CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-449/s-029

MEDICAL REVIEW(S)

Division Director's Memorandum

Date:	August 19, 2004
NDA:	20-449/s-029
Sponsor:	Aventis Pharmaceuticals, Inc
Proprietary Name:	Taxotere® (docetaxel) for Injection Concentrate

Regulatory History

October 2, 1990: Original IND 35,555 submitted.

Taxotere (docetaxel) has been previously approved as a single agent or in combination with other drugs for the treatment of breast cancer, advanced or metastatic non-small cell lung cancer, or metastatic androgen-independent (hormone-refractory) prostate cancer.

March 17, 2004: Aventis submitted the current sNDA.

May 10, 2004: Aventis presented a summary of the findings supportive of their sNDA to DODP in a post-submission meeting.

The PDUFA goal date for this priority review is September 17, 2004.

Proposed Indication

Taxotere (docetaxel) in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Available Therapies (see review by Dr. Cortazar)

The standard of care for adjuvant therapy of breast cancer is anthracycline-based therapy. Anthracycline-based regimens have been associated with improved disease-free survival (DFS) and a reduction in the risk of death compared with non-anthracycline-containing regimens.

Clinical & Biostatistical Review (see reviews by Drs. Cortazar and Y.F. Chen)

Safety and efficacy were demonstrated in TAX316, a randomized, multi-center global clinical trial which randomized 1491 patients to receive either docetaxel 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years.

The primary efficacy endpoint was DFS in this study which was stratified by number of positive lymph nodes (1-3 or 4+). Results from a second interim analysis (55 months follow-up) are as follows: The overall reduction in risk of relapse was 25.7% for TAC- treated patients ($p = 0.0047$ stratified logrank test). At the time of this interim analysis, the overall

relative reduction in risk of death appears to be 31% (not statistically significant when adjusted for interim analysis).

Women receiving TAC had an increase in anemia, grade ≥ 3 neutropenia, stomatitis, amenorrhea, fever in absence of infection, hypersensitivity reactions, peripheral edema, neurosensory and skin events compared to those receiving FAC. The toxicity, while significant, did not cause a large number of patients to withdraw from treatment. As with other anthracycline/cyclophosphamide-containing regimens, long-term serious toxicity for the TAC regimen included leukemia (0.4%) and congestive heart failure (1.6%).

In the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel dose 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 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.

Clinical Pharmacology & Biopharmaceutic Review (see Dr. Abraham's review)

A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

Chemistry, Manufacturing and Controls (CMC) Review (see Dr. Y. Hsieh's review)

The CMC team approved the applicant's request for categorical exclusion for an Environmental Assessment.

Nonclinical Review

There was no review of this application by the Pharmacology/Toxicology team.

Data Integrity Issues

The Division did not request any site inspections for this sNDA because a preliminary review conducted by the medical officer found that results were comparable across centers with respect to the primary efficacy endpoint.

Tradename and Labeling Consultation

As this is an approved drug, the Division did not send a consult to the Division of Medication Errors and Tech Support (DMETS) for either the tradename or the labeling. On August 3, 2004, the Division provided the labeling to a safety evaluator from the Division of Drug Risk and Evaluation (DDRE), however, the reviewer did not have any comments after review of the label.

Pediatric Considerations

Adjuvant breast cancer does not exist in children so the Division granted a full waiver to the applicant regarding conduct of pediatric studies.

Conclusions and Recommendations: Regular Approval

Disease-free survival is an accepted endpoint providing evidence of clinical benefit in the setting of adjuvant breast cancer therapy. Therefore, the DODP/CDER/FDA is granting regular approval for this indication.

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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/s/

Dianne Spillman
8/19/04 03:54:46 PM
CSO
sNDA approved 8-18-04.

Richard Pazdur
8/19/04 04:42:39 PM
MEDICAL OFFICER

TAXOTERE® (docetaxel)
Aventis
Efficacy Supplement Clinical Review

sNDA Number: 20,449
Submission Code S-029
Date of submission: March 17, 2004
Completion Date: August 17, 2004

Division of Oncology Drug Products:
Medical Reviewer: Patricia Cortazar, M.D.
Team Leader: Ramzi Dagher, M.D.

Sponsor's Proposed Indication:
"Taxotere in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer"

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1 Executive Summary

This medical review addresses an efficacy supplement to NDA 20,449 for use of Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.

The original NDA for Taxotere was approved in May 1996 for the treatment of patients with locally advanced or metastatic breast cancer who had progressed during or relapsed after anthracycline-based therapy. Supplemental NDA approvals were subsequently granted for the treatment of locally advanced or metastatic non-small cell lung carcinoma and for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

The current supplement presents the results of a single, randomized trial comparing Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide with 5-Fluorouracil in combination with doxorubicin and cyclophosphamide, as adjuvant treatment in women with operable node-positive breast cancer.

1.1 Recommendation on Approvability

The Division of Oncology Drug Products recommends approval of Docetaxel in combination with Doxorubicin and Cyclophosphamide (TAC) for the proposed indication: *"adjuvant treatment of operable breast cancer patients with* [redacted]

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial entitled, "A multicenter Phase III 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 operable breast cancer patients with positive axillary lymph nodes." The protocol-specified primary endpoint was disease free survival of breast cancer; secondary endpoints were survival, toxicity and to evaluate pathologic and molecular markers for predicting efficacy. At the second interim analysis with 55 months of follow-up, the docetaxel (TAC) arm demonstrated statistically significant and clinically relevant superiority in the traditional oncology endpoint of interest in the treatment of adjuvant breast cancer (disease free survival), and also prolonged survival as measured against an accepted control arm (FAC).

The safety profile of Taxotere in combination with Doxorubicin and Cyclophosphamide is consistent with the known toxicities of both agents and typical of antineoplastic therapy. Common toxicities included anemia, neutropenia, fever in the absence of infection, nausea and stomatitis, which are currently identified in the Taxotere label. The incidence of grade 3 and 4 adverse events was higher in the TAC combination arm as were dose modifications and treatment discontinuations.

1.2 Recommendation on Post-marketing Actions

The Division recommends that the sponsor submit complete efficacy and safety data at the time of the Study TAX 316 Final Analysis.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The original NDA for Taxotere was granted accelerated approval in May 1996 for the treatment of patients with locally advanced or metastatic breast cancer who had progressed during or relapsed after anthracycline-based therapy. Approval for this indication was granted in June of 1998. In December 1999, Taxotere was approved for the treatment of locally advanced or metastatic non-small cell lung carcinoma previously treated with platinum-based chemotherapy. In April 2000, Taxotere received approval in combination with Cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy. Taxotere has also been approved in combination with Prednisone, for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

1.3.2 Efficacy

Study TAX 316 is a Phase III, multicenter, multinational, randomized study that compares the efficacy and safety of Docetaxel in combination with Doxorubicin and Cyclophosphamide (TAC) versus 5-Fluorouracil in combination with Doxorubicin and Cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes. After stratification according to the number of positive axillary lymph nodes (1-3 and $\geq$ 4), a total of 1941 patients are randomized from 112 centers worldwide.

The median follow-up of the study is 55 months. The treatment arms are well balanced for important baseline characteristics. Seventy-six percent of the patients in each arm are estrogen receptor (ER) and or progesterone receptor (PgR) positive. Disease free survival is the primary endpoint; survival, toxicity and evaluation of pathologic and molecular markers for predicting efficacy are secondary endpoints. The primary endpoint of disease-free survival included local and distant recurrences, contralateral breast cancer and deaths from any cause. Results from a second interim analysis (55 months follow-up) shows that the docetaxel-containing combination regimen (TAC) has significantly longer disease-free survival (DFS) compared to FAC (hazard ratio=0.743; 2-sided 95% CI=0.604, 0.915, stratified log rank p=0.0048). The overall reduction in risk of relapse is 25.7% for TAC- treated patients. The overall relative reduction in the risk of death is 31% (HR:0.69, 95% CI: 0.53, 0.90, stratified log rank p=0.0067, not statistically significant based on interim analyses results).

Overall, the consistency of outcome across the study endpoints demonstrates the efficacy of Docetaxel in combination with Doxorubicin and Cyclophosphamide (TAC) in adjuvant treatment of positive axillary lymph nodes breast cancer.

1.3.3 Safety

The safety profile of Docetaxel given as monotherapy is contained in the current label based on clinical trial data in patients with metastatic breast cancer, metastatic lung cancer, prostate cancer as well as post-marketing reports.

The safety profile of Docetaxel given as a combination therapy is consistent with the toxicities described in the label for the individual study drugs.

Toxicity in Study TAX 316 was greater in the TAC treatment arm. The toxicity consisted predominantly of alopecia (97.8%), anemia (91.5%), asthenia (80.8%), nausea (80.5%), neutropenia (71.4%), stomatitis (69.4%), amenorrhea (61.7%), fever in absence of infection (46.5%) and vomiting (44.5%). The toxicity while significant, did not cause a large number of patients to withdraw from treatment (6% in the TAC arm and 4% in the FAC arm). The most frequent reason leading to withdrawal was fever in the absence of infection and allergy in the TAC arm.
Long-term serious toxicity included leukemia and cardiac toxicity. Four patients were diagnosed with leukemia (AML), 3 in the TAC arm and 1 in the FAC arm. The cumulative risk of developing treatment-related AML at 5 years in TAX 316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens. Twelve patients on TAC and 4 patients on FAC were reported to have developed CHF (grade 3-4 cardiac toxicity) during the treatment or follow-up phase. It is likely that the TAC combination is associated with increased risk for cardiac toxicity. However, it is not possible to conclude from these data whether risk is related to the drug combination or to estimate the true incidence of the cardiac toxicity.

1.3.4 Dosing Regimen and Administration

The recommended dose of Taxotere is 75 mg/m^2 administered intravenously after Doxorubicin (at a dose of 50 mg/m^2) and Cyclophosphamide (at a dose of 500 mg/m^2) every 3 weeks.

The percentage of patients requiring dose reductions in study TAX 316 is higher in the docetaxel (TAC) arm (12%) compared to the monotherapy arm (3%). Most of the dose reductions are due to adverse events.

In the current label, Taxotere is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or other drugs formulated with polysorbate 80. Taxotere should not be used in patients with neutrophil counts of < 1500 cells/mm^3. The Taxotere label also has a box warning for patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase, since these patients are at increased risk for the development of grade 4 neutropenia, infections, severe thrombocytopenia, stomatitis, skin toxicity and toxic death.

1.3.5 Drug-Drug Interactions

The potential for drug-drug interactions between docetaxel, doxorubicin, and

cyclophosphamide was assessed in a separate study (Study XRP6976D/1001) in 30 women with advanced breast cancer. The results of this study indicated that docetaxel has no effect on the pharmacokinetics of doxorubicin or cyclophosphamide when the three drugs are given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy. Please see Clinical pharmacology/biopharmaceutics review by Sophia Abraham, Ph.D.

1.3.6 Special Populations

In the adjuvant breast cancer trial (TAX316), TAXOTERE in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) are 65 years of age or older. The number of elderly patients who receive this regimen is not sufficient to determine whether there are differences in safety and efficacy between elderly and younger patients

2 Introduction and Background

2.1 Product Information

Docetaxel is a semisynthetic antineoplastic agent that is very similar to paclitaxel in structure, mechanism of action, and spectrum of antitumor activity. Docetaxel differs structurally from paclitaxel at the C-10 position where docetaxel has a hydroxy group instead of an acetyl group and contains an -$OC(CH_3)_3$ moiety on the C-13 side chain as opposed to a benzamide phenyl group as in paclitaxel. Docetaxel is synthesized from [redacted], a non-cytotoxic substance extracted from the needles of the European yew tree (Taxus baccata).

See Taxotere label for additional information.

2.2 State of Armamentarium For Indication(s)

The standard of care for adjuvant therapy of breast cancer is anthracycline-based therapy. Anthracycline/Cyclophosphamide combination chemotherapy improves DFS in women with node-positive early breast cancer irrespective of the menopausal and hormone receptor status (NSABP B-15 and B-16)(JCO Sep 1 1990: 1483-1496). A SWOG study showed that the combination of 5 FU to Doxorubicin and Cyclophosphamide in addition to Tamoxifen had increased efficacy in postmenopausal women with node-positive, receptor-positive breast cancer (Proceedings of ASCO16:128a, 1997). In addition, EBCCTCG reported a relative risk reduction of 15.7% for death with the use of anthracycline-based regimens relative to non-anthracycline regimens.

Phase III trials have also established the benefit of incorporating taxanes into anthracycline based regimens. The intergroup trial C-9344 and NSABP B-28 trial demonstrated increased event-free and overall survival with the addition of 4 cycles of paclitaxel every 3 weeks after 4 cycles of

AC (JCO Mar 15 2003: 976-983). Anthracycline-cyclophosphamide followed by paclitaxel is an approved regimen and is increasingly used for node positive patients.

The activity of docetaxel administered every 3 weeks for 4 cycles following 4 cycles of AC was evaluated in the neoadjuvant setting (NSABP B-27) showing the pathologic complete response had doubled with the addition of docetaxel. Therefore, current practice includes the addition of a taxane to anthracycline/cyclophosphamide combination.

2.3 Important Issues with Pharmacologically Related Products

Safety profile of Taxotere is well described. For additional information please refer to the Taxotere label.

3 Significant Findings from Other Review Disciplines

Taxotere is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. No new information with regard to chemistry, pharmacology, toxicology and microbiology is submitted with this sNDA.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The sNDA consisted of an electronic submission of 1 DLT 35/70 digital tape, approximately 5 GB.

4.2 Data Quality and Integrity

The protocol for study TAX 316 was submitted to IND 35,555 on August 13, 1997 (Serial No. 602), in full compliance with the principles of the Declaration of Helsinki, including all current amendments, or with the laws and regulations of the country in which the study was conducted. Prior to initiation of the study, the protocol, and the patient informed consent were reviewed and approved by the ethics committees or institutional review boards of the centers involved in the study. Subsequent protocol amendments were also submitted, reviewed and approved by FDA before implementation. A statistical analysis plan (SAP, version 2.0) for this study was submitted on September 27, 2001 (Serial No. 972) and reviewed by the FDA statisticians.

4.3 Financial Disclosures

Requirements for Financial Disclosure were discussed with the applicant during the pre-NDA meeting on August 21, 2003. The study was completed after 2/2/99 and therefore was subject to the financial disclosure requirements.

Disclosures
Form 3454 was submitted with the application.

- Compensation affected by the outcome of the clinical studies
  None stated or apparent
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
  None stated or apparent

Reviewer's assessment:

- Analysis and publication of the results and submission of an application are based on the completion date of May 11,2000. Although follow-up continues, patient accrual is complete and the majority of events have occurred.
- The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

5 Clinical Pharmacology

See review by Sophia Abraham, Ph.D.

6 Integrated Review of Efficacy

6.1 Methods

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial entitled, "A multicenter Phase III 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 operable breast cancer patients with positive axillary lymph nodes." The data used in the efficacy review consisted of a study report, databases of raw and derived data, case report forms and listings from this trial

6.2 Detailed Review of Protocol TAX 316

"A multicenter Phase III 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 operable breast cancer patients with positive axillary lymph nodes"

6.2.1 Principal Investigators

Jean-Marc Nabholtz, MD, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, Canada.

6.2.2 Protocol Milestones

Milestone	Dates
Protocol Final Version	March 17, 1997
Protocol Version 2 Submission	September 19, 1997
Protocol Version 3 Submission	November 24, 1997
Protocol Version 4 Submission	January 13, 1999
First Patient recruited	May 1997
Last Patient recruited	October 1999
Data Cutoff	July 15, 2003
NDA Submission	March 17, 2004
Planned interim analysis	October 2001
Planned Final Analysis	Fourth quarter 2003
First planned follow-up analysis	2006
Second planned follow-up analysis	2008

6.2.3 Objectives

Primary:
"The primary objectives of this trial are to compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (TAC) in operable breast cancer patients with positive axillary lymph nodes."

Secondary:
"The secondary objectives of this trial are:

a) to compare overall survival between the 2 above mentioned arms.
b) To compare toxicity and quality of life between the 2 above mentioned arms.
c) To evaluate pathologic and molecular markers for predicting efficacy

An independent socio-economic study will be conducted in parallel with the clinical study."

6.2.4 Overall Study Design

The protocol design was a Phase III, multicenter, multinational, randomized, non-blinded study comparing the efficacy and safety of docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide as adjuvant treatment for breast cancer patients with positive axillary lymph nodes. Patients were to be post-surgically stratified according to the participating institution,

number of axillary lymph nodes involved (1 to 3; 4 and more) and then were to be randomized into one of two treatment arms:

a) TAC
b) FAC

Randomization was to take place at a central randomization center. Patients were to receive a fixed number of 6 cycles of treatment. Patients were to be assessed for tumor recurrence every 6 months for the first 5 years, thereafter annually at up to 10 years.

Reviewers Comments:
This Phase III trial is a randomized, large, multicenter study whose intent is to be used as a registration trial to support the adjuvant indication. The following are some concerns with the protocol design:

a) There is a potential for imbalance of Stage I, II and III patients.
b) There is a lack of prospective stratification for important prognostic factors such as age and hormone receptor status. Hormonal receptor status is related to the use of adjuvant hormonal therapy, which conveys an additive survival advantage to chemotherapy.
c) The use of postmastectomy radiotherapy at the discretion of the investigator is problematic. This lack of control over radiation therapy may result in treatment arm imbalances if patients receive suboptimal therapies. Since there is no control over the therapies given, the trial should be stratified to account for the survival benefit of the radiation therapy.

6.2.5 Protocol Amendments

The protocol was amended six times.
First amendment dated September 19, 1997 included a modification of the follow-up after chemotherapy. The protocol decrease the frequency and number of required investigative procedures such as chest x-rays from every 6 months to yearly and abdominal ultrasound, CT scans and bone scans from yearly to be performed only in presence of signs and or symptoms suggestive of cancer recurrence.

Second amendment dated November 24, 1997 included an update of the concomitant treatment (aminofostine and cardioprotectors use not allowed during study treatment).

Third amendment dated January 13, 1999 included the following:

- A revision of the protocol sample size calculation in order to increase the power to detect a statistically and clinically meaningful difference in the subgroup of patients with one to three positive axillary nodes. The number of patients to be recruited was to be increased by 360 (from 1056 to 1416). These changes were proposedin the light of a paper published in JCO (Levine et al., Randomized Trial of Intensive CEF Chemotherapy Compared With CMF in Premenopausal Women With Node-Positive Breast Cancer, Journal of Clinical Oncology, Vol. 16, No 8 (August), 1998: pp2651-2658). The sponsor stated that the sample size revision was

independent from data review. At the date of the sample size revision, three events have been observed.

- The definition of intent to treat population was modified (ICH E9). Patients randomized to group A who were subsequently treated in group B were to be analyzed in treatment group A for efficacy parameters and in group B for safety parameters.
- A modification specific to the European Union Countries of a preparation guides for use with taxotere concentrate for infusion and solvent.
- A modification to the Informed Consent in order to add the procedures on pathology and molecular marker studies.
- Patients with congestive heart failure were to be reported as having a serious adverse event regardless of relation to study therapy.

Forth amendment dated February 25, 2002 included the following:

- The sample size was increased in order to have sufficient power to compare TAC and FAC for all patients randomized with stratification by nodal status as well as for the separate strata for patients with one to three positive axillary nodes and patients with 4+ positive axillary nodes. The planned sample size per treatment group was changed from 528 to 708 patients per treatment with 495 in the 1-3node stratum and 213 in the 4+node stratum.
- The group sequential design, according to Peto's method was to be used for the interim analysis to a significance level of 0.001 allowing an unadjusted level of 0.05 for the final analysis.
- Further analysis of the primary endpoint was to be performed during years 6 to 10 of study follow-up. FDA suggested using a significance level of 0.048 for the final analysis in order to protect the overall experiment-wise type 1 error at the 0.05 level.

Reviewer's comments:
The Agency agreed with the amendments.

6.2.6 Eligibility Criteria

Inclusion Criteria:

- Histologically proven breast cancer. Interval between definitive surgery that includes axillary lymph node dissection and registration is less than 60 days.
- Definitive surgical treatment must be either mastectomy, or breast conserving surgery with axillary lymph node dissection for operable breast cancer (T1-3, Clinical N0-1, M0). Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and ductal carcinoma in situ (DCIS). Lobular carcinoma in-situ does not count as a positive margin.
- Histologic examination of the tumor: Invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes. At least one paraffin block from the primary tumor and nodes submitted to the central operational office (Edmonton, Canada) for post-randomization confirmation of diagnosis and molecular studies.
- Estrogen and progesterone receptors performed on the primary tumor prior to randomization. Results must be known by the end of chemotherapy in order to decide whether hormonal therapy is indicated.

- Age ≥ 18 years and age ≤ 70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TAC regimen for women > 70 years of age.
- Karnofsky Performance status index ≥ 80%.
- Normal cardiac function must be confirmed by assessment of LVEF or shortening fraction (MUGA scan or echocardiography respectively). The result must be above the lower limit of normal for the institution.
- Laboratory requirements: (within 14 days prior to registration)
  a) Hematology:
     i) Neutrophils ≥ 2.0 10^9/L
     ii) Platelets ≥ 100 10^9/L
     iii) Hemoglobin ≥ 10 g/dL
  b) Hepatic function:
     i) Total bilirubin < 1 UNL
     ii) ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 UNL
     iii) Alkaline phosphatase ≤ 5 UNL
     iv) Patients with ASAT and/or ALAT > 1.5 x UNL associated with alkaline phosphatase > 2.5 x UNL are not eligible for the study.
  c) Renal function:
     i) Creatinine ≤ 1.75 μmol/L (2 mg/dL);
     ii) If limit values, the calculated creatinine clearance should be ≥ 60 mL/min.
- Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest X-ray (PA and lateral), abdominal ultrasound and/or CT scan, and bone scan. In case of positive bone scan, bone X-ray is mandatory to rule out the possibility of non metastatic hot spots. Other tests may be performed as clinically indicated.
- Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.

Exclusion Criteria:

- Prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy).
- Prior anthracycline therapy or taxoids (paclitaxel, docetaxel) for any malignancy.
- Prior radiation therapy for breast cancer.
- Bilateral invasive breast cancer.
- Pregnant, or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration.
- Any T4 or N2 or known N3 or M1 breast cancer.
- Pre-existing motor or sensory neurotoxicity of a severity ≥ grade 2 by NCI criteria.
- Other serious illness or medical condition:
  a) congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or high-risk uncontrolled arrhythmias
  b) history of significant neurologic or psychiatric disorders
  c) active uncontrolled infection

- Past or current history of neoplasm other than breast carcinoma, except for: curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, other cancer curatively treated and with no evidence of disease for at least 10 years, ipsilateral ductal carcinoma in-situ (DCIS) of the breast and lobular carcinoma in-situ (LCIS) of the breast.
- Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment should be stopped before study entry.

Reviewer's comments:
The following are concerns with the inclusion criteria:
- Uncontrolled therapy prior to randomization
- The protocol does not mention eligibility of patients with prior use of other aromatase inhibitors
- The protocol does not mention eligibility of patients with prior or concomitant use of biphosphonates

6.2.7 Study Therapy

Formulation
Docetaxel was to be supplied as vials concentrate for infusion. Each vial with 80 mg/2mL. Doxorubicin, cyclophosphamide and 5-Fluororacil were prepared according to the package insert instructions.

Dosage schedule
Patients were to be randomized to receive one of the three following intravenous regimens:

1. TAC:
- Doxorubicin was to be given first on Day 1, at a dose of 50 mg/m², by 15 minute intravenous bolus every 3 weeks, followed by:
- Cyclophosphamide at a dose of 500 mg/m², day 1, 1 to 5 minute intravenous bolus every 3 weeks.
- Docetaxel was to be given at a dose of 75 mg/m², as a 1 hour intravenous infusion every 3 weeks. During the first 5 minutes, the infusion was to be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).

2. FAC:
- Doxorubicin was to be given first on Day 1, at a dose of 50 mg/m², by 15 minute intravenous bolus every 3 weeks, followed by:
- 5-fluorouracil at a dose of 500 mg/m², ², by 15 minute intravenous bolus every 3 weeks.
- Cyclophosphamide at a dose of 500 mg/m², day 1, 1 to 5 minute intravenous bolus every 3 weeks.

Prophylactic Antibiotic Therapy:
Prophylactic antibiotic therapy was to be administered to patients treated with docetaxel (TAC). Ciprofloxacin was recommended at 500 mg p.o. b.i.d. for 10 days starting day 5 of each cycle. Patients on FAC were to be treated with prophylactic antibiotics and G-CSF for all cycles following an episode of febrile neutropenia or infection.

Prophylactic Premedication Regimen for Fluid Retention:
The following premedication regimen was to be administered for all patients treated with docetaxel (TAC) only:
Dexamethasone 8 mg p.o. for total of 6 doses.
1. night before chemotherapy
2. immediately upon waking the morning of chemotherapy
3. one hour before infusion of docetaxel
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy

Prophylactic anti-emetic treatment:
Recommended in both arms at the discretion of the investigator.

Post therapy treatment:
Both treatment arms were to receive:

- Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there was a contraindication.
- Patients treated with lumpectomy were to undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, was to be used at the discretion of the treating radiation oncologist according to the guidelines at each institution.

Dose Reduction in Both Arms:
The protocol specified treatment interruptions and dose modifications for grades 2 to 4 toxicity using the NCI Common toxicity criteria.
The protocol specified the following dose modifications for *neutropenia*:

Table 1 Dose reductions for neutropenia

Neutropenia	Action taken	Dose Modification for all chemotherapeutic drugs
Febrile neutropenia or documented infection	• 1st episode: TAC: G-CSF to all next cycles FAC: G-CSF and Ciprofloxacin to all next cycles • 2nd episode: Same plus dose modified	Maintain dose level 80%
Neutrophils on Day 21 (x 10^9/L		
≥ 1.5	Maintain dose level if neutrophil count ≥ 1.5 x 10^9/L	Maintain dose level
< 1.5	Add G-CSF, CBC every other day till day 35	Maintain dose level if recovered ≥ 1.5 No recovery by day 35 (< 1.5) will go off chemotherapy

Reviewer's Comment:

- The protocol does not specify dose adjustments for platelet nadir.
- The reviewer agrees with the protocol criteria for Granulocyte colony-stimulating factor (G-CSF) support and dose modifications.

The protocol specified the following modifications:

Table 2 Dose modifications for Grade ≥ 3 toxicity.

	Action taken
Diarrhea ≥ grade 3	TAC: Docetaxel reduced from 75 to 60 mg/m^2 FAC: 5-FU reduced from 500 to 400 mg/m^2
Stomatitis grade 3	TAC: Docetaxel reduced from 75 to 60 mg/m^2 FAC: 5-FU reduced from 500 to 400 mg/m^2 If stomatitis continue: Reduce Doxorubicin from 50 to 40 mg/m^2
Grade 3 toxicities in general except anemia	Withheld treatment 2 weeks until recovery to < 1 then reinstituted
Grade 4 toxicities except anemia	Patient will go off chemotherapy

The protocol required the following modifications for *hepatic impairment*:

- Docetaxel was not to be given to patients with serum bilirubin above the upper limit of normal.
- In the event that abnormal values for ASAT, ALAT, and alkaline phosphatase levels were determined prior to any cycle, the following dose modifications were to apply at this cycle:

Table 3 Docetaxel Dose Modifications for impaired liver function tests (from sponsor's submission 316 pdf, page 959)

ASAT and/or ALAT values		Alkaline Phosphatase values	Dose Modification
≤ 1.5 x UNL	and	< 5 x UNL	No dose modification
> 1.5 x UNL ≤ 2.5 x UNL	and	≤ 2.5 x UNL	No dose modification
> 2.5 x UNL ≤ 5 x UNL	and	≤ 2.5 x UNL	TAC: Docetaxel reduced from 75 to 60 mg/m^2 and doxorubicin from 50 to 40 mg/m^2 FAC: reduce dose of doxorubicin from 50 to 40 mg/m^2
> 1.5 x UNL ≤ 5 x UNL	and	> 2.5 x UNL ≤ 5 x UNL	Same as above
> 5 x UNL	0r	> 5 x UNL	Both arms: Dose delay by 2 weeks. If no recovery, discontinue chemotherapy

Dose Reduction Docetaxel Arms:
The protocol specified dose modifications for *neurologic* toxicity were as follows:

Table 4 Neurologic Toxicity Drug Modifications

Toxicity NCIC Criteria *	Action taken
Grade 1	Maintain dose level
Grade 2	TAC: Docetaxel reduced from 75 to 60 mg/m^2
Grade 3	Discontinue chemotherapy

The protocol stated that patients with severe Grade 3 or 4 *fluid retention* (pleural effusion, pericardial effusion or ascites) should be withdrawn from chemotherapy. Patients are to start furosemide 20 mg daily as soon as any sign of fluid retention is observed. If the fluid retention can not be controlled, the furosemide dose is to be increased to 40 mg daily.

The protocol specified the following dose modifications for *hypersensitivity reactions*:

Table 5 Hypersensitivity Reactions Drug Modifications

Symptoms	Action taken
Mild: localized cutaneous reaction: pruritus, flushing, rash	• Decrease the infusion rate until recovery
Moderate: generalized pruritus, flushing, rash, dyspnea, hypotension with systolic > 80 mm Hg	• Stop docetaxel infusion • Dexamethasone i.v. 10 mg and diphenhydramine 50 mg i.v. • Resume infusion after recovery
Severe: bronchospasm, generalized urticaria, hypotension with systolic < 80 mm Hg, angioedema	• Stop docetaxel infusion • Dexamethasone i.v. 10 mg and diphenhydramine 50 mg i.v. and epinephrine as needed • Resume infusion after recovery
Anaphylaxis	No further drug therapy

The protocol specified the following guidelines for monitoring *cardiotoxicity*:
Baseline measurements of LVEF were to be performed by either MUGA or echocardiography. No routine LVEF assessments were planned. Clinical symptoms suggestive of congestive heart failure were to be investigated and a LVEF was to be determined. Patients who had a LVEF decrease were to have a LVEF during the follow-up every 6 months for the first year and then yearly. Patients who had a decrease of LVEF) < lower limit of normal for institution and greater than 10% change) were to be off chemotherapy.

Radiation Therapy:
Radiation was to begin 3 to 8 weeks after completion of chemotherapy. Indications for radiation therapy were according to the guidelines for each institution. The protocol advised the following indications:

- Mandatory in patients with breast conserving surgery.
- Allowed but not mandatory in case of mastectomy.
- Boost radiation therapy was left at the discretion of the investigator.

Treatment duration:
Both regimens were to be administered for a maximum of 6 cycles.

6.2.8 Patient Evaluations

Patient monitoring is summarized in the following table.

Table 6 Patient monitoring

	Baseline	During therapy Q 3 weeks	End of Chemotherapy	Follow-up
Informed Consent	X			
Physical Examination	X	X	X	Q 3 months for the first 2 years, q 6 months for years 3-5 then yearly up to 10 years
Pregnancy test	X			
Signs and symptoms	X	X	X	
ECG	X			
LVEF	X			
Mandatory Imaging: • Chest X-ray, • bilateral mammogram • abdominal US and or CT • Bone scan and x-ray if hot spot	X			Yearly years (1-5) mammogram yearly years (1-10)
Hematology: Hgb, WBC, Platelets	X	X	X	Q 6 months for 5 years then q 12 months until relapse or 10 years
Blood chemistry:creatinine, alk phos, SGOT, SGPT, bilirubin	X	X	X	Q 6 months for 5 years then q 12 months until relapse or 10 years
Quality of life Questionnaire	X	X	X	6, 12 and 24 months
Adverse events	X	X	X	X

Reviewer's Comments:

- The protocol does not clearly state the frequency of follow-up for tumor assessments of patients who were to discontinue the study drug in the absence of progressive disease.

- The interval for follow-up might be larger than the expected effect size. However, as long as both treatment groups are handled the same in terms of diagnostic modalities and frequency of follow-up, the disease free survival can be compared by treatment arm.
- The reviewer is concerned with a protocol statement in section 5.11 Follow-up After End of Chemotherapy: "Clinical follow-up may be more frequent according to the standard of practice at the participating center". If the frequency of follow-up varies among centers, it might produce imbalance between arms and could make disease free survival an unreliable endpoint.

6.2.9 Criteria for Efficacy Assessment

Per protocol the following defines the rules for efficacy evaluation:

Disease Free Survival:
"DFS will be calculated from the date of randomization up to the first date of local, regional or distant relapse, second primary cancer or death."

Objective relapse:
"Any clinical or radiologic evidence of tumor relapse including the central nervous system."
The protocol states that histology or cytology proof of relapse will de obtained if feasible.

Local relapse:
Defined as: "evidence of tumor in the breast surgical scar, ipsilateral breast (conservative surgery), or evidence of tumor in the ipsilateral anterior chest wall (mastectomy) or skin or soft tissues within the local area".

Regional relapse:
Defined as:"evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, and infraclavicular) as well as skin or soft tissues within the regional area".

Distant relapse:
Defined as: "evidence of tumor beyond the local-regional level as previously defined.
This includes the following: 1) lymph nodes not included in the areas defined above (i.e. supraclavicular, contralateral axilla, paratracheal, etc.) 2) skin not included in the areas defined above 3) liver 4) lung 5) bone 6) central nervous system 7) contralateral breast 8) other sites not defined above.

The protocol states that positive bone scans must be correlated with bone X-ray. However, multiple pulmonary nodules on chest X-ray, multiple liver nodules on liver ultrasound or CT-scan, multiple lytic or blastic bone lesions or multiple hot spots on the bone scan were to be acceptable without pathologic correlation. In addition, new breast malignancy is to be biopsied if possible and blocks are to be sent to the central operational office [redacted] for confirmation of primary or metastatic status along with pathologic and molecular studies.
Second Primary Cancer:

Defined as: "any other histopathologically proven cancer including second invasive primary breast cancer in ipsilateral or contralateral breast. Excluded are non-melanoma skin cancer, in-situ carcinoma of the cervix, and in-situ carcinoma of the breast (LCIS/DCIS).

Disease Free Survival:
Defined in the protocol as the date of randomization up to the first date of local, regional or distant relapse, second primary cancer, or death.

Reviewer's Comments:
FDA does not agree with the protocol's definition of disease-free survival: "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 occurs first".
Currently there is no standard definition of disease free survival. However, FDA had accepted in previous applications the following components of this composite endpoint: local recurrence, distal recurrence, contralateral breast new primaries and unrelated deaths.

- Second primary cancers are considered unrelated to the primary breast cancer and therefore cannot be accepted as an event for disease-free survival.
- Contralateral new breast cancers are considered separate events from distant recurrence of an already-diagnosed breast cancer and therefore have a different prognosis. Although controversial, FDA has accepted in previous applications, the occurrence of contralateral breast cancers as DFS events

6.2.10 Criteria for Safety Assessment

Safety was to be evaluated using the NCI-CTC criteria. Adverse event is defined in the protocol as "any undesirable event associated with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reactions. It also includes any undesirable clinical or laboratory change which does not commonly occur in the patient".
Adverse events are to be reported within 1 to 3 days. All adverse events are to be followed until resolution.

Serious Adverse Event
Defined in the protocol as any experience that was fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization resulting in persistent or significant disability/incapacity.

6.2.11 Endpoints/Statistical Considerations

Endpoints:
Primary Endpoint:
The primary endpoint for this study was the comparison of Disease-Free Survival (DFS) between the two treatment groups at 5 years. 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 occurs first".

Secondary Endpoints:

The following were the protocol secondary endpoints:
a) To compare overall survival between the 2 above mentioned arms.
b) To compare toxicity and quality of life between the 2 above mentioned arms.
c) To evaluate pathologic and molecular markers for predicting efficacy

Sample Size:
The study was planned to have sufficient power to compare TAC and FAC for all patients randomized with stratification by nodal status as well as for the separate strata for patients with one to three positive axillary nodes and patients with 4 or more positive axillary nodes.

The study was originally designed to have 90% power to detect a 26% risk reduction of relapsing for patients treated with TAC compared to FAC (hazard ratio=0.74) at final analysis, after 450 DFS events with a two-sided 5% significance level. The calculated sample size of 1056 allowed detecting a 50% and 60% 5-year DFS with FAC and TAC and a 33% risk reduction in deaths in favor of TAC with 85% power.

In January 1999, the protocol sample size was amended, in response to the NCICTG adjuvant epirubicin versus CMF trial that did not have enough power to demonstrate superiority of the treatment arm in the nodal subgroups. The amended protocol was to target a sample size of 708 patients per treatment arm, with 495 in the 1-3 node stratum and 213 in the 4+node stratum.

Power calculations were based on the primary analysis for disease free survival. The sample size was determined by estimating the 5-year DFS for patients treated with FAC as 60 % for the 1-3 stratum and 40 % for the 4+ stratum. The expected 5-year DFS for all FAC patients was 0.70 (60 %) + 0.30 (40%) = 54%. The expected 5-year DFS for patients treated with TAC was 69 % for the 1-3 stratum (hazard ratio = 1.38 versus FAC) and 52 % for the 4+ stratum (hazard ratio = 1.40). The expected 5-year DFS for all TAC patients was 0.70 (69 %) + 0.30 (52 %) = 63.9 %.

Analysis Populations:
The primary statistical analysis for each of the efficacy endpoints was to include all randomized patients (intent to treat population).

Analysis Methods
The analysis for the primary endpoint was planned to be the log-rank test in the ITT population. All tests of hypotheses were to be two-sided. Confidence intervals of the median survival were to be calculated using the Simon method.

Cox's multiple regression analysis was to be performed for DFS and OS to adjust the treatment comparison for major prognostic factors such as number of axillary lymph nodes involved, age, menopausal status, type of surgery, histopathological findings, ER/PR status, tumor size and pathological markers. The covariates, which appear unbalanced at baseline, were to be added in the Cox model.

Interim and Follow-Up Analysis:
One interim efficacy analysis was planned 3 years after recruitment of 50% of the expected patients (708 patients). At the time of the interim analysis, all patients should have been recruited.

Except in the case of overwhelming interim results, the recommendation to use FAC or TAC in the target patients population was to be given after the final analysis (5-year analysis) at the discretion of the Steering Committee.
Some patients are expected to have a very long disease free survival. Consequently, a 10-year clinical follow-up was planned. Two confirmatory analyses to update DFS and OS are to be performed: one at 8 years and a final analysis at 10 years.

Nominal Significance Level:
For the analysis of disease free survival, the Peto stopping rule was incorporated at the nominal significance level of 0.001. The significance was to be adjusted due to the interim analysis of this endpoint in order to maintain the overall significance at 0.05 for the final analysis.

The SAP was amended by IDMC recommendation to implement a 2nd interim analysis and to set the significance level for the final analysis at 0.048.

Reviewer's Comments:
- The study was powered to detect superiority of TAC to FAC.
- The sample size amendment was appropriate.
- FDA agreed with the protocol amendments of the significance level for the final analysis.

6.3 Study Results

6.3.1 Patient Demographics/Disposition

Patient Demographics
The following results are from the sponsor's analyses and tables:
Enrollment:
One thousand four hundred ninety one patients from 112 centers worldwide were enrolled in the study, 745 on TAC and 746 on FAC. As of the data cut-off (July 15, 2003), the median duration of follow-up time is 61 months, which was similar for the two treatment arms.

The following table summarizes all countries and the number of patients enrolled. Seventy-one percent (71%) of the patient population was from North America, Spain and Poland.

Table 7 Clinical Sites Information (From sponsor's table page 818 of study report)

Country/Study Sites		Patients Enrolled N (%)		
		TAC	FAC	ALL
Canada	23	221 (29.7%)	217 (29.1%)	438 (29.4%)
USA	41	114 (15.3%)	128 (17.2%)	242 (16.2%)
Spain	14	97 (13.0%)	97 (13.0%)	194 (13.0%)
Poland	3	94 (12.6%)	95 (12.7%)	189 (12.7%)
United Kingdom	4	38 (5.1%)	39 (5.2%)	75 (5.0%)
Hungary	3	35 (4.7%)	30 (4.o%)	65 (4.4%)
France	1	23 (3.1%)	25 (3.4%)	48 (3.2%)
Brazil	2	20 (2.7%)	19 (2.5%)	39 (2.6%)
Sweden	2	17 (2.3%)	17 (2.3%)	34 (2.3%)
Israel	3	17 (2.3%)	14 (1.9%)	31 (2.1%)
Argentina	3	13 (1.7%)	17 (2.3%)	26 (2.3%)
Uruguay	2	11 (1.5%)	10 (1.3%)	21 (1.4%)
Greece	1	9 (1.2%)	7 (0.9%)	16 (1.1%)
Germany	1	8 (1.1%)	7 (0.9%)	15 (1.0%)
South Africa	1	8 (1.1%)	6 (0.8%)	14 (0.9%)
Egypt	2	5 (0.7%)	7 (0.9%)	12 (0.8%)
Austria	1	5 (0.7%)	6 (0.8%)	11 (0.7%)
Czech Republic	2	6 (0.8%)	5 (0.7%)	11 (0.7%)
Portugal	2	4 (0.5%)	3 (0.4%)	7 (0.5%)
Slovakia	1	0	1 (0.1%)	1 (0.1%)

Reviewer's Comments:

Detailed information on the length of follow-up was not included in the submission. As per FDA request, on June 16, 2004, the sponsor submitted complete information on the length of follow-up (see table below). Most of the patients (75%) have been followed for more than 4 years with 19% been followed for 5 years or more.

Table 8 Distribution of patients randomized by treatment and length of follow-up.

Length of Follow-up (months)	Arimidex Arm 745	Tamoxifen Arm 746	All Patients 1491
< 12	13 (1.7%)	16 (2.1%)	29 (1.9%)
12-to <18	14 (1.9%)	9 (1.2%)	23 (1.5%)
18- to <24	14 (1.9%)	20 (2.7%)	34 (2.3%)
24- to <30	11 (1.5%)	20 (2.7%)	31 (2.1%)
30 to <36	16 (2.1%)	28 (3.8%)	44 (3.0%)
36 to <42	17 (2.3%)	17 (2.3%)	34 (2.3%)
42 to <48	82 (11.0%)	87 (11.7%)	169 (11.3%)
48 to <54	231 (21.0%)	212 (28.4%)	443 (29.7%)
54 to <60	209 (28.1%)	197 (26.4%)	406 (27.2%)
≥ 60	138 (18.5%)	140 (18.8%)	278 (18.6%)

The primary analysis of efficacy included the ITT population. The table below shows the number of patients included in the ITT and safety populations. Of the 1491 randomized patients, 11 did not receive any study treatment: 1 in the TAC arm
and 10 in the FAC arm (eight were unhappy with randomized treatment and withdrew consent, one was lost to follow-up, one refused to be followed-up, one was not eligible for having a low neutrophil count and on one patient there was a misunderstanding of post-admission exclusion criteria). Patient # 12214 was randomized in the TAC group but received a combination of Taxotere®, doxorubicin and 5-fluorouracil (TAF) for the first three cycles by error and then 3 cycles of TAC. The sponsor analyzed this patient for efficacy and safety in her randomized group (TAC).

Table 9 Protocol ITT and Safety population

Patient (n)	TAC Arm	FAC Arm	All Patients (n)
ITT Population (patients randomized)	**745**	**746**	**1491**
Did not start therapy	**1**	**10**	**11**
Safety Population (patients who received study drug)	**744**	**736**	**1480**
Eligible Population	709	712	1421
Major violations	63	39	102

Patient Disposition

Protocol violations:

A protocol violation was defined as any infringement of the protocol selection criteria.

There were 70 ineligible patients, 36 in the TAC arm and 35 in the FAC arm. The table below shows the reasons for ineligibility. Most of these patients failed to have estrogen and progesterone receptors performed on the primary tumor prior to randomization.

Table 10 Reviewer's Table: Reasons for ineligibility (from sponsor's Tables 14 and 15)

Reason for non eligibility	TAC Arm	FAC Arm	All Patients (n)
ER/PgR not done or only one done	21	19	40
Margins in the definitive specimen	4	3	7
Distant metastases present	1	4	5
Prior anticancer treatment (> 7 days Tamoxifen)	2	2	4
Regional lymph node metastases	1	2	3
Contralateral mammogram not done or > 6 months prior to registration	2	1	3
ALAT, ASAT or bilirubin >ULN	2	1	3
Definitive breast cancer surgery > 70 days prior to randomization		1	1
Hemoglobin < 10 g/dL		1	1
LVEF < normal limit for institution		1	1
Alkaline phosphatase not done at baseline	2		2
Past history of neoplasm other than breast		1	1
Abdominal work-up not done	1		1
Total	36	36	72

Reviewer's Comments:

There were 5 patients in the TAC arm and 10 patients in the FAC arm that had major protocol violations at baseline (see table below).. The reviewer retrieved some information from the CRFs and requested the sponsor to provide further information on these patients.

Table 11 Major Protocol Violations

Protocol Violation	TAC Arm	FAC Arm
Margins in the definitive specimen	# 10703, # 11302: no additional surgery or adjuvant radiotherapy. At cut-off date, there were no events. # 12608: right mastectomy followed by adjuvant radiotherapy, one month after finishing chemotherapy treatment. At cut-off date, there were no events.	# 13612: had no record of additional surgery but the patient had adjuvant radiotherapy. No events at cut-off date. 17404, 26606 and 26608: no record of additional surgery but had adjuvant radiotherapy. At cut-off date, the patients had a distant recurrence.
Distant metastases present	#27302: supraclavicular node confirmed to be metastases at baseline. At cut-off date, the patient had local and distant recurrence.	#12212: at baseline liver ultrasound suspicious for liver involvement. Confirmed to be metastatic disease at cycle # 6. At cut-off date, there were no events reported. # 20613:bone scan showed tumor involvement. At cut-off date, the patient had a distant recurrence. # 21204:Baseline CT of the right supraclavicular area suspicious for tumor involvement. Confirmed at cycle #2. At cut-off date, there were no events. # 25501: Baseline bone scan and x-ray suspicious for tumor involvement. Indicative of metastasis at cycle #3. At cut-off date, the patient had a distant recurrence.
Regional lymph node metastases	#24507: N2 at baseline (ipsilateral lymph nodes fixed to each other or adjacent structures). At cut-off date, there were no events.	#18302: N2 at baseline. At cut-off date, there were no events. # 26807: N2 at baseline. At cut-off date, there were no events.
Other neoplasm at baseline		Patient # 30806 had a history of endometrial carcinoma. The diagnosis resulted from tests triggered by the presence of vaginal bleeding at baseline. At cut-off date the patient did not have any event.
Total	**5**	**11**

The protocol stated that in the absence of recurrent breast cancer, patients were not to receive additional chemotherapy after the completion of 6 cycles of study therapy. Eighty six patients, 58 (7%) in the TAC arm and 28 (4%) in the FAC arm, received additional antitumor therapy before any event. The sponsor states that reasons for administration, doses and schedule were not available since they were not reported.

Reviewer's Comments:
There were a higher number of protocol violation therapies in the TAC arm compared to the FAC arm. A review of the submitted CRFs showed the following non-allowed therapies were received prior to disease recurrence:

Table 12 Protocol violation therapies

Antitumor therapy before relapse	**TAC Arm 745 (100%)**	**FAC Arm 746 (100%)**	**All Patients 1491 (100%)**
Chemotherapy	33	12	45
Hormonotherapy	3	2	5
Surgery	1	0	1
Radiotherapy	2	3	5
Ovarian ablation	19	11	30
Total	58	28	86

The reasons for the investigator's deviation from protocol therapy (hormonotherapy, ovarian ablation and radiotherapy) were not recorded in the CRFs and according to the sponsor these are not available.
The medical reviewer retrieved information from CRF's and data listings and found the number of cycles of randomized therapy received, non-allowed chemotherapy and reasons for changing therapy (see table below). Most of the patients received non-allowed therapy due to withdrawal of consent and or adverse events. Five patients (2 in the TAC arm and 3 in the FAC arm) received additional therapy after completing 5 -6 cycles of the randomized therapy. The number of cycles of non-protocol therapy and the reason for receiving additional therapy were not recorded. The FDA reviewer asked the sponsor to complete the information regarding the number of cycles received of non-allowed therapy and reason for receiving non-protocol therapy. In a July 15, 2004, the sponsor provided information on 21 patients. For the remaining 24 patients, information was not available since it was not recorded in the CRFs.

Table 13 Patients starting non-allowed therapy known to prevent recurrence, during trial and prior to recurrence (Reviewer's table from CRFs)

Patient ID	TAC Arm 745 (100%)		FAC Arm746 (100%)	
	TAC	Other therapy received/ # cycles/ reason for not receiving randomized therapy	FAC	Other therapy received/ # cycles/ reason for not receiving randomized therapy
12502	1	FAC/ 5 cy/ AE: G3 vomiting, skin		
22502			6	FEC/Thiotepa/ unknown/ unknown
11207	1	AC/ 3 cy/ Patient request & AE:G3 stomatitis, abdominal pain, anorexia		
21202				FAC plus Taxotere/ 1 cy/ consent withdrawal
21716	2	FAC/ 4 cy/ consent withdrawal, AE: G2 diarrhea, nausea, alopecia		
21728	1	FAC/ 5 cy/ AE: G3 allergy		
21731	0	FAC/ 6 cy/ neutropenia prior to 1st chemotherapy		
21733	3	FAC/ 3 cy/ AE: G3 allergy		
11803	2	AC/ unknown cy/ AE: G3 skin		
12103	2	FAC/ 1 cy/ consent withdrawn, AE: lifethreatening colitis		
12109	4	FAC/ 2 cy/ AE increased creatinine		
12308	4	FAC/ 2 cy/ AE: fever with no infection		
12314	3	FAC/ 3 cy/ AE: fever with no infection		
12317	4	FAC/ 2 cy/ AE: generalized edema		
22312	2	FAC/ 4 cy/ AE: G3 allergy		
22702	2	FAC/ 4 cy/ AE: G2 allergy		
12002	1	AC/ unknown # cy/ withdrew consent & several G2 adverse events.		
22004	3	AC/ unknown # cy/ AE: G3 pulmonary		
20803			0	AC followed by Taxol/ unknown # cy/ consent withdrawn
21312			0	TAC/ unknown # cy/ consent withdrawn
12211	5	FAC/ 1 cy/ AE: fever with no infection, cardiac arrhythmia		
12214	3	TFA/ 3 cy/ investigator error		
25501			6	Taxotere/Pamidronate/ unknown # cy
15002	1	AC/ unknown # cy/ AE: enteritis		
15006	1	AC/ unknown # cy/ AE: G4 allergy		
25010	4	Epirubicin/Cyclophosphamide/ unknown # cy/ AE: fever with no infection		

Patient ID	TAC Arm 745 (100%)		FAC Arm746 (100%)	
	TAC	Other therapy received/ # cycles/ reason for not receiving randomized therapy	FAC	Other therapy received/ # cycles/ reason for not receiving randomized therapy
16301			3	Metotrexate/5FU/Genoxal/ unknown # cy/ G4 infection
13418	1	FAC/ 5 cy/ AE: G2 allergy		
26802	5	AC/ unknown # cy/ AE: G2 neurosensory		
23904	6	5FU/Carboplatin/Vblastin/ unknown # cy		
13705			0	TAC/ 6 cy/ withdrew consent
32311	2	FAC/ 4 cy/ AE: G3 allergy		
17608	2	AC/ unknown # cy/ withdrew consent		
27601			6	HDCT/ unknown # cy
27602	5	Thiotepa/Mitoxantrone/aminof/ unknown # cy/ AE: fever with no infection		
17902	2	FAC/ 4 cy/ AE: G3 allergy		
28402			4	Taxol/ unknown # cy/ investigator wanted to treat with taxol
17206	2	FAC/ 4 cy/ AE: cardiac ischemia G3		
29701	3	AC/ unknown # cy/ AE: fever with no infection		
17423			0	AC/Taxol/ unknown # cy/ withdrew consent
18001	2	CMF/ unknown # cy/ AE: G3 infection		
19201	1	AC/ unknown # cy/ AE: G3 allergy		
30301			0	AC/ unknown # cy/ misunderstanding of post admission exclusion criteria
42001			0	TAC/ unknown # cy/ consent withdrawn
40401	3	AC/ unknown # cy/ AE: fever with no infection		

Removal from study:

Seven percent of the patients withdrew from the study. A higher percentage of patients in the TAC arm withdrew due to adverse events and a higher percentage of patients in the FAC arm withdrew due to disease recurrence (see table below).

Table 14 Reason for withdrawal (modified from sponsor's Table 9 of Study Report)

Safety Population (patients who received study drug)	**TAC Arm 744 (100%)**		**FAC Arm 736 (100%)**		**All Patients 1480 (100%)**	
Safety-Related						
Adverse Event	45	(6)	8	(1.1)	53	(3.6)
Efficacy-Related						
Disease recurrence	1	(0.1)	4	(0.5)	5	(0.3)
Death irrespective of cause	2	(0.3)	2	(0.3)	4	(0.3)
Administrative						
Withdrawn Consent	17	(2.3)	17	(2.3)	34	(2.3)
Lost to follow-up	0	(0)	1	(0.1)	1	(0.1)
Other	1	(0.1)	3	(0.4)	4	(0.3)
Total	66	(8.9)	35	(4.7)	101	(6.8)

Four percent of the patients withdrew from the study due to adverse events (see table below). The most frequent adverse events leading to withdrawal were fever in the absence of infection (13) and allergy (9) in the TAC arm and infection (3) and cardiac dysfunction (2) in the TAC arm.

Table 15 Important adverse events leading to patient withdrawal (modified from sponsor's tables 10 and 11 of study report)

Safety Population (patients who received study drug)	TAC Arm 744 (100%)		FAC Arm 736 (100%)	
Vascular-Events				
Cardiac function	2	(0.3)	2	(0.3)
Cardiac ischemia	2	(0.3)		
Cardiac arrhythmia	0		1	(0.1)
Deep thrombophlebitis	0		1	(0.1)
Pulmonary embolus	1	(0.1)	1	(0.1)
Constitutional Symptoms				
Fever w/o infection	13	(1.7)	0	
Asthenia	2	(0.3)		
Allergy	9	(1.2)	0	
Gastrointestinal Events				
Nausea and vomiting	3	(0.4)		
Colitis/enteritis	4	(0.5)		
Diarrhea	2	(0.3)		
Stomatitis	1	(0.1)		
Large intestine perforation	1	(0.1)		
Renal				
Kidney function	1	(0.1)		
Blood/ Bone Marrow				
Thrombocytopenia	1	(0.1)		
Hemorrhage			1	(0.1)
Pain	2	(0.3)		
Infection	3	(0.4)	3	(0.4)
Neurology Events				
Mood change	1	(0.1)		
Neuro-cerebellar	1	(0.1)		
Neuro-sensory	1	(0.1)		
Metabolic/Laboratory				
Peripheral edema	1	(0.1)		
Transaminitis	1	(0.1)		
Skin Events	1	(0.1)		
Pulmonary Events				
Lung Fibrosis	1	(0.1)		
Not specified	2	(0.3)		

6.3.2 Patient Characteristics

The demographics and clinical characteristics of the intent-to-treat population are shown in the table below. There were no significant differences between the two treatment groups. The median age in each arm was 49 years. There was no significant difference in the distribution of performance status between arms. Laboratory tests and hematology parameters were balanced between the two arms. There were two patients with abnormal baseline hematologic findings. Patient # 12505 (FAC) had a grade 2 anemia and patient # 21731 (TAC) had a grade 2 neutropenia. Two patients in the TAC arm (15406, 42206) and 4 in the FAC arm (15501, 11501, 11750, 22502) had LVEF below normal. The frequency of abnormal physical findings and vital signs at baseline were similar among the two treatment groups. The treatment arms were also balanced with respect to menopausal status at baseline. See Table below.

Table 16 Demographic characteristics (modified from sponsor's Table 16 of Study Report)

Characteristics	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Age (median)	49	49
< 35	52 (7)	36 (5)
35-49	349 (47)	358 (48)
50-64	296 (40)	311 (42)
≥ 65	48 (6)	41 (6)
Karnofsky Performance Status (median)	100	100

Previous breast cancer treatment:
The proportion of patients who had previous mastectomy, breast conservation, axillary lymph node surgery and radiation therapy is comparable between the two treatment groups.

Table 17 Summary of surgical procedures.

Surgical procedure	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Mastectomy	445 (60)	438 (59)
Breast conservation	300 (40)	308 (41)

Reviewer's Comments:
The treatment groups are well balanced with respect to previous treatment received for breast cancer. Ten patients had prior anti-tumor treatments: surgery (1 patient in the FAC arm), radiotherapy (1 patient in the TAC arm and 3 in the FAC arm), chemotherapy (1 patient in the

TAC arm) and hormonotherapy (2 patients in the TAC arm and 2 in the FAC arm). However, there are no differences between treatment arms.

Tumor Characteristics:
Invasive ductal carcinoma was the most common histopathological type. Most of the tumors were moderately differentiated. Poorly differentiated tumors were evenly distributed among the two arms. For the majority of patients in all treatment arms the primary tumor size was less than 5 cm. Three patients had N2 involvement (1 patient in the TAC arm and 2 in the FAC arm). Five patients had metastatic disease at baseline (1 patient in the TAC arm and 4 patients in the FAC arm. Estrogen-receptor status was comparable between treatment arms. Seventy-six percent of the patients were estrogen receptor positive or estrogen receptor negative/progesterone positive, 24% were estrogen receptor negative or unknown.

Table 18 Summary of tumor characteristics

Tumor Characteristics	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Tumor dimension		
T1: ≤ 2	296 (40)	320 (43)
T2: $2 \leq 5$	392 (53)	383 (51)
T3: >5	57 (8)	43 (6)
Nodal Status		
N1: metastasis to movable ipsilateral axillary nodes	744 (99)	744 (99)
N2: metastasis to ipsilateral axillary nodes fixed to each other and to structures	1 (0.1)	2 (0.3)
Distant metastasis		
M0	744 (99)	742 (99)
M1	1 (0.1)	4 (0.5)
Tumor grade		
Well differentiated	134 (18)	129 (17)
Moderately differentiated	346 (46)	325 (44)
Poorly differentiated/undifferentiated	259 (35)	288 (39)
Not assessed/Not recorded	6 (0.8)	4 (0.5)
Tumor margins		
Free	742 (99)	743 (99)
Involved by tumor	3 (0.4)	3 (0.4)
Hormone receptor status		
Positive ER and/or PgR	567 (76)	565 (76)
Negative ER and PgR	175 (23)	178 (24)
Unknown	3 (0.4)	3 (0.4)

Axillary lymph nodes:
Number of axillary lymph nodes was a stratification variable for the study. Nine hundred twenty six patients (62.1%) were found to have 1-3 positive nodes and 565 patients (37.9%) were found to have 4+ positive nodes. At the time of data validation, the sponsor found that 9 patients (0.6%) have been misclassified. Six (6) patients randomized to the 1-3 positive nodes stratum had more than 4 positive nodes (4 in the TAC arm and 2 in FAC arm). Three (3) patients randomized to the 4+ positive nodes stratum had 1-3 positive nodes (all treated in the FAC arm). As per protocol and SAP, the efficacy analyses were conducted according to the intention-to-treat population, and therefore used the information available at time of randomization.

Table 19 Characteristics of axillary lymph nodes (modified from sponsor's Table 21 of Study Report)

Axillary Lymph Nodes Characteristics	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Median number of resected lymph nodes	14	14
Number of positive lymph nodes		
1-3	463 (62)	460 (62)
≥ 4-10	222 (30)	232 (31)
> 10	60 (8)	54 (7)
Positive lymph nodes per randomization		
1-3	467 (63)	459 (62)
≥ 4	278 (37)	287 (38)

Reviewer's comments:
The median number of resected axillary lymph nodes was 14 in both treatment arms. There was a similar range and frequency distribution between the maximum and minimum number in each arm and by strata for axillary node involvement within each treatment arm. Although a small number of patients were randomized in the wrong stratum, the distribution was similar between the two treatment arms.

Prior history of other tumors:
Forty-four patients (3.0%) had a history of other tumors; 23 (1.5%) within the last 10 years. In situ carcinoma of the cervix (17 cases, 38.6%) and basal cell skin carcinoma (8 cases, 18.2%) were the most commonly identified types. The type and timing of previous neoplasms was similar for both TAC and FAC.

6.3.3 Treatment Delivered

Study Therapy:
Of the 1491 randomized patients, 1480 received trial treatment, 744 (50.3%) were treated with TAC, and 736 (49%) were treated with FAC. Eleven patients in the two arms did not start

therapy, 1 in the TAC arm, and 10 in the FAC arm. One patient (#12214) in the TAC arm started the wrong therapy. The patient received a combination of Taxotere®, doxorubicin and 5-fluorouracil (TAF) for the first three cycles by error and then 3 cycles of TAC. The sponsor analyzed this patient for efficacy and safety in her randomized group (TAC). Four patients, 2 on each arm died during treatment. Of these four, three died from pulmonary embolism (TAC: 26302, 16506, FAC: 25801) and one on the FAC (21311) arm from hypovolemic shock. One hundred one (7%) patients withdrew from the study. A higher number of patients withdrew in the TAC arm compared to the FAC arm (see Table 9 for reasons for withdrawal).

Table 20 Treatment Status

Treatment status	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Patients randomized	745 (100)	746 (100)
Treatment not started	1 (0.1)	10 (1.5)
Treatment misallocation	1 (0.1)	0
Treatment started	744 (99)	736 (98)
Treatment withdrawn	64 (8.6)	33 (4.4)
Patients died during treatment	2 (0.3)	2 (0.3)

Adjuvant hormonotherapy

Ninety-four percent of the hormone receptor positive patients in each arm received tamoxifen. Fifty-eight ER/PR positive patients (26 in the TAC arm and 32 in the FAC arm) did not receive hormonal therapy. However, the reason for the investigators' decision not to treat these patients with hormonal therapy was not a datum that was reported in the case report form; therefore it is not available in the clinical database.

At the time of the current interim analysis the median duration of tamoxifen treatment was 4.0 years for both TAC and FAC arms. More than 80% of subjects receiving tamoxifen in each treatment arm had done so for at least 3 years.

Adjuvant Radiotherapy:

According to the protocol, adjuvant radiotherapy was to be given to patients who had undergone breast conserving surgery or mastectomy, if recommended by institution guidelines. The table below describes the administration of radiotherapy in patients by type of surgery. Compliance with the protocol requirement for radiotherapy in the setting of breast-conserving surgery was high. Only 2.0% and 1.4% of TAC-and FAC-treated patients, respectively, did not received radiotherapy. The use of radiotherapy in the setting of a mastectomy was decided according to individual institution guidelines and was well balanced between the two treatment groups.

Table 21 Adjuvant radiotherapy

Adjuvant Radiotherapy	TAC Arm 745 (100%)	FAC Arm 746 (100%)
Any adjuvant radiotherapy	512	529
Breast conserving surgery	300	303
With radiotherapy	285	293
Without radiotherapy	15	10
Mastectomy	444	433
With radiotherapy	227	236
Without radiotherapy	217	197

Subsequent therapy

For patients who had disease recurrence, details of the first therapy received after recurrence is provided in the table below.

Table 22 Treatment after first recurrence

Subsequent Therapy	TAC Arm 745 (100%)		FAC Arm 746 (100%)	
Patients who recurred	144		197	
Chemotherapy	84	(58)	136	(69)
Hormone Therapy	44	(30)	63	(32)
Radiotherapy	22	(15)	40	(20)
Surgery	21	(15)	26	(13)
Other	22	(15)	34	(17)

Information on non-allowed therapy prior to recurrence was supplied in Table 13 from the Protocol Violation Section.

Biphosphonates therapy

The protocol did not prohibit the concomitant use of biphosphonates. The sponsor was asked to provide information on biphosphonates use. Thirty-eight patients, 17 in the TAC treatment arm and 21 in the FAC arm, received bisphosphonates after randomization.

Reviewer's Comments:
The potential role of biphosphonates in the adjuvant setting is not well defined. Biphosphonates use was reported in a higher percent of patients on the TAC arm. Since this is a relatively small numbers of patients, the difference is not likely to affect the outcome of the study.

6.4 Efficacy Findings

For reporting the primary efficacy parameter, disease-free survival (DFS), the sponsor used the intent-to-treat population. At the data cut-off, the median duration of follow-up was 55 months. The submitted NDA report is based on the results of the 2nd interim analysis that was to be conducted after 400 DFS events had been recorded. Based on the event rate observed in the study population subsequent to the first, the sponsor predicted 15 July 2003 as the best estimate for a cut-off date at which time 400 DFS events would have been recorded. At this date, 399 DFS were recorded.

6.4.1 Sponsor's Analysis of Disease Free Survival

At the cut-off date of 15 July 2003, a total of 399 patients (27%) had an event (including disease recurrence, second primary malignancies and death from any cause). One hundred seventy two of the 745 patients in the TAC arm had disease recurrence (23%) compared to 227 of the 746 patients in the FAC arm (30%). TAC is associated with a 28% relapse risk reduction compared to FAC (HR 0.72, 95% CI 0.59-0.88). DFS was significantly different between the two treatment arms using the logrank test stratified on the number of axillary lymph nodes involved at randomization (logrank p-value = 0.001) The table below summarizes the recurrence status.

Table 23 Type of primary disease free survival event (summary from sponsor's Table 29 of Study Report)

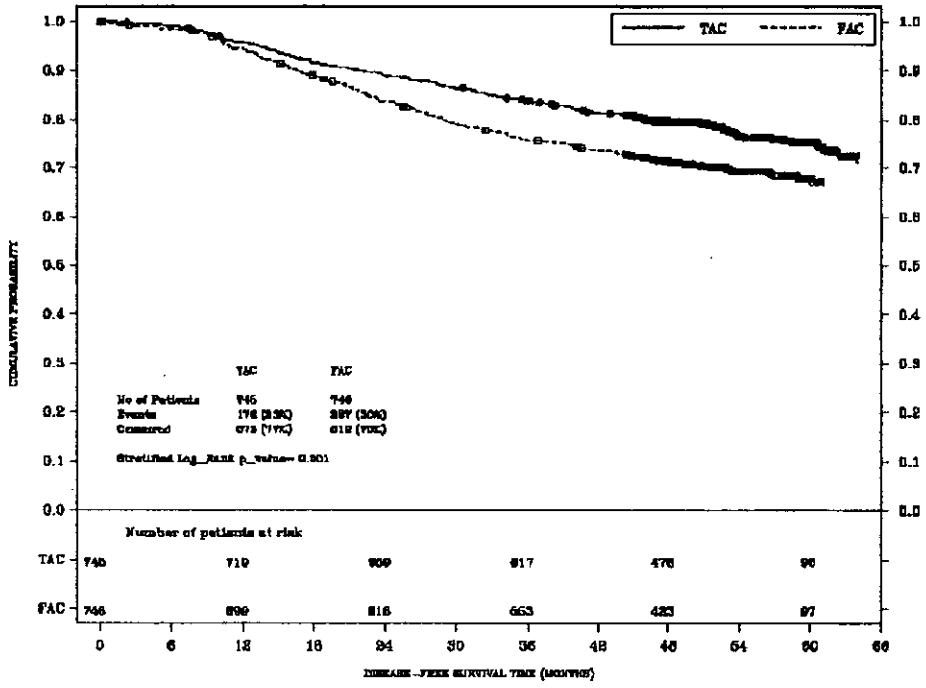
Recurrence Status	TAC Arm 745 n (%)	FAC Arm 746 n (%)
Total number of events	172 (23.1)	227 (30.4)
Breast cancer relapse	144 (83.7)	197 (86.8)
Loco-regional recurrence	29 (16,8)	39 (17)
Distant recurrence	115 (66.8)	158 (69.6)
Second primary malignancy	20 (11.6)	26 (11.5)
Contralateral breast	7	8
Endometrium	0	4
Ovarian	0	1
Leukemia	2	0
Other	11	13
Deaths Unrelated to breast cancer	8 (4.6)	4 (1.8)

The sponsor's reasons for censoring DFS in the efficacy analysis are described in the table below. Twenty-one patients were lost to follow-up (8 in the TAC arm and 13 in the FAC arm). In addition, 1 patient in each arm did not have an appropriate disease assessment available. Event-free patients were censored in the DFS analysis with absence of evidence of breast cancer relapse, secondary malignancies or death.

Table 24 Reasons for censoring

Reasons for censoring	TAC Arm 745 n (%)	FAC Arm 746 n (%)
Lost to follow-up	8 (1.1)	13 (1.7)
No follow-up visits	1 (0.1)	1 (0.1)
No BCR, SPM or death	564 (75.7)	505 (67.7)
Total Censored patients	573 (76.9)	519 (69.6)

Figure 1 – Disease-Free Survival – ITT Analysis – by Randomization Group



As specified in the protocol, DFS analysis was done within each of the two strata 1-3 and 4 or more positive axillary lymph nodes (see table below). In the stratum 1-3 positive nodes, seventy-six of the 467 patients in the TAC arm had an event compared to 114 of the 459 patients in the FAC arm. These data showed a 39% reduction in the risk of disease recurrence for TAC arm patients (hazard ratio 0.61, p=0.0009). In the 4 or more positive axillary lymph nodes

stratum, 96 of the 278 patients in the TAC arm and 113 of the 287 patients in the FAC arm had an event. For these stratum, has a 17% reduction in the risk of disease recurrence (hazard ratio 0.83, p=0.1663) compared to patients treated in the FAC arm. This difference did not reach statistical significance.

Table 25 Disease free survival per axillary lymph nodes (modified from sponsor's Table 28 of Study Report)

Number of + axillary lymph nodes	Recurrence Status	TAC Arm 745 n (%)	FAC Arm 746 n (%)
ITT	Events	172 (23.1%)	227 (30.4%)
	5-year DFS	75%	68%
	Hazard ratio/ 95% CI	0.72 (0.59 – 0.88)	
	P-value (2-sided)	p=0.001	
1-3 + nodes	Events	76 (16%)	114 (25%)
	5-year DFS	82%	74%
	Hazard ratio/ 95% CI	0.61 (0.46 – 0.82)	
	P-value (2-sided)	p=0.0009	
≥ 4 + nodes	Events	96 (35%)	113 (39%)
	5-year DFS	64%	58%
	Hazard ratio/ 95% CI	0.83 (0.63– 1.08)	
	P-value (2-sided)	p=0.1663	

Subgroup Analyses:
Subset analyses by hormone receptor status and HER 2 Neu status were prespecified in the Statistical Analysis Plan. The reduction in disease recurrence was also seen in these subgroup of patients, in favor of the TAC arm (see table below).

Table 26 Subgroup Analyses for DFS (modified from sponsor's Table 31 of Study Report)

Subgroups	TAC n	FAC n	Hazard Ratio TAC/FAC	95% CI	p-value 2-sided
Hormonal Receptor Status					
Negative	178	181	0.69	(0,49 – 0.97)	0.0296
Positive	567	565	0.72	(0.56 – 0.92)	0.0076
Her 2 Neu Status					
Negative	475	468	0.76	(0,59 – 1.00)	
Positive	155	164	0.60	(0.41 – 0.88)	
Unknown	115	114	0.72	(0.45 – 1.17)	

Reviewer's Comments:
The sponsor did not submit data on the sites of loco-regional recurrence.

6.4.2 FDA's Analysis of Disease Free Survival

FDA does not agree with the protocol's definition of disease-free survival: "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 occurs first".
Currently there is no standard definition of disease free survival. However, FDA had accepted in previous applications the following components of this composite endpoint: local recurrence, distal recurrence, contralateral breast new primaries and unrelated deaths. Second primary cancers are considered unrelated to the primary breast cancer and therefore cannot be accepted as an event for disease-free survival.

The FDA analysis of disease-free survival includes the following differences from the sponsor's analysis:

- Thirty-one patients who had events due to second primary malignancy are censored at the time of diagnosis except patients with contralateral breast primary malignancy who are counted as DFS event. Patients who died are counted as death events.

Table 27 Patients with second primary malignancy

Patients with second primary malignancy as DFS events	**TAC Arm**	**FAC Arm**
Second Primary Malignancy	12105, 13510, 13707, 15601, 17501, 20701, 21715, 22313, 24508, 25102, 26609, 31201, 40701	10301, 11730, 12312, 12503, 13423, 14535, 15101, 15801, 16204, 17413, 17502, 17901, 18601, 20504, 23405, 23915, 25901, 26810
Contralateral breast primary malignancy	10506, 13408, 14201, 15109, 18201, 21007, 26803	10714, 14431, 23908, 24301, 24305, 24513, 25805, 26306
Total	**20**	**26**
Patients who died	40701, 21715, 15601, 13510	18601, 17901, 15801, 10301

- Fifteen patients were found to have major protocol violations at baseline (5 in the TAC arm and 10 in the FAC arm). Five patients (one in the TAC arm and 4 in the FAC arm) with distant metastases at baseline are excluded from the analysis. Patients with regional lymph node metastases and positive margins in the definite specimen were not excluded because they did not have a DFS event at the cut off date. See Table below.

Table 28 Patients with a major protocol violation at baseline

Protocol Violation	TAC Arm	FAC Arm
Regional lymph node metastases	24507	18302, 26807
Margins in the definitive specimen	10703, 11302, 12608	13612, 17404, 26606, 26608
Distant metastases present	27302: supraclavicular node confirmed to be metastases at baseline.	12212: at baseline liver ultrasound suspicious for liver involvement. Confirmed to be metastatic disease at cycle # 6. 20613:bone scan showed tumor involvement. 21204:Baseline CT of right supraclavicular area suspicious for tumor involvement. Confirmed at cycle #2. 25501: Baseline bone scan and x-ray suspicious for tumor involvement. Indicative of metastasis at cycle #3.
Total	**5**	**10**

- Given the imbalance in post-therapy treatment before documentation of progressive disease, 43 patients (32 in the TAC arm and 11 in the FAC arm) are censored at the time they start non-protocol chemotherapy prior to recurrence. This will decrease the likelihood that a benefit that resulted from the new therapy is mistakenly attributed to the study therapy.

Table 29 Patients with post-therapy treatment before documentation of progresive disease

	TAC Arm	FAC Arm
Patient	12502, 13418, 26802, 23904, 32311, 17608, 11207, 27602, 17902, 17206, 29701, 18001, 19201, 40401, 21716, 21728, 21731, 21733, 11803, 12103, 12109, 12308, 12314, 12317, 22312, 22702, 12002, 22004, 12211, 15002, 15006, 25010	22502, 16301, 13705, 27601, 28402, 17423, 21202, 30301, 42001, 20803, 21312
Total	**32**	**11**

- Thirty patients (19 in the TAC arm and 11 in the FAC arm) had ovarian ablation (surgical or radiotherapy) before relapse. From these patients, 7 were premenopausal (6 TAC arm and 1 in the FAC arm) and are censored at the time of treatment.

Table 30 Premenopausal patients who had ovarian ablation

	TAC Arm	FAC Arm
Patients	12402, 13601, 13607, 15306, 17104, 25008	16602
Total	**6**	**1**

At the cut-off date of 15 July 2003, 172 of the 745 (23%) patients treated in the TAC arm had an event (recurrence, death or second primary malignancies) compared to 227 of the 746 (30%) patients treated with FAC. This difference is equivalent to a 28% reduction the risk of relapse for the TAC arm (hazard ratio 0.72, p=0.0001. Although the protocol prohibited additional therapy prior to clinical evidence of progression, 49 patients in the TAC arm and 14 patients in the FAC arm, started post-study treatment before progressive disease.

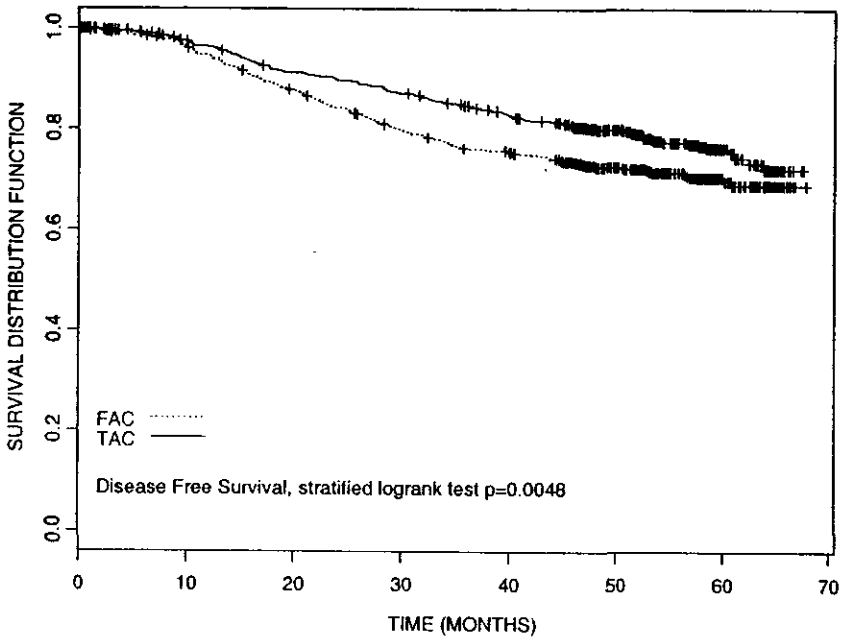
The following table summarizes the DFS results using FDA's analysis.

Table 31 DFS events by FDA's analysis

Recurrence Status	TAC Arm 744 n (%)	FAC Arm 742 n (%)
Total number of events	156	206
Breast cancer relapse	137	190
Contralateral breast	7	8
Deaths Unrelated to breast cancer	12	8
Hazard Ratio 95% CI	0.743 (0.604, 0.915)	
Log-Rank p-value	P= 0.0048	

Reviewer's Comments:

- Regardless of the method used (Sponsor ITT analysis or FDA's analysis as described above), treatment with TAC resulted in a significantly longer disease free survival.
- The disease free survival of the control arm (FAC) is comparable to those cited in the literature.
- This finding represents significant clinical benefit



6.4.3 Sponsor's Analysis of Overall Survival

At the time of data base closure (July 15, 2003), and with a median follow-up time of 55 months, 221 (15%) patients had died in the study. Ninety-one (12%) patients in the TAC arm died versus 130 (17%) in the FAC arm. The stratified log-rank p-value was 0.008 and the Hazard risk ratio was 0.70. The survival analysis results are summarized in the following table.

Table 32 Subgroup Analyses by axillary lymph node status for overall survival (modified from sponsor's Table 35 of Study Report)

Subgroups	TAC n	FAC n	Hazard Ratio TAC/FAC	95% CI	p-value 2-sided
ITT Population	91	130	0.70	(0,53 – 0.91)	0.008
1-3 Nodes	30	63	0.45	(0,29 – 0.70)	0.0002
≥ 4	61	67	0.94	(0,66 – 1.33)	0.7224

Table 33 Survival status (from sponsor's table 33 of study report)

Survival Status	TAC Arm 745	FAC Arm 746
Alive	654 (88%)	616 (83%)
Dead	91 (12%)	130 (17%)
Breast cancer	78 (10%)	116 (15%)
Other reasons	13 (2%)	14 (2%)

6.4.4 FDA's Analysis of Overall Survival

At the time of data base closure, 221 patients had died in the study. Median survival was not available since there have not been enough events. The incidence of all deaths was higher in the FAC arm. A majority of deaths in all treatment groups were considered by the investigators to be due to progressive disease.

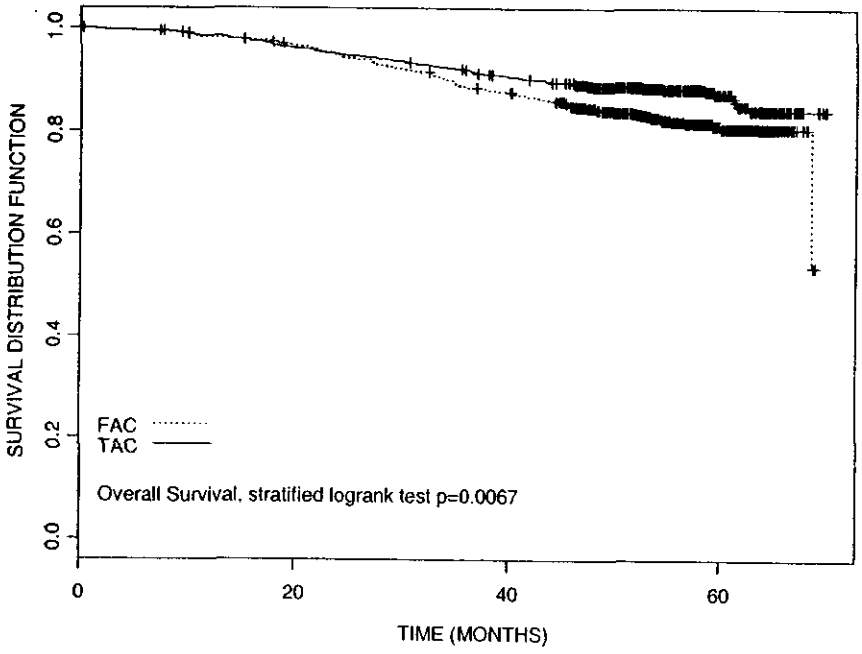
Overall survival appears to be longer for the docetaxel containing combination regimen (TAC) than for the FAC regimen: hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90, p-value= 0.0067 (not statistically significant when adjusted for interim analyses). At the time of this interim analysis, the overall relative reduction in the risk of death appears to be 31%. See Table below.

Survival Status	TAC Arm 745		FAC Arm 746	
Total number of events	91	(12)	130	(17))
Breast cancer	78	(10)	116	(15)
Other	13	(2)	14	(2)
New primary followed by death	4	(0.5)	4	(0.5)
Unrelated to breast cancer	8	(1.1)	8	(1.1)

The Table below describes the results of subgroup analyses for OS:

Subgroups	TAC Arm 745		TAC Arm 745		Hazard Ratio TAC/FAC	95% CI	P-value 2-sided
ITT	91	(12)	130	(17))	0.69	(0.53, 0.90)	0.0067
1-3 Nodes	30	(6)	63	(14)	0.45	(0.29, 0.70)	0.0002
≥ 4	60	(22)	66	(23)	0.93	(0.66, 1.32)	0.6823
Receptor +	50	(9)	71	(13)	0.69	(0.48, 0.99)	0.0408
Receptor -	40	(22)	58	(32)	0.66	(0.44, 0.98)	0.0389

The figure below gives the Kaplan-Meir Plot of overall survival in the two treatment arms.



Reviewer's Comments:
Survival data is not mature at the time of the 2nd interim analysis. The sponsor should submit follow-up data at the time of study completion and when survival data matures.

6.5 Efficacy Conclusions

Study TAX316 primary endpoint, disease-free survival (DFS) included local and distant recurrences, contralateral breast cancer second primary malignancies and deaths from any cause. FDA does not agree with the protocol's definition of disease-free survival: "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 occurs first".
Currently there is no standard definition of disease free survival. However, FDA had accepted in previous applications the following components of this composite endpoint: local recurrence, distal recurrence, contralateral breast new primaries and unrelated deaths. Second primary cancers are considered unrelated to the primary breast cancer and therefore can not be accepted as an event for disease-free survival.

Results from a second interim analysis at 55 months of median follow-up and using FDA's definition of disease-free survival which included local and distant recurrences, contralateral breast cancer and deaths from any cause, showed that docetaxel containing combination regimen (TAC) had significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0048). The overall reduction in risk of relapse was 25.7% for TAC- treated patients.

Overall survival appeared to be longer for the docetaxel containing combination regimen (TAC) than for the FAC regimen (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90; p-value not statistically significant when adjusted for interim analyses). At the time of this interim analysis, the overall relative reduction in the risk of death appears to be 31%.

7 Integrated Review of Safety

7.1 Methods and Findings

In both treatment groups, most patients had at least one adverse event reported during the study (100% in the TAC arm and 99.7% in the FAC arm). The number of Grade 3-4 or COSTART severe adverse events was higher in the TAC arm (36.3%) than the FAC arm (26.6%). Forty-five (6.0%) patients in the TAC arm discontinued study therapy due to an adverse event compared to 8 (1.1%) patients in the FAC arm. There were 2 deaths, within 30 days of the treatment period, one in each treatment arm, attributed to drug toxicity.

In the 744 patients in the TAC treatment arm, the 10 most common TEAEs (regardless of severity grades), in the order of decreasing frequency, were: alopecia (97.8%), anemia (91.5%), asthenia (80.8%), nausea (80.5%), neutropenia (71.4%), stomatitis (69.4%), amenorrhea (61.7%), fever in absence of infection (46.5%), vomiting (44.5%) and pain (44.5%). Among the 736 patients in the FAC arm, the 10 most common TEAEs in the order of decreasing frequency were: alopecia (97.1%), nausea (88.0%), neutropenia (82.0%), anemia (71.7%), asthenia (71.2%), vomiting (59.2%), stomatitis (52.9%), amenorrhea (52.4%), pain (37.5%), and infection (36.3%).
The rate of observation of TEAEs was higher for TAC than FAC in most but not all instances. The following events occurred more frequently in TAC than in FAC with a >10% difference: fever in absence of infection, febrile neutropenia, fluid retention, anemia, myalgia, stomatitis, neuro-sensory, taste perversion, thrombocytopenia, and arthralgia. Vomiting and neutropenia were observed more frequently in FAC than TAC, with greater than 10% difference.

While the overall rate of TEAEs was high, severe events (NCI grades 3 and 4, or severe/lifethreatening for COSTART terms) were infrequent with the exception of neutropenia (65.5% and 9.3% for TAC and FAC arms, respectively).

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Table 34 Important adverse events regardless of causal relationship (Modified from Sponsor's Table 47 of Study Report)

Adverse Event	TAC Arm 744 N (100%)		FAC Arm 736 N (100%)		P values
ALOPECIA					
All Grades	728	(97.8)	715	(97.1)	0.4844
ANEMIA					
All Grades	680	(91.5)	526	(71.7)	<0.0001
Grade ≥ 3	32	(4.3)	12	(1.6)	0.0041
NEUTROPENIA					
All Grades	530	(71.4)	600	(82)	<0.0001
Grade ≥ 3	486	(65.5)	361	(49.3)	<0.0001
FEBRILE NEUTROPENIA					
All Grades	183	(24.7)	18	(2.5)	<0.0001
FEVER WITHOUT INFECTION					
All Grades	346	(46.5)	126	(17.1)	<0.0001
Grade ≥ 3	10	(1.3)	0	(0)	0.0045
INFECTION					
All Grades	293	(39.4)	267	(36.3)	0.2389
Grade ≥ 3	29	(3.9)	16	(2.2)	0.0751
THROMBOCYTOPENIA					
All Grades	293	(39.4)	203	(27.7)	<0.0001
Grade ≥ 3	15	(2.0)	9	(1.2)	0.3162
HYPERSENSITIVITY REACTIONS					
All Grades	100	(13.4)	27	(3.7)	<0.0001
Grade ≥ 3	10	(1.3)	1	(0.1)	0.0163
PERIPHERAL EDEMA					
All Grades	251	(33.7)	93	(12.6)	<0.0001
Grade ≥ 3	4	(0.5)	1	(0.1)	0.3768
NEUROSENSORY					
All Grades	190	(25.5)	75	(10.2)	<0.0001
Grade ≥ 3	0	(0)	0	(0)	1
NAUSEA					
All Grades	599	(80.5)	648	(88)	<0.0001
Grade ≥ 3	38	(5.1)	70	(9.5)	0.0016
VOMITING					
All Grades	331	(44.5)	436	(59.2)	<0.0001
Grade ≥ 3	32	(4.3)	54	(7.3)	0.0171
STOMATITIS					
All Grades	516	(69.4)	389	(52.9)	<0.0001
Grade ≥ 3	53	(7.1)	15	(2.0)	<0.0001

Adverse Event	TAC Arm 744 N (100%)		FAC Arm 736 N (100%)		P values
SKIN TOXICITY					
All Grades	197	(26.5)	130	(17.7)	<0.0001
Grade ≥ 3	6	(0.8)	3	(0.4)	0.5141
DIARRHEA					
All Grades	262	(35.2)	205	(27.9)	0.0028
Grade ≥ 3	28	(3.8)	13	(1.8)	0.0291
CARDIAC DYSRHYTHMIAS					
All Grades	59	(7.9)	44	(6.0)	0.1697
Grade ≥ 3	2	(0.3)	2	(0.3)	1
PULMONARY EMBOLUS					
All Grades	5	(0.7)	4	(0.5)	1
Grade ≥ 3	3	(0.4)	1	(0.1)	0.6242
COLITIS					
All Grades	6	(0.8)	1	(0.1)	0.1333
Grade ≥ 3	4	(0.5)	0	(0)	0.1359
LARGE INTESTINE PERFORATION	1	(0.1)	0	(0)	1
All Grades	1	(0.1)	0	(0)	1
Grade ≥ 3					

7.1.1 Deaths

The incidence of all deaths (related and unrelated) was higher in the control arm (91 deaths or 12.2% in the TAC therapy arm and 129 deaths or 17.5% in the FAC arm).

The incidence of treatment-related deaths occurring during study period was higher (3 deaths) in the TAC therapy arm (one death in the FAC arm). Three patients died from massive pulmonary embolism and one patient died from hypovolemic shock secondary to a hemothorax after a catheter placement. A majority of deaths in both treatment groups were considered by the investigators to be due to progressive disease and unrelated to treatment. The following table summarizes key information regarding deaths in this trial:

Table 35 Mortality during treatment or follow-up period (Modified from sponsor's Tables 56, 58)

General Cause of Death	Specific Cause of Death	Cycle/day Days from last IV	Treatment Arm	
			TAC Patient ID (age)	FAC Patient ID (age)
Death < 30 days of study treatment				
Treatment Related	Massive pulmonary embolism	C2/D14-19 C4/D2	26302 (61) 16506 (51)	25801 (59)
	Hypovolemic Shock due to hemothorax (catheter)	C4/D6	21311 (56)	
Death < 30 days of study treatment				
Treatment Related	Cardiac arrhythmia or cardiomyopathy	C6/D992 C6/D892 C6/D729	27202	 10301 16703
Other chemotherapy	Febrile neutropenia	D1179		10625
Other malignancy	Leukemia	D959 D1333 D1461	40701 13510	 24105
	SCC Esophagus	D1135	21715	
	Adrenal Carcinoma	D1123	15601	
	Lung Cancer	D1348 D80		15801 18601
	Pancreatic Cancer	D792		17901
Other	Cardiac arrest	D694 D191	21710	 40301
	Cardiomyopathy	D556	10403	
	Suicide	D51 D658 D235	22204 30807	 18402
	Intracerebral hemorrhage	D209	24519	
	Hypercalcemia	D1275		23203
	Portal vein thrombosis	D37		27304
	Unknown, can not rule out metastases	D984	24107	
Breast Cancer			**78**	**116**
Total Number of Deaths			**91**	**130**

Reviewer's Comment:

- Overall, the most common cause of death was progressive disease, which accounted for more deaths on the FAC arm than on TAC arm.
- There is no apparent difference in death rate from complications of therapy between the two treatment arms.
- Difference between the categories for cause of death is somewhat artificial. The sponsor attributes two deaths, one on the TAC arm (#21710) and one on the FAC arm (#27304), to "other causes", after reviewing the patients narratives the reviewer concludes that these deaths could also be attributed to progressive disease.

7.1.2 Second Primary Cancers

Twenty-nine (4%) patients in the TAC arm and 33 (4%) patients in the FAC arm were reported to develop second primary malignancy. These tumors are summarized in the table below:

Table 36 Second malignancy

Neoplasm	TAC Arm 745	FAC Arm 746
Contralateral Breast Cancer	10506, 13408, 14201, 15109, 18201, 21007, 22202, 26803, 28101	10714, 12003, 14431, 21704, 23908, 24301, 24305, 24513, 25805, 26306, 11403
Lung	17501, 31201, 20701	17502, 15801, 18601
Basal Cell Carcinoma Melanoma Non-melanoma sq.	24103, 16201, 17904 26609 26202 10617	18102 23915, 22501, 25901 28104
Lymphoma	30002	
Colorectal	25102	23405, 17413, 12312 13423, 20504, 14535
Cervical Cancer	13707	
Endometrial		10301, 11730, 12111 12503, 26810
Ovarian	14402	15101
Kidney	24508	
Retroperitoneal	15601	
Leukemia	13510, 40701	24105
Pancreatic		17901
Esophagus	21715	
Bladder		16204
Thyroid	22313, 12105	
Total	**29 (4%)**	**34 (4%)**

Reviewer's Comments:

- A similar number of patients in the two treatment arms developed second primary malignancies.
- Four patients, three patients in the TAC arm and one patient in the FAC arm developed leukemia. Patient # 13510, was diagnosed with AML, 20 months after finishing study therapy (TAC). Patient # 40701 developed acute myelomonocytic leukemia, 2 years after completion of study therapy (TAC). No cytogenetic studies were performed. Patient # 24105 developed AML after receiving FAC chemotherapy and CMF for a breast cancer relapse. A fourth case of leukemia (patient # 10621, treated in the TAC arm) was also reported after the data base lock for the second interim analysis. Treatment effect can not be evaluated since the number of patients with secondary leukemias was small.
- The occurrence of 3 cases of leukemia in 745 patients treated with TAC represents an incidence of 0.4%. However, the true incidence of leukemia cannot be accurately estimated from the small numbers in this study.

The sponsor submitted additional information, which is included in the table below:

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Table 37 Secondary Leukemias from Study TAX316

Patient I.D.	10621	13510	40701	24105
Time since treatment start	4 years, 4 months	20 months	34 months	4 years, 3 months
Chemotherapy cumulative dose	T= 448 mg/m2 A= 299 mg/m2 C= 2991 mg/m2	T= 562 mg/m2 A= 293 mg/m2 C= 2935 mg/m2	T= 442 mg/m2 A= 294 mg/m2 C= 2948 mg/m2	F= 3002 mg/m2 A= 300 mg/m2 C= 3002 mg/m2
G-CSF	No	Yes 2 cycles	Yes	No
Radiotherapy dose	LR Chest: 50 Gy Supraclav: 50 Gy Post-axil:13.5 Gy	None	R. breast: 50 Gy R. boost chest wall: 14.40 Gy R. chest wall: 50.40 Gy Supraclav: 45 Gy	LR Breast: 50.4 Gy Axill: 50.4 Gy Supraclav: 50.4 Gy Breast: 16 Gy/F/u Hip: unknown
BM results	AML M4	AML M1	AML M4 Transformation of CLL	AML M4
Cytogenetics	11g23 (spMLLx2)(32)/(MLLx2)	(8-11)/(6p21;11g21); no fish results	Not available	Trisomy of 6, 21,22; no fish performed
Outcome	ongoing	Death	Death	Death
BC relapse	No	No	No	Yes

7.1.3 Other Serious Adverse Events

During the treatment period, a total of 268 TAC patients (36%) experienced a SAE, with 34.1% considered to be related to study treatment, 10.2% grade 3-4 or severe/life-threatening SAE, and 8.3% grade 3-4 or severe/lifethreatening SAE considered related to study therapy. In the FAC arm, a total of 68 patients (9.2%) had a SAE, with 6.7% considered related to study treatment, 4.9% grade 3-4 or severe/life-threatening SAE, and 2.6% considered treatment related.

Table 38 Serious adverse events (from sponsor's Table 53)

	TAC Arm 745	FAC Arm 746
During Treatment Phase		
Serious Adverse Events	268 (36)	68 (9)
SAE related to study treatment	254 (34)	49 (7)
Grade 3, 4, or severe SAE	76 (10)	36 (5)
Grade 3, 4, or severe SAE related to treatment	62 (8)	19 (3)
During the Follow-up period		
Serious Adverse Events	21 (3)	9 (1)
SAE related to study treatment	16 (2)	6 (1)
Grade 3, 4, or severe SAE	18 (2)	9 (1)
Grade 3, 4, or severe SAE related to treatment	14 (2)	6 (1)

The table below shows the most frequent SAE.

Table 39 Frequent Safety Adverse Events from Study TAX316

Adverse Event	TAC Arm 744 N (100%)		FAC Arm 736 N (100%)		P values
FEVER WITHOUT INFECTION					
All Grades	189	(25)	27	(3.7)	
Grade ≥ 3	7	(0.9)	0	(0)	
INFECTION					
All Grades	57	(7.7)	21	(2.9)	
Grade ≥ 3	23	(3.1)	11	(1.5)	
VOMITING					
All Grades	11	(1.5)	6	(0.8)	
Grade ≥ 3	5	(0.7)	6	(0.8)	
NAUSEA					
All Grades	8	(1.1)	3	(0.4)	
Grade ≥ 3	8	(1.1)	3	(0.4)	
DIARRHEA					
All Grades	6	(0.8)	1	(0.1)	
Grade ≥ 3	4	(0.5)	1	(0.1)	
PULMONARY EMBOLUS					
All Grades	5	(0.7)	4	(0.5)	
Grade ≥ 3	3	(0.4)	1	(0.1)	
ALLERGY					
All Grades	4	(0.5)	0	(0)	
Grade ≥ 3	3	(0.4)	0	(0)	
DEEP THROMBOPHLEBITIS					
All Grades	1	(0.1)	4	(0.5)	
Grade ≥ 3	1	(0.1)	3	(0.4)	
CARDIAC ARRHYTHMIA					
All Grades	0	(0)	2	(0.3)	
Grade ≥ 3	0	(0)	2	(0.3)	
GRANULOCYTES					
All Grades	2	(0.3)	1	(0.1)	
Grade ≥ 3	2	(0.3)	1	(0.1)	

7.1.4 Cardiac Toxicity

Most of the enrolled patients had normal cardiac function at baseline. Left ventricular ejection fraction (LVEF) was required to be measured at baseline and repeat measurements were only performed when considered clinically relevant by
the investigator. As a result, LVEF data are available in 66 patients (8.9%) in the TAC arm and 48 (6.5%) patients in the FAC arm. As shown in the table below, a ≥10% decline in LVEF was noted in 43.9% of patients in the TAC group (21.2% with a 10%-20% decline and 22.7% with a >20% decline) and in 31.2% in the FAC group (20.8% with a 10%-20% decline and 10.4% with

a >20% decline). All patients with a decrease in LVEF had a cumulative dose of ≤300 mg/m² of doxorubicin administered as part of the protocol therapy.

Table 40 Decrease in LVEF in evaluable patients

	TAC Arm 66 evaluable	FAC Arm 48 evaluable
No LVEF decrease	20 (30)	18 (37)
LVEF decrease 10% - 20%	14 (21)	10 (21)
Decrease within normal limits	11 (17)	9 (18)
Decrease below lower normal limits	3 (4)	1 (2)
LVEF decrease > 20%	15 (23)	5 (10)
Decrease within normal limits	4 (6)	2 (4)
Decrease below lower normal limits	11 (17)	3 (6)

The sponsor reported more cardiac adverse events in the TAC arm than in the FAC arm. See Table below.

Table 41 Cardiac Adverse Events

Cardiac Adverse Event	TAC Arm 744 N (100%)		FAC Arm 736 N (100%)		P values
CARDIAC DYSRHYTHMIAS					
All Grades	59	(7.9)	44	(6.0)	
Grade ≥ 3	2	(0.3)	2	(0.3)	
HYPOTENSION					
All Grades	19	(2.6)	8	(1.1)	
Grade ≥ 3	0	(0)	1	(0.1)	
CARDIAC FUNCTION					
All Grades	12	(1.6)	5	(0.7)	
Grade ≥ 3	1	(0.1)	1	(0.1)	
CARDIAC ISCHEMIA					
All Grades	4	(0.5)	2	(0.3)	
Grade ≥ 3	3	(0.4)	0	(0)	

Twelve patients on TAC and 4 patients on FAC were reported to have developed CHF (grade 3-4 cardiac toxicity) during the treatment or follow-up phase. CHF was documented as emerging before the completion of study chemotherapy (both cycle 5) in 1 patient on both arms, while CHF was a post-treatment emergent event in the remaining 14 patients. All patients reporting CHF had each received a cumulative dose of doxorubicin of ≤300 mg/m² during the conduct of the study, while 1 patient on FAC (15607) received additional anthracycline in the follow-up period for metastatic breast cancer. Seven of the 12 patients in the TAC arms and 1 of the 4 patients in the FAC arm had left breast irradiation.

Table 42 Cardiac events from Study TAX316

Cardiac Event	TAC Arm	FAC Arm
Congestive heart failure	12	4
Grade 3	9	4
Grade 4	3	0
Serious Adverse Event (cardiac function)	11	4
Death due to CHF	1	1

Reviewer's Comments:

- Cardiotoxicity from TAC therapy is difficult to evaluate in this trial. Cardiac evaluations after baseline were optional and only 9% patients in the TAC arm and 6% patients in the FAC arm had LVEF available after baseline. Most cardiac toxicity occurs during follow-up, therefore, case ascertainment may be incomplete, especially for patients with subtle manifestations of cardiac toxicity.
- Seven of the 12 patients in the TAC arms and only 1 of the 4 patients in the FAC arm had left breast irradiation, which might have contribute to the cardiac toxicity. In addition only 1 patient had additional chemotherapy after relapse which could have contributed to the cardiac event.
- It is likely that the TAC combination is associated with increased risk for cardiac toxicity. However, it is not possible to conclude from these data whether risk is related to the drug combination or to estimate the true incidence of the cardiac toxicity.

7.1.4.1 Hematologic Toxicities

The incidence of hematologic toxicities is summarized in the table below.

Table 43 Hematologic Toxicity

Hematologic Toxicities	TAC Arm 744 N (100%)		FAC Arm 736 N (100%)		P values
ANEMIA					
All Grades	680	(91.5)	526	(71.7)	<0.0001
Grade ≥ 3	32	(4.3)	12	(1.6)	0.0041
NEUTROPENIA					
All Grades	530	(71.4)	600	(82)	<0.0001
Grade ≥ 3	486	(65.5)	361	(49.3)	<0.0001
FEBRILE NEUTROPENIA					
All Grades	183	(24.7)	18	(2.5)	<0.0001
INFECTION					
All Grades	293	(39.4)	267	(36.3)	0.2389
Grade ≥ 3	29	(3.9)	16	(2.2)	0.0751
THROMBOCYTOPENIA					
All Grades	293	(39.4)	203	(27.7)	<0.0001
Grade ≥ 3	15	(2.0)	9	(1.2)	0.3162

Reviewer's Comments:

- The incidence of anemia was high in both treatment arms predominantly in the TAC arm.
- The frequency of neutropenia was higher in the FAC arm, however, patients treated on the TAC arm had an increased incidence of neutropenia Grade 3 or 4 and febrile neutropenia. The incidence of infection was higher in patients treated in the TAC arm but the difference is not statistically significant.

7.1.4.2 Non-hematologic laboratory abnormalities

The most common Grade 3 and 4 blood chemistry abnormalities are detailed on sponsor's Table 72 of Study Report. Most of the laboratory abnormalities were Grade 1 and rarely Grade 4. Hyperbilirrubinemia occurred with a low frequency in both arms (3 %). Elevation of transaminases were higher in the FAC arm (40% in the FAC treatment arm and 30% in the TAC). One TTAC patient was withdrawn from the study for having elevated transaminases during cycle 1, worsening in cycle 2 but resolved by the 6 month follow-up visit. Two patients (12109, 31202) treated in the TAC arm had renal insufficiency leading to discontinuation of study therapy. One of the patients renal insufficiency was associated to neutropenic sepsis and colitis.

Reviewer's Comments:

- Hyperbilirubinemia was less frequent in this trial (3%) compared to previous taxotere studies in patients with either metastatic breast or lung cancer (9%). Dose modification parameters were stricter in the current trial. Half of the patients with hepatic dysfunctions were due to liver metastases.

7.1.4.3 Fluid Retention

The protocol definition of fluid retention was one or more of the following signs or symptoms: edema/peripheral, edema/lung edema, effusion (pleural effusion, ascites, pericardial effusion), and/or weight gain. The table below shows the incidence of fluid retention that the sponsor considered to be related to study treatment.

Table 44 Fluid retention in the Safety Population (modified from Sponsor's Table 85)

Fluid Retention	TAC Arm 744	FAC Arm 736
Patients with fluid retention	261 (35%)	108 (15%)
Patient withdrawals due to f.r.	1 (0.1)	0
Severity		
Mild	174 (23%)	79 (11%)
Moderate	80 (11%)	28 (4%)
Severe	7 (1%)	1 (0.1%)

Reviewer's Comments:

- Fluid retention was more frequent in the TAC arm (35% versus 15%). Only one patient in the TAC arm (#12317) was withdrawn from the study during cycle 4 due to severe fluid retention.
- Most of the patients with fluid retention had peripheral edema and or weight gain. Two patients in the TAC arm had pericardial effusion and 3 patients had pulmonary edema.

7.1.4.4 Gastrointestinal toxicity

The most common Grade 3 and 4 gastrointestinal toxicities are detailed on table 27. Nausea and vomiting was more frequent in the FAC arm (88.0% vs. 80.5% for nausea and 59.2% vs. 44.5% for vomiting); while stomatitis and diarrhea were observed more often in the TAC treatment arm (69%vs. 59% for stomatitis and 35% vs. 28% for diarrhea). Colitis with large intestine perforation was reported in 7 patients treated in the TAC arm.

7.1.4.5 Neurological Toxicity

The incidence of neuro-sensory events was higher in the TAC arm as compared to the FAC arm. Most of the neurological events were grades 1 and 2, with few events considered as SAE and/or leading to discontinuation.
Two patients (26802, 22401) treated with TAC had a neuro-sensory event that led to study withdrawal.

7.2 Safety Conclusions

Toxicity in Study TAX 316 was greater in the TAC treatment arm. The toxicity consisted predominantly of alopecia (97.8%), anemia (91.5%), asthenia (80.8%), nausea (80.5%), neutropenia (71.4%), stomatitis (69.4%), amenorrhea (61.7%), fever in absence of infection (46.5%) and vomiting (44.5%). The toxicity while significant, did not cause a large number of patients to withdraw from treatment (6% in the TAC arm and 4% in the FAC arm). The most frequent reason leading to withdrawal was fever in the absence of infection and allergy in the TAC arm.

Long-term serious toxicity included leukemia and cardiac toxicity. Four patients were diagnosed with leukemia (AML), 3 in the TAC arm and 1 in the FAC arm. The cumulative risk of developing treatment-related AML at 5 years in TAX 316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens. Twelve patients on TAC and 4 patients on FAC were reported to have developed CHF (grade 3-4 cardiac toxicity) during the treatment or follow-up phase. It is likely that the TAC combination is associated with increased risk for cardiac toxicity. However, it is not possible to conclude from these data whether risk is related to the drug combination or to estimate the true incidence of the cardiac toxicity.

7.3 Advisory Committee Meeting

This NDA was not taken to ODAC. The review team consulted two ODAC members, Dr. Sylvana Martino and Dr. Johanna Mortimer who concur with FDAs decision to approve this application.

8 Summative Assessment

8.1 Conclusions

This review addresses an efficacy supplement to NDA 20-449 for use of Taxotere® (docetaxel) for the adjuvant treatment of patients with operable node-positive breast cancer. The original NDA for Taxotere, was approved in May 1996 for the treatment of patients with locally advanced or metastatic breast cancer who had progressed during or relapsed after anthracycline-based therapy. Supplemental NDA approvals were subsequently granted for the treatment of locally advanced or metastatic non-small cell lung carcinoma and for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer. The current supplement presents the results of a single, randomized trial comparing Taxotere® (docetaxel) in combination with doxorubicin and cyclophosphamide with 5-Fluorouracil in combination with doxorubicin and cyclophosphamide, as adjuvant treatment in women with operable node-positive breast cancer.

The efficacy claims in support of this application are based on the results of a single large randomized well controlled trial entitled, "A multicenter Phase III 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 operable breast cancer patients with positive axillary lymph nodes." The protocol-specified primary endpoint was disease free survival of breast cancer; secondary endpoints was survival. At the second interim analysis and 55 months of median follow-up, the docetaxel (TAC) arm had significantly longer disease-free survival (DFS) measured against an accepted control arm, FAC (hazard ratio=0.74; 2-sided 95% CI=0.60, 0.92, stratified log rank p=0.0048). The overall reduction in risk of relapse was 25.7% for TAC- treated patients. Overall survival appeared to be longer for the docetaxel containing combination regimen (TAC) than for the FAC regimen (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.90 p-value not statistically significant when adjusted for interim analyses). At the time of this interim analysis, the overall relative reduction in the risk of death appears to be 31%.

The safety profile of Taxotere in combination with Doxorubicin and Cyclophosphamide is consistent with the known toxicities of both agents and typical of antineoplastic therapy. Common toxicities included anemia, neutropenia, fever in the absence of infection, nausea and stomatitis, which are currently identified in the Taxotere label. The incidence of grade 3 and 4 adverse events was higher in the combination arm as were dose modifications and treatment discontinuations.

8.2 Recommendation on Regulatory Action

The Division of Oncology Drug Products recommends approval of Docetaxel in combination with Doxorubicin and Cyclophosphamide (TAC) for the proposed indication: *"adjuvant treatment of operable breast cancer patients with* —

The efficacy claims in support of this application are based on the results of Study TAX 316, a single large randomized well-controlled trial, in patients with breast cancer and positive axillary lymph nodes. At the second interim analysis and 55 months of follow-up, the docetaxel (TAC) arm demonstrated statistically significant and clinically relevant superiority in the traditional oncology endpoint of interest in the treatment of adjuvant breast cancer (disease free survival), and also appeared to improve survival as measured against an accepted control arm (FAC). The protocol primary endpoint was disease free survival of breast cancer; secondary endpoint was survival.

The following Table summarizes the results of the submitted pivotal adjuvant trial:

Recurrence Status	TAC Arm 744 n (%)	FAC Arm 742 n (%)
Total number of events	156	206
Breast cancer relapse	137	190
Contralateral breast	7	8
Deaths Unrelated to breast cancer	12	8
Hazard Ratio 95% CI	0.743 (0.604, 0.915)	
Log-Rank p-value	P= 0.0048	

Reductions in risk resulting from therapy in the control arm are comparable to those reported by the Early Breast Cancer Trialists' Collaborative Group (Lancet 339:71-85, 1992). Reductions in the chances of recurrence were reported to be 28% in the meta-analysis.

The safety profile of Taxotere in combination with Doxorubicin and Cyclophosphamide is consistent with the known toxicities of both agents and typical of antineoplastic therapy. Common toxicities included anemia, neutropenia, fever in the absence of infection, nausea and stomatitis, which are currently identified in the Taxotere label. The incidence of grade 3 and 4 adverse events was higher in the combination arm as were dose modifications and treatment discontinuations. The incidence of leukemia is difficult to estimate unless a large database is available. It is likely that the TAC combination is associated with increased risk for cardiac toxicity. However, it is not possible to

conclude from these data whether risk is related to the drug combination or to estimate the true incidence of the cardiac toxicity.

Overall, the submitted trial demonstrated efficacy and clinical benefit for TAC as adjuvant therapy of node-positive breast cancer. While there is increased toxicity with the TAC therapy, the benefit conveyed is greater than the incide3nceof serious adverse events. The data from Study TAX 316 support approval for this indication.

8.3 Recommendation on Post-Marketing Actions

We recommend the following postmarketing commitment, along with any completion dates agreed upon:

> To submit a complete report of the updated TAX316 data to verify the efficacy based on 700 events of DFS and safety of Taxotere in the adjuvant treatment of women with operable node-positive breast cancer. To submit the final analysis of overall survival.

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Patricia Cortazar
8/18/04 01:54:37 PM
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