (28.1) | 21 (1.6) | 233 (18.6) | 12 (1.0) |
| Infection [c] | 82 (15.4) | 6 (1.1) | 46 (8.9) | 3 (0.6) | 217 (29.2) | 24 (3.2) | 146 (19.8) | 10 (1.4) | 299 (23.4) | 30 (2.4) | 192 (15.3) | 13 (1.0) |
| Febrile neutropenia [d] | 51 (9.6) | N/A | 12 (2.3) | N/A | 183 (24.6) | N/A | 18 (2.4) | N/A | 234 (18.3) | N/A | 30 (2.4) | N/A |
| Neutropenic infection | 35 (6.6) [e] | 7 (1.3) [f] | 14 (2.7) [e] | 4 (0.8) [f] | 130 (17.5) [e] | 27 (3.6) [f] | 96 (13.0) [e] | 13 (1.8) [f] | 165 (12.9) [e] | 34 (2.7) [f] | 110 (8.8) [e] | 17 (1.4) [f] |
| Hypersensitivity | 19 (3.6) | 1 (0.2) | 3 (0.6) | 1 (0.2) | 67 (9.0) | 7 (0.9) | 12 (1.6) | 0 | 86 (6.7) | 8 (0.6) | 15 (1.2) | 1 (<0.1) |
| Peripheral edema | 87 (16.4) | 0 | 15 (2.9) | 0 | 198 (26.6) | 3 (0.4) | 53 (7.2) | 0 | 285 (22.3) | 3 (0.2) | 68 (5.4) | 0 |
| Lymphedema | 4 (0.8) | 0 | 1 (0.2) | 0 | 2 (0.3) | 0 | 0 | 0 | 6 (0.5) | 0 | 1 (<0.1) | 0 |
| Weight increased | 18 (3.4) | 0 | 6 (1.2) | 0 | 93 (12.5) | 0 | 57 (7.7) | 0 | 111 (8.7) | 0 | 63 (5.0) | 0 |
| Weight decreased | 4 (0.8) | 0 | 0 | 0 | 19 (2.6) | 2 (0.3) | 8 (1.1) | 0 | 23 (1.8) | 2 (0.2) | 8 (0.6) | 0 |
| Peripheral sensory neuropathy | 78 (14.7) | 1 (0.2) | 33 (6.4) | 0 | 172 (23.1) | 0 | 55 (7.5) | 0 | 250 (19.6) | 1 (<0.1) | 88 (7.0) | 0 |
| Somnolence | 1 (0.2) | 0 | 3 (0.6) | 0 | 2 (0.3) | 0 | 0 | 0 | 3 (0.2) | 0 | 3 (0.2) | 0 |
| Peripheral motor neuropathy | 12 (2.3) | 0 | 0 | 0 | 20 (2.7) | 0 | 9 (1.2) | 0 | 32 (2.5) | 0 | 9 (0.7) | 0 |
| Neurotoxicity | 3 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.2) | 0 | 0 | 0 |
| Syncope | 3 (0.6) | 0 | 3 (0.6) | 0 | 3 (0.4) | 0 | 2 (0.3) | 0 | 6 (0.5) | 0 | 5 (0.4) | 0 |
| Alopecia | 507 (95.3) | 1 (0.2) | 503 (96.9) | 2 (0.4) | 727 (97.7) | 0 | 715 (97.1) | 0 | 1234 (96.7) | 1 (<0.1) | 1218 (97.1) | 2 (0.2) |
| Skin disorder | 88 (16.5) | 3 (0.6) | 42 (8.1) | 0 | 120 (16.1) | 5 (0.7) | 59 (8.0) | 0 | 208 (16.3) | 8 (0.6) | 101 (8.0) | 0 |
| Nail disorder [g] | 104 (19.5) | 2 (0.4) | 79 (15.2) | 1 (0.2) | 137 (18.4) | 3 (0.4) | 102 (13.9) | 1 (0.1) | 241 (18.9) | 5 (0.4) | 181 (14.4) | 2 (0.2) |
| Nausea | 376 (70.7) | 26 (4.9) | 385 (74.2) | 19 (3.7) | 598 (80.4) | 38 (5.1) | 643 (87.4) | 70 (9.5) | 974 (76.3) | 64 (5.0) | 1028 (81.9) | 89 (7.1) |
| Stomatitis | 290 (54.5) | 24 (4.5) | 264 (50.9) | 18 (3.5) | 509 (68.4) | 53 (7.1) | 373 (50.7) | 15 (2.0) | 799 (62.6) | 77 (6.0) | 637 (50.8) | 33 (2.6) |
| Vomiting | 289 (54.3) | 22 (4.1) | 290 (55.9) | 32 (6.2) | 316 (42.5) | 32 (4.3) | 428 (58.2) | 54 (7.3) | 605 (47.4) | 54 (4.2) | 718 (57.2) | 86 (6.9) |
| Diarrhea | 140 (26.3) | 19 (3.6) | 63 (12.1) | 3 (0.6) | 230 (30.9) | 24 (3.2) | 173 (23.5) | 7 (1.0) | 370 (29.0) | 43 (3.4) | 236 (18.8) | 10 (0.8) |
| Dysgeusia | 84 (15.8) | 3 (0.6) | 71 (13.7) | 0 | 203 (27.3) | 5 (0.7) | 112 (15.2) | 0 | 287 (22.5) | 8 (0.6) | 183 (14.6) | 0 |
| Constipation | 105 (19.7) | 4 (0.8) | 106 (20.4) | 2 (0.4) | 182 (24.5) | 3 (0.4) | 174 (23.6) | 9 (1.2) | 287 (22.5) | 7 (0.5) | 280 (22.3) | 11 (0.9) |

*(continued)*

| | GEICAM 9805 | | | | TAX 316 | | | | Integrated | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TAC (N=532) | | FAC (N=519) | | TAC (N=744) | | FAC (N=736) | | TAC (N=1276) | | FAC (N=1255) | |
| MedDRA PT | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) | All n (%) | Grade 3-4[a] n (%) |
| Anorexia [h] | 86 (16.2) | 3 (0.6) | 68 (13.1) | 2 (0.4) | 148 (19.9) | 16 (2.2) | 121 (16.4) | 9 (1.2) | 234 (18.3) | 19 (1.5) | 189 (15.1) | 11 (0.9) |
| Abdominal pain [i] | 61 (11.5) | 1 (0.2) | 51 (9.8) | 1 (0.2) | 48 (6.5) | 4 (0.5) | 18 (2.4) | 0 | 109 (8.5) | 5 (0.4) | 69 (5.5) | 1 (<0.1) |
| Amenorrhea | 108 (20.3) | N/A | 64 (12.3) | N/A | 195 (26.2) | N/A | 122 (16.6) | N/A | 303 (23.7) | N/A | 186 (14.8) | N/A |
| Cough | 11 (2.1) | 0 | 11 (2.1) | 0 | 22 (3.0) | 0 | 15 (2.0) | 0 | 33 (2.6) | 0 | 26 (2.1) | 0 |
| Arrhythmia [j] | 10 (1.9) | 1 (0.2) | 3 (0.6) | 0 | 21 (2.8) | 2 (0.3) | 20 (2.7) | 2 (0.3) | 31 (2.4) | 3 (0.2) | 23 (1.8) | 2 (0.2) |
| Hot flush [k] | 70 (13.2) | 0 | 49 (9.4) | 1 (0.2) | 159 (21.4) | 7 (0.9) | 122 (16.6) | 4 (0.5) | 229 (17.9) | 7 (0.5) | 171 (13.6) | 5 (0.4) |
| Hypotension [l] | 4 (0.8) | 0 | 1 (0.2) | 0 | 11 (1.5) | 0 | 4 (0.5) | 0 | 15 (1.2) | 0 | 5 (0.4) | 0 |
| Phlebitis | 6 (1.1) | 0 | 9 (1.7) | 0 | 7 (0.9) | 0 | 4 (0.5) | 0 | 13 (1.0) | 0 | 13 (1.0) | 0 |
| Asthenia [m] | 383 (72.0) | 45 (8.5) | 305 (58.8) | 10 (1.9) | 589 (79.2) | 82 (11.0) | 511 (69.4) | 38 (5.2) | 972 (76.2) | 127 (10.0) | 816 (65.0) | 48 (3.8) |
| Myalgia | 103 (19.4) | 3 (0.6) | 11 (2.1) | 0 | 170 (22.8) | 6 (0.8) | 59 (8.0) | 0 | 273 (21.4) | 9 (0.7) | 70 (5.6) | 0 |
| Arthralgia | 87 (16.4) | 0 | 22 (4.2) | 0 | 112 (15.1) | 3 (0.4) | 42 (5.7) | 2 (0.3) | 199 (15.6) | 3 (0.2) | 64 (5.1) | 2 (0.2) |
| Lacrimation increased | 23 (4.3) | 0 | 16 (3.1) | 0 | 75 (10.1) | 1 (0.1) | 47 (6.4) | 0 | 98 (7.7) | 1 (<0.1) | 63 (5.0) | 0 |
| Conjunctivitis | 104 (19.5) | 1 (0.2) | 95 (18.3) | 1 (0.2) | 28 (3.8) | 0 | 31 (4.2) | 0 | 132 (10.3) | 1 (<0.1) | 126 (10.0) | 1 (<0.1) |

Note: Clinical importance was determined with respect to the TAC regimen based upon frequency (>10%), or severity, or clinical impact of the TEAE. TEAEs are grouped by body system.

[a] Derived from laboratory data, regardless of causal relationship

[b] The term pyrexia represents fever in the absence of infection (not a MedDRA PT) reported on a CRF page for febrile neutropenia.

[c] Infection values are based on all MedDRA PTs mapped to SOC infections and infestations.

[d] Derived as Grade 4 neutropenia (as per blood count) and fever ≥38.1°C (NCI Grade ≥2) in the same cycle, in the absence of infection, when fever requires hospitalization (ie, is deemed "serious" by the Investigator) and/or administration of iv antibiotics, regardless of causal relationship

[e] Defined as Grade 3-4 neutropenia (as per blood count) and Grade 2-4 infection, regardless of causal relationship

[f] Defined as Grade 3-4 neutropenia (as per blood count) and Grade 3-4 infection, regardless of causal relationship

[g] The term nail disorder includes all PTs mapped to HLT nail and nail bed conditions.

[h] The term anorexia includes decreased appetite.

[i] The term abdominal pain includes all PTs mapped to HLT gastrointestinal and abdominal pains.

[j] The term arrhythmia includes all PTs mapped to HLGT cardiac arrhythmias.

[k] The term hot flush includes flushing.

[l] The term hypotension includes includes all PTs mapped to HLT vascular hypotensive disorders.

[m] The term asthenia includes fatigue.

CRF = case report form; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; GEICAM = Grupo Espanol de Investigacion en Cancer de Mama; HLGT = high level group term; HLT = high level term; iv = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable; NCI = National Cancer Institute; PT = preferred term; SOC = system organ class; TAC = docetaxel, doxorubicin, and cyclophosphamide

***Discussion on Clinical Safety***

In study GEICAM 9805, patients from TAC group, experienced higher frequency of TEAEs. There were significantly more SAEs in the TAC group compared to the FAC group during chemotherapy (22.4% vs. 4.2%). Study drug related SAEs were also more frequently reported in the TAC group compared to the FAC group (20.3 vs. 3.3). Treatment discontinuations due to TEAEs were also more frequently reported in the TAC group compared to the FAC group.

Haematological toxicity was clearly higher in the TAC arm, but was managed with systematic G-CSF and compulsory prophylactic antibiotiotherapy.

The most frequent non haematological serious TEAEs reported during chemotherapy in both treatment groups were diarrhoea (1.7% vs. 0.6%), nausea, and vomiting (1.3% vs. 0.2% each).

In particular, based on the provided safety data from GEICAM study, it was not possible to assess cardiac toxicity including asymptomatic decrease in LVEF. Indeed, despite obvious risk of cardiac toxicity due to associated anthracycline in the TAC regimen and potential decrease in LVEF with docetaxel, the study protocol was amended not being able to detect asymptomatic cardiac dysfunctions.

Due to the lack of data on cardiotoxicity from study GEICAM 9805, data from study TAX 316 were provided. Cardiac toxicity was higher in the TAC group compared to the FAC group in study Tax 316.

In total, all-grade cardiac failure, congestive heart failure (CHF), or cardiomyopathy were reported in 4 patients in the TAC arm and 5 patients in the FAC arm, while Grade 3-4 cardiac failure, CHF, or cardiomyopathy were reported in 1 patient in the TAC arm and 2 patients in the FAC arm.

Overall, according to the TAX 316 data, as of the first SUR of March 2005, there were 17 cumulative reports (2.3%) of CHF in the TAC arm, and 7 in the FAC arm (1%). Between March 2005 and March 2009, an increase in the incidence of CHF was reported in both arms. As of March 2009, 2.8% of patients from the TAC group (21) and 1.9% of patients from the FAC group (14) had grade 3 or 4 cardiac heart failure. The risk of cardiac failure is already addressed in sections 4.4 and 4.8 of the SPC.

A total of 28 patients in the FAC arm had a diagnosis of SPM as an efficacy endpoint, and 16 patients in the TAC arm had a diagnosis of SPM as an efficacy endpoint (14 patients). The histopathological diagnoses seem to be similar between the two treatment groups. Only 3 SPM were reported as TEAEs in the TAC group (0 in the FAC group):

The risk of delayed myelodysplasia and or myeloid leukaemia in the TAC treated patients is already addressed in the SPC. Given the high hematotoxicity of the TAC regimen requiring the use of G-CSF, the risk of delayed myelodysplasia and or myeloid leukaemia should be monitored.

As of 04 March 2009, 25 (4.7%) TAC patients and 34 (6.6%) FAC patients died, all during the follow-up period. No patient died within 30 days of the last study treatment. In the FAC group 1 out of the 34 reported deaths was assessed as study drug related. In the TAC group, all the deaths were assessed as not related to study drug.

Overall, docetaxel in combination with doxorubicin and cyclophosphamide is more toxic than the FAC regimen particularly regarding haematotoxicity. Overall, the TAC regimen was associated to a higher incidence of haematological (mainly neutropenic events), cardiac, neurological, gastrointestinal and fluid retention events.

The safety profile of docetaxel in combination with doxorubicin and cyclophosphamide in node negative breast cancer is not unexpected, but should be put in balance with efficacy data in this indication.

### *1.2.5 Risk Management Plan*

As part of the variation application the MAH submitted a justification why for this extension of indication no Risk Management Plan is required. This justification was considered acceptable.

# 2. Benefit-Risk Balance

The present application is supported by one pivotal, non-blinded, randomized, Phase III study (GEICAM 9805 /TAX.ES1.301), designed to compare DFS (disease-free survival) after adjuvant chemotherapy following primary surgery for breast cancer in high-risk node-negative patients receiving one of the following adjuvant combination chemotherapy regimens:

- TAC (Taxotere, doxorubicin, and cyclophosphamide),
- FAC (5-fluorouracil, doxorubicin, and cyclophosphamide).

In breast cancer adjuvant setting, surgery could result in a cure of the malignant disease. However, many patients will relapse and can die from their cancer. This is related to silent residual diseases/micrometastases not eliminated by surgery. This silent disease in relation to the removed tumour can be local or distant (metastases).

An adjuvant medical treatment is expected to suppress or eliminate this undetectable residual disease avoiding (or delaying) relapses. This delay in relapses is per se a clinical benefit since it provides a prolonged time free from toxic treatments and major health concerns to the patients.

Nevertheless, the benefit of an adjuvant therapy is directly related to the risk of relapse and patients in whom a relapse is unlikely should not have proposed chemotherapy whereas patients at high risk of relapse may be the ideal target of this treatment.

The adjuvant treatment selection algorithm for the management of early breast cancer radically changed during the last decade. As a consequence, and according to the most recent concepts, the benefit of adjuvant chemotherapy is clear for triple negative patients and for HER2 positive disease. For the latter, chemotherapy is given with or preceding Herceptin. For patients with ER positive, HER2 negative disease, the decision for adjuvant chemotherapy is more difficult.

**Benefits**

– **Beneficial effects**

Adjuvant chemotherapy benefit should be demonstrated in terms of DFS translating ultimately into beneficial effect on survival. At least, demonstration of the absence of negative effects on survival is expected.

Data from this multicenter open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with operable node negative breast cancer eligible to receive chemotherapy. 1060 patients were randomized to receive either TAXOTERE 75 mg/m$^2$ administered 1-hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 (539 patients in TAC arm), or doxorubicin 50 mg/m2 followed by fluorouracil 500 mg/m$^2$ and cyclosphosphamide 500 mg/m$^2$ (521 patients in FAC arm), as adjuvant treatment of operable node negative breast cancer patients with high risk of relapse according to 1998 St. Gallen criteria (tumour size >2cm and/or negative ER and PR and/or high histological/nuclear grade (grade 2 to 3) and/or age <35 years). Median duration of follow-up was 77 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was observed. TAC-treated patients had a 32% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.68, 95% CI (0.49-0.93), p = 0.01). Overall survival (OS) was also longer in the TAC arm with TAC-treated patients having a 24% reduction in the risk of death compared to FAC (hazard ratio = 0.76, 95% CI (0.46-1.26, p = 0.29). However, the distribution of OS was not significantly different between the 2 groups.

– **Uncertainty in the knowledge about the beneficial effects**

A total of 4 unplanned interim efficacy analyses were performed. The CHMP was concerned that the single pivotal trial for this application may lack robustness and the final statistical significance of the proposed conclusion may not be convincing. Although the methodological weaknesses were acknowledged, the CHMP concluded that in view of the supportive evidence and the overall coherent results, this did not constitute a major issue.

According to the most recent clinical standards (St Gallen 2009 conference), one part of the population included in study GEICAM 9805 would not be treated at all today with adjuvant chemotherapy. Until further data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

OS data are still premature. As a preliminary assessment it can, however, be stated that TAC is a least not worse than FAC in terms of OS. The MAH committed to submit mature OS data as soon as this becomes available.

**Risks**

- **Unfavourable effects**

TAC regimen was authorised for the adjuvant treatment of patients with operable node- positive breast cancer in 2004. This indication is based on a single pivotal phase III study, TAX316. The safety profile of docetaxel associated with AC is as expected. However in comparison with FAC, TAC safety profile is expected to be worse in terms of haematotoxicity, cardiotoxicity, colitis, and leukaemia.
Regarding study GEICAM 9805 in the adjuvant treatment of patients with node negative breast cancer, overall, docetaxel in combination with doxorubicin and cyclophosphamide is more toxic than the FAC regimen particularly regarding haematotoxicity.

Haematological TEAEs were more frequent in the TAC group (anaemia, thrombocytopenia, neutropenia, and febrile neutropenia).

Systematic use of G-CSF in the group TAC reduced occurrence of neutropenic events. However, incidence of neutropenia, febrile neutropenia and neutropenic infection remains higher in the TAC group compared to the FAC group (44.9% vs. 13.3%; 9.6% vs. 2.3% and 6.6% vs. 2.7% respectively).

- **Uncertainty in the knowledge about the unfavourable effects**

Concerning the pre-clinical assessment, several issues regarding the Environmental Risk Assessment, remain. Therefore, a commitment from the MAH to report in due dates the responses to the additional questions, is necessary.
On a clinical view, despite obvious risk of cardiac toxicity due to associated anthracycline in the TAC regimen and potential decrease in LVEF with docetaxel, the study protocol was amended in order to not detect asymptomatic cardiac dysfunctions. This protocol amendment remains not comprehensible and should have been justified. However, the risk of cardiotoxicity is addressed in the proposed SPC for this variation.

When second primary malignancies occurred prior to Breast Cancer Relapse (BCR), they were reported as DFS events. The number of Second Primary Malignancies (SPM) reported as events in terms of the primary endpoint was higher in the FAC group in comparison to the TAC group. Given the high haematotoxicity of the TAC regimen requiring the use of G-CSF, the risk of delayed myelodysplasia and or myeloid leukaemia should be monitored.

Currently there is a trend to an improved OS, the uncertainties for this endpoint, resulting from the large 95%-CIs and the low number of events observed, however, are large.

**Benefit-Risk Balance**

- **Importance of favourable and unfavourable effects**

The CHMP questioned whether the selection criteria in this study correspond to a population that could be expected to benefit from an adjuvant chemotherapy. Indeed, according to recent clinical recommendation (Goldhirsch et al., 2009) one part of the population recruited in the pivotal trial would not be treated at all with adjuvant chemotherapy. The adjuvant treatment selection algorithm for the management of early breast cancer radically changed during the last decade. As a consequence and according to the most recent concepts, the benefit of adjuvant chemotherapy is clear for triple negative patients and for HER2 positive disease. For the latter, chemotherapy is given with or preceding Herceptin. Patients with ER positive, HER2 negative disease constitute a group for whom the decision for adjuvant chemotherapy is most difficult. Patients with small primary tumours (pT1a pN0 and ER negative) might avoid adjuvant systemic therapy. There is no agreement on a standard chemotherapy regimen for any disease subset. Until conclusive data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to the most recent internationally established criteria for primary therapy of early breast cancer.

The CHMP considered that the benefit-risk balance of TAC in the adjuvant treatment of patients with operable node negative breast cancer eligible to receive chemotherapy according to current clinical guidance is positive. Until further data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

# 3. Conclusion

On 20 May 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.