CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20753

MEDICAL REVIEW(S)

A Slaten
OCT 20 1999

Deputy Director Comments on a New Drug Application

NDA 20-753
Drug: Aromasin® (exemestane) Tablets
Applicant: Pharmacia and Upjohn
Date: October 20, 1999

The clinical data supporting this NDA are well summarized in the Medical/Statistical and Medical Team Leader reviews. The indication "for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy" is supported by three clinical trials in this patient population. The primary endpoint in all three trials was objective response rate (CR+PR). Although objective response is not adequate for traditional approval of cytotoxic drugs, it has been accepted as adequate evidence of clinical benefit for traditional approval of hormonal agents. Previous precedents include the approvals of tamoxifen, toremifene, anastrazole, and letrozole. The anastrazole and letrozole applications also established the acceptability of a demonstration of non-inferiority to megestrol acetate in objective response rate as an adequate basis of approval of hormonal agents for this indication. Since the precedents are well established, the application was not presented to the Oncologic Drugs Advisory Committee.

In the comparative trial, a randomized, double-blind, multicenter, multinational study, 769 women were randomized to treatment with exemstane 25 mg once daily (N=366) or to megestrol acetate 40 mg q.i.d. (N=403). Although the randomization was unbalanced, this was satisfactorily addressed in the medical/statistical review. The treatment groups were otherwise balanced for demographic and baseline characteristics. The objective response rate was 15.0% for exemestane and 12.4% for megestrol acetate, a difference of 2.6% (95% C.I.: 7.5%, -2.3%). The median duration of response was 76.1 weeks for exemestane and 71.0 weeks for megestrol. These results demonstrate that exemestane is non-inferior to megestrol in objective response rates. Secondary endpoints included time to progression and survival. The median time to progression was 20.3 weeks for exemestane and 16.6 weeks for megestrol (p=0.037). The hazard ratio (AR:MA) for progression was 0.84 (95% C.I.: .72, 0.99). Although the p value and 95% confidence intervals for TTP suggest a significant improvement in favor of exemestane, they have not been adjusted for multiple comparisons. For this reason and CDER's developing policy of not including secondary endpoints in labeling, especially their p values, I agree that only the medians should be included. Median survival could not be estimated for exemestane and was 123 weeks for megestrol. Although a p value of 0.039 was reported for survival, it was again not adjusted for multiple comparisons. In addition, the survival results are too early to be convincing. Seventy-three percent were censored on the exemestane arm 73% and 68% on the megestrol arm. For these reasons, I concur that the survival data should not be included in the labeling. When the data are mature they should be submitted and reviewed for possible inclusion in the labeling. In the two single-arm supportive trials, the objective response rates were 23.4% and 28.1%.

The applicant also requested approval of an indication for the treatment of postmenopausal women with advanced breast cancer failing multiple standard hormonal therapies. Three single arm trials (total N=419) were submitted. I concur that the combined objective response rate of 9% is too low to warrant approval of this indication.

As noted in the reviews, the toxicity profile of exemestane is modest and similar to that of other approved aromatase inhibitors. A total of 1058 patients were treated at the proposed dose. One death from coronary artery disease was considered possibly related to the drug. Only 3% of patients discontinued treatment because of adverse events. In the double-blind comparative study, the most common adverse events (exemestane vs. megestrol) were hot flashes (13% vs. 5%), nausea (9% vs. 5%), fatigue (8% vs. 10%), increased sweating (4% vs. 8%), and increased appetite (3% vs. 6%). Although the proportion of patients with weight gain >10% of baseline was "significantly" greater in the megestrol group (17% vs. 8%, p=0.001), the p value should be discounted and not included in labeling because of the many multiple comparisons involved in the safety analysis.

The clinical pharmacology reviewers have identified two additional labeling issues of importance. The first is that both hepatic and renal insufficiency increased the AUC of exemestane approximately 3 fold. Although there is no data on the safety of chronic dosing of exemestane at the proposed dose in these populations repeated doses of 200 mg daily have been tolerated. Therefore, a dose adjustment does not appear to be needed. The second issue concerns the effect of food on absorption. Since plasma levels increased approximately 40% after a high-fat diet, food effects must be considered. In the clinical trials exemestane was given after a meal. Although sponsor argues that estrogen suppression is the mechanism of action and that this occurs at lower doses, it is conceivable that aromatase inhibitors could have other mechanisms of action. For this reason the label should state that exemestane is to be given after a meal.

Recommended Regulatory Action:

The application should be approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

/S/

Robert L. Justice, M.D.

Cc:
Orig. NDA 20-753
Division File
HFD-100/RTemple
HFD-150/AMartin
HFD-150/JBeitz
HFD-150/AStaten

A. Slater

OCT 20 1999

Medical Team Leader Review of New Drug Application

NDA 20-753
Drug: **Aromasin[R] (exemestane)**
Sponsor: **Pharmacia & Upjohn**
Subject: **Status of Clinical Inspections**

This NDA was submitted to the Division of Oncology Drug Products on December 21, 1998 and granted a standard priority. The user fee date for action on this application is October 21, 1999. Exemestane is a steroidal irreversible (Type I) aromatase inhibitor that is structurally related to the natural substrate androstenedione.

The sponsor has submitted one randomized, controlled, double blind trial in 769 patients with advanced breast cancer, and two single arm trials in support of a claim for the treatment of postmenopausal women with advanced breast cancer failing tamoxifen therapy. The randomized trial (study #018) was an international, multicenter trial comparing exemestane 25 mg once daily with megestrol acetate 40 mg qid, both given orally.

A request for clinical inspections was made on February 1, 1999. Four sites were selected for inspection, two domestic and two foreign. The domestic sites were[ ]the largest accruing site for the randomized study in the U.S. (N=26), and[ ]the physician with the highest accrual in the U.S. (N=9). The staff of the Division of Scientific Investigations satisfactorily completed these audits and no further action is indicated.

The two foreign sites selected were[ ](N=53), and](N=23), the first and third highest accruing sites for the randomized study, respectively.[ ]completed the audit of the[ ]site in April 1999 and reported that no further action was indicated. The audit of the]site is scheduled for November 1, 1999.

Conclusion: Three of four clinical sites accruing to the pivotal randomized trial (study #018) have been satisfactorily audited with no further action indicated. It is anticipated that the audit of the Milan site will also prove favorable, given that this site is in close proximity to the sponsor and likely received intensive monitoring. There should be no obstacle to an approval action on this NDA because of the delinquent audit of the site. The audit of the site should proceed as planned.

/S/

10/20/99

Julie Beitz, MD Date

cc
NDA 20-753, HFD-150 Division File

Stenfen

OCT 13 1999

Medical Team Leader Review of New Drug Application

NDA 20-753
Drug: **Aromasin[R] (exemestane)**
Sponsor: **Pharmacia & Upjohn**

This NDA was submitted to the Division of Oncology Drug Products on December 21, 1998 and granted a standard priority. The user fee date for action on this application is October 21, 1999. Exemestane is a steroidal irreversible (Type I) aromatase inhibitor that is structurally related to the natural substrate androstenedione. Exemestane produces marked inhibitory effects on estrogen production but negligible effects on circulating levels of androstenedione, testosterone, 17-hydroxyprogesterone, DHEA-S, cortisol or aldosterone. Clinical efficacy and safety data are submitted in support of the following claims:

- **Treatment of postmenopausal women with advanced breast cancer failing conventional antiestrogen therapy**

The sponsor has submitted one randomized, controlled, double blind trial in 769 patients with advanced breast cancer, and two single arm trials in support of this claim. The randomized trial (study #018) was an international, multicenter trial comparing exemestane 25 mg once daily with megestrol acetate 40 mg qid, both given orally. Prior treatment with hormonal agents other than tamoxifen was prohibited. Patients on the two arms were balanced in terms of baseline demographics and other disease characteristics.

Equivalence in objective tumor response rate (CR+PR), the primary endpoint, was demonstrated with a 15.0% response rate for exemestane (95% CI: 11.5 – 19.1) and a 12.4% response rate for megestrol acetate (95% CI: 9.4 – 16.0). The duration of response for the two arms was similar: 76 weeks vs. 71 weeks. There was a trend towards a longer median time to progression for exemestane: 20.3 weeks vs. 16.6 weeks. Logrank analysis revealed a p=0.037, however, no adjustment had been made for the multiple secondary endpoints in the trial. There is also a trend towards a longer median survival with exemestane by logrank analysis (p=0.039), but this analysis suffers from the same issues of multiplicity as the TTP analysis. In addition, there are insufficient events at this time to make any definitive conclusions regarding survival, with 73% censored observations on exemestane and 68% on megestrol acetate. A responders analysis of overall pain score revealed improvement for exemestane in 51.4% as compared to 46.2% with megestrol acetate. Quality of life was evaluated using the 30-item EORTC QLQ-C30 questionnaire. Quality of life outcomes are difficult to interpret because of the observed attrition after week 24 and the high degree of multiplicity involved in assessing comparisons to baseline for individual items.

The safety profile of exemestane 25 mg daily is consistent with that of other marketed aromatase inhibitors (e.g., Arimidex, Femara), with nausea, vomiting and hot flushes as the most commonly reported adverse events.

Two supportive single arm studies enrolled a total of 265 postmenopausal patients with advanced breast cancer whose disease had failed tamoxifen (studies 010 and 999). Exemestane 25 mg orally daily was administered. The objective response rates in these studies were 23.4% and 28.1%, respectively.

Conclusion: The proposed indication is approvable with the following labeling considerations:

The sponsor has submitted three single arm trials that accrued a total of 419 patients in support of this claim. Exemestane 25 mg orally daily was administered. Prior therapies included megestrol acetate, antiestrogens and aromatase inhibitors. At an end-of-phase 2 meeting held on December 21, 1994, the sponsor was advised that for uncontrolled trials to support approval in this setting, response rates would have to be dramatic, i.e., at least 20%. At the October 1, 1997 pre-NDA meeting, the sponsor presented mature response rate data from these three trials of 6.6%, 9.4% and 13.2%, respectively. The agency accepts the sponsor's estimate of a 9% objective tumor response rate for the three trials combined. The availability of other agents for this patient population weakens the sponsor's argument for a strict sequence of treatment in this setting.

Conclusion: The proposed indication is not approvable.

/S/ 10/3/99

Julie Beitz, MD Date

cc
NDA 20-753, HFD-150 Division File

SUMMARY OF MEDICAL AND STATISTICAL REVIEW ISSUES FOR NDA #20-753

1. **Response Rate.** For the pivotal trial #018 of NDA #20-753, the protocol-specified primary endpoint was demonstration of equivalency in response rates between exemestane and megace as determined in the intent-to-treat population (ITT). Subsequent to the regulatory history of this NDA, the International Committee for Harmonization (ICH) issued their statistical guidance (E9) that the hypothesis of equivalency tested in the ITT population is not conservative. The ITT population had been accepted by the Division and also had been the population in which demonstration of endpoints won approval for two other hormones in the class–anastrozole (Arimidex®) and letrozole (Femara®). It could be argued that the trials for these approved agents were designed for superiority, demonstration of which is appropriate in the ITT population. However, neither hormone achieved their protocol-specified primary objective of demonstration of superiority and each was, in the end, approved for "similarity" as demonstrated in an ITT population.

2. **Multiplicity/false positive error inflation.** Secondary endpoints included multiple time to event measures (time to progression, time to treatment failure, time to response, response duration, duration of overall success and survival) as well as overall success rate, tumor related signs and symptoms, Purohit overall pain score, and a large number (15) of QOL measures. The sponsor has not adjusted the statistical significance level to account for multiplicities.

3. **Superiority in time to progression (TTP).** The sponsor claims superiority in TTP (medians of 20.3 vs. 16.6 weeks, p=0.037). The robustness of the sponsor's finding may be questioned for the following reasons: (a) no adjustment for multiplicity for a large number of secondary endpoints; (b) ascertainment bias–despite the intent of a double-blind trial, treatment code breaking was continuous over the duration of the protocol; (c) this advantage is not seen in the U.S., the single largest accruing country, where the direction favors megace; (d) exploratory analyses indicate that TTP is not only dependent on non-US countries, but low contributing countries (< 25 patients); (e) median TTP for megace in countries with low and high enrollments is stable at 16.1 and 16.7 weeks, while exemestane ranges from 17.7 to 24.7 weeks.

4. **Superiority in survival.** The sponsor reports a significant logrank test result favoring exemestane (p=0.039) for survival. However, these data are immature (73% censored observations in patients receiving exemestane and 68% on megace).

5. **Sponsor's responder analyses for pain control and tumor related signs and symptoms (TRSS).** A responder analysis lacks statistical validity since nonrandomized groups are compared. The protocol specified a descriptive approach to TRSS, rather than comparative, and did not prospectively rank measures by clinical importance.

1.0 General Information

1.1 Name of Drug:

Established: Exemestane (PNU-155971, FCE 24304)
Proprietary: Aromasin®

1.2 Applicant:

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

1.3 Pharmacologic Category:

Aromatase inhibitor, steroidal, Type I (irreversible)

1.4 Proposed Indication

"Aromasin Tablets are indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy. Aromasin Tablets are also indicated for the treatment of postmenopausal women with advanced breast cancer whose disease has progressed following multiple hormonal therapies."

Medical Officer Comment: *The indication for patients with progressive disease despite multiple hormonal therapies was not accepted by the Agency in the pre-NDA meeting (see Section 2.0, Regulatory History).*

1.5 Dosage and Administration

The proposed label recommends a single 25 mg tablet to be taken orally once daily.

1.6 How Supplied

Sugar coated capsules containing 25 mg of exemestane for once daily oral administration.

2.0 Regulatory History

Reference: Appendix I: Phase 2 and 3 Trials Conducted with Aromasin®

The initial IND was filed January 31, 1991. The End of Phase 2 (EOP2) meeting, held December 21, 1994, discussed two potential NDA applications: (1) treatment of postmenopausal women with metastatic breast cancer progressing after treatment with tamoxifen, i.e., second line treatment; and, (2) treatment of postmenopausal women with metastatic breast cancer progressing after two prior hormonal treatments, i.e., third-line treatment. As data from the clinical trials become available, three subsequent pre-NDA meetings were held--on May 15, 1996, October 1, 1997 and November 25, 1998. The Agency, in conjunction with ODAC representation, stated that data supported only the indication of treatment of postmenopausal women with metastatic breast cancer progressing after treatment with tamoxifen. Further details are discussed by indication, below.

- **Postmenopausal Women with Progressive Metastatic Breast Cancer following Tamoxifen**

The Agency agreed, in concept, that a single, large randomized multicenter trial, if supported by Phase 2 data, could suffice for this indication. A control arm of megestrol acetate (megace) 40 mg q.i.d. was accepted. The primary endpoint would be equivalence in response rate. Demonstration of equivalence in terms of TTP was not considered an acceptable primary endpoint since no data exist that megace confers a benefit with this measure–a superiority design would be required if this endpoint were to be chosen.

In a teleconference on December 17, 1997, following the pre-NDA meeting October 1, 1997, the Agency suggested that the sponsor consider revision of their statistical plan of the pivotal phase 3 trial #018. The response rate of megace had been demonstrated in recent randomized trials to be lower than assumed when planning the original sample size. In addition, two recent approvals based on these randomized trials had sample sizes totaling 750, albeit derived from two independent randomized trials. The discussion resulted in protocol amendment #3 dated June 1, 1998, that converted the planned interim analysis to a final analysis, resulting in reduction of the sample size from 1480 to 750. The November 25, 1998 meeting agreed to an NDA submission with efficacy claims based on the randomized trial, #018, and supported by the two phase 2 trials, #010 and #120002, which were conducted in a similar patient population.

- **Postmenopausal Women with Progressive Metastatic Breast Cancer following Multiple Hormonal Therapies**

In the December 21, 1994 EOP2 meeting, the sponsor asked if their Phase 2 program would be adequate to support approval for third line hormonal therapy of postmenopausal metastatic breast cancer. The Agency, in conjunction with an ODAC representative, stated that for uncontrolled trials to be the sole basis of approval, response rates must be dramatic, which in this population would be at least 20%. In addition, a reasonable duration of response must be demonstrated in conjunction with minimal toxicity. The pre-NDA meeting May 15, 1996 reviewed preliminary phase 2 data and no conclusions could yet be drawn. At the pre-NDA meeting October 1, 1997, the sponsor presented mature data from three Phase 2 trials. The response rates from three trials averaged 10% (6.6%, 9.4%, 13.2%). Furthermore, the Agency noted that the usual outcome of review at FDA is that the response rate from uncontrolled trials falls. In addition, with approval of other hormones for this patient population, a strict sequence of treatment was no longer clinically plausible.

3.0 Scope of Review

The medical review of NDA #20-753 included:

- Regulatory history of the application
- Original submission of protocol 94-OEXE-018 to IND with amendments
- The following volumes of the NDA submission:
  - 3.1 Index
  - 3.2 Proposed label
  - 3.3 Summary
  - 3.9-3.91 Clinical Data
- MS Access database files and selected electronic case report forms and tabulations (12/11/98)
- Four Month Safety Update, correspondence date 4/29/99
- New Correspondence, dated 3/3/99 providing responses to the pre-NDA meeting
- Other related submissions dated 4/22/99 (BS), 8/30/99 (BS and BM), 9/7/99 (BM), 9/10/99 (BM), 9/14/99 (BS, and BM), 9/15/99 (BS) and BM) and 9/20/99 (BM)
- Consult to HFD-510 for review of pharmacodynamic effects.

The statistical review of the NDA included:

- The following volumes of the NDA submission:
  - 3.1 Index

3.2 Proposed label
3.3 Summary
3.9-10, 3.66, 3.70, 3.79, 3.81, 3.86, 3.90 Clinical Data

- MS Access database files
- SAS files and programming code.

4.0 Chemistry and Manufacturing (see Chemistry Review)

5.0 Clinical Pharmacology/Pharmacokinetics Summary (see Clinical Biopharmaceutical [CPB] Review)

Reference: Appendix I: Phase 1 or PK/PD Studies Conducted with Aromasin®

The following summary points are reviewed in detail in the Clinical Biopharmaceutical review.

- **Overview.** Five phase 1 and 14 PK/PD trials have been conducted with exemestane. Single doses ranged from 25 to 800 mg; doses given daily ranged from 0.5 to 600 mg/day; and weekly doses ranged from 25 to 1600 mg. Three of the 19 trials have interim summaries only--#015 evaluating effect of hepatic impairment, #016 evaluating effect of renal impairment; and #022, a nested estrogen suppresion study within a phase 2.

- **Selection of a Phase 3 Dose.** "In selecting the dose to be used in phase 2 and phase 3 studies, the following aspects were considered: (1) pharmacologic effect (circulating plasma estrogen level was used as a surrogate endpoint..); (2) safety profile; and (3) preliminary antitumor efficacy data...

  While maximal estrogen suppression was seen with the 5 mg daily dose, preliminary efficacy information suggested that this dose level was associated with lower antitumor efficacy than were higher doses..." (excerpted from the sponsor's Section 2.2.2, vol. 3.9, pp. 77-78)

  Three protocols treated patients with doses higher than the final recommended dose. Protocols #017 and #022 gave 100 mg daily to patients progressing on 25 mg/day. Further responses could not be elicited at the higher dose. Protocol #009 evaluated exemestane at 200 mg/day in patients progressing on aminoglutethimide. "At the high range of the doses tested, there appeared to be an increase in the incidence of adverse events, particularly virilizing effects" and the sponsor made the decision that the risk/benefit profile was not superior to the 25 mg/day dose. Possible reasons for androgenic effects due to exemestane include: (1) an increase in aromatase substrates, androstenedione and testosterone, which were seen at 200 mg in Phase 1; and/or, (2) higher levels of the metabolite 17-hydroexemestane, which has androgenic activity, with higher levels of parent drug. The ability of the metabolite to bind to the androgen receptor is 100X the ability of the parent compound.

- **Bioequivalence.** Pharmacokinetic studies were conducted with three preparations--an exemestane suspension, gelatin capsule and tablet. The two supportive phase 2 trials were conducted with the gelatin capsule while the randomized trial #018 supplied exemestane as a tablet. The gelatin and tablet formulations were shown to be bioequivalent with respect to AUC but not with respect to Cmax. Both formulations had a similar effect in decreasing plasma E_1S levels. Bioinequivalence of the Cmax is of arguable clinical relevance since efficacy has not been correlated to plasma levels and dose-limiting toxicities were not seen in the Phase 1 trials.

- **Pharmacokinetics.** Absorption of intact drug from the gastrointestinal tract results in peak concentrations typically within 2 hours of ingestion. The plasma concentration-time profile has a polyexponential decline with a terminal half-life of approximately 24 hours. Exemestane significantly binds (93-95%) to plasma proteins. Due to its lipophilicity, it distributes extensively throughout the body tissues and is cleared rapidly and extensively by metabolism from the

systemic circulation. Less than 1% of intact drug is excreted in the urine. Metabolism involves an initial oxidation of the methylene group in position 6 and reduction of the 17-keto group. A large number of metabolites are formed and excreted equally in urine and feces. One metabolite, 17-hydroexemestane, is considered to have significant aromatase inhibition, albeit 2.6 times less than the parent compound, as well as androgenic effects and was therefore measured in PK studies. Pharmacokinetic studies did not demonstrate marked dose or time dependency.

- **Food Effect.** Two food effect studies demonstrate an increased Cmax (59% and 52%) and AUC (39% and 46%) when exemestane is given either with a high fat meal or a standard breakfast, respectively. Whether this is due to increased absorption or decreased first pass metabolism associated with increased splanchnic blood flow is unknown.

  The randomized and supportive phase 2 trials instructed patients to take study drug after a meal. The label does not make a recommendation regarding timing of administration; however, CBP recommends taking exemestane "preferably after a meal."

- **Age.** No formal studies were conducted to evaluate the effect of age on PK. The sponsor pooled data from their PK program which enrolled patients 45-65 years of age and plots oral clearance vs. age. There was no significant difference (p=0.02) in the slope of the regression line from zero.

  The sponsor has analyzed the safety database of 25 mg daily administration by patients < 65 vs ≥ 65 years old.

- **Renal Function.** The AUC of exemestane after a single 25 mg dose was approximately 3 times higher in subjects with severe renal insufficiency (creatinine clearance < 35 mL/min/1.73 m^2) compared with the AUC in healthy volunteers.

- **Hepatic Impairment.** The AUC of exemestane after a single 25 mg dose was approximately 3 times higher in subjects with moderate or severe hepatic insufficiency compared with the AUC in healthy volunteers.

- **Ethnicity.** No formal study of the influence of race on exemestane pharmacokinetics has been conducted.

  Study #024 measured the effect of exemestane on estrogen suppression in 32 healthy postmenopausal Japanese volunteers at doses ranging from 0.5 mg/day for 7 days. Exemestane showed a dose dependent decrease in serum and urinary estrogens still present 1 week after discontinuation with return to baseline values at 2 weeks. However, comparison with caucasians requires cross-study comparisons, is limited by assay differences, handling of samples, etc. For the cross-study comparison, see CPB review.

- **Pharmacodynamic effect.** A variety of hormones, primarily estrogens, were measured in a number of studies; however, PK-PD correlations were not studied.

  The ability of exemestane to suppress estrogens (E_2, E_1 and E_1S) was evaluated in 10 phase 1 studies (6 in postmenopausal healthy volunteers and 4 in postmenopausal women with advanced breast cancer), in 6 phase 2 studies (sponsor's Table 8.C2-1, vol. 3.9, pp. 166-170) and in a subset of patients from the phase 3 trial. Exemestane 25 mg suppressed circulating E_2, E_1 and E_1S by at least 80-90% of baseline. Estrogens were measured in the 6 Phase 2 and pivotal trial by [redacted] all but one phase 1 study measured estrogens by [redacted] considered less sensitive and indicating less estrogen suppression). Levels return to normal after a single dose within 7-14 days, depending in part upon dose and schedule.

  The sponsor states data from four phase 2 studies and the pivotal phase 3 study showed "no correlation...between estrogen suppression and tumor response, as estrogens were generally

suppressed in all patients. In addition, at time of disease progression no escape from estrogen suppression was observed" (sponsor's figure 8.C2-6, vol. 3.9, p. 182). In Protocol #022, which increased exemestane from 25 mg/day to 100 mg/day at time of disease progression, no further suppression of circulating estrogens (and no further ability to induce an objective response) was observed.

- **Effects on other hormones.** In all studies, a dose-related decrease in sex hormone binding globulin (SHBG) was seen. At the recommended dose of 25 mg/day, the decrease ranged between 21 and 49%. The sponsor postulates that this is due to the androgenic effect of the metabolite 17-hydroexemestane at the level of production in the liver.

  In all studies, a non-dose-related increase in LH and FSH (29 and 45%, respectively) was observed and presumed secondary to an effect on the feedback loop governing estrogens.

  Increases in circulating levels of the aromatase substrates, androstenedione and testosterone, were seen at the 200 mg/day dose in a phase 1 study, although it has been suggested that this finding may be subject to assay cross-reactivity with 17-hydroexemestane. This metabolite's binding affinity to the androgen receptor is 100-fold more potent than exemestane. This, and/or an increase in circulating testosterone, may explain the sponsor's statement that "virilizing effects" are seen at higher doses.

  No effect on cortisol or aldosterone secretion was apparent, nor was there a blunting of response to ACTH stimulation (as measured in the phase 1 trial #003).

- **Steroidal and reversible aromatase inhibitors vs. steroidal and irreversible exemestane.** The sponsor states the degree of suppression of estrogens seen with exemestane is similar to the new generation of nonsteroidal aromatase inhibitors. This conclusion is based on comparing estrogen levels on the last day of treatment with a nonsteroidal inhibitor in progressing patients who were then treated with exemestane (protocol #017). This data also implies that progression on the nonsteroidal inhibitors was not correlated to escape from estrogen suppression.

  Whole body aromatization was evaluated by injection of radiolabeled androstenedione into10 patients as part of protocol #010. "After 6-8 weeks of treatment with exemestane 15 mg/day, whole body aromatization (measured from the urinary excretion of labelled estrogens) was reduced by 97.9% and plasma levels of estradiol, estrone and estrone sulphate (measured by [ ] were reduced by 92.2, 94.5 and 93.2%, respectively. This was considered comparable to published results with anastrozole (96% at 1 mg/day, Br J Cancer 1996; 74:1286-1291) and letrozole (> 98.9% at 2.5 mg/day, Clin Cancer Res 1995; 1:1511-1515).

6.0 Related INDs

Reference: Appendix I: Phase 1 or PK/PD Studies Conducted with Aromasin®
Phase 2 and 3 Trials Conducted with Aromasin®
Clinical Studies Not Reported in the NDA

7.0 Pivotal Trial: 94-OEXE-018: Exemestane versus megestrol acetate in postmenopausal patients with metastatic breast cancer failing tamoxifen: A Phase III, double-blind, randomized, parallel-group, comparative study

7.1 Protocol Review

Principal Investigator: M. Kaufmann
Zentrum fur Frauenheilkunde und Geburtshilfe
Frankfurt, Germany

Protocol Milestones

Reviewer Table 1:
Protocol #018 Milestones

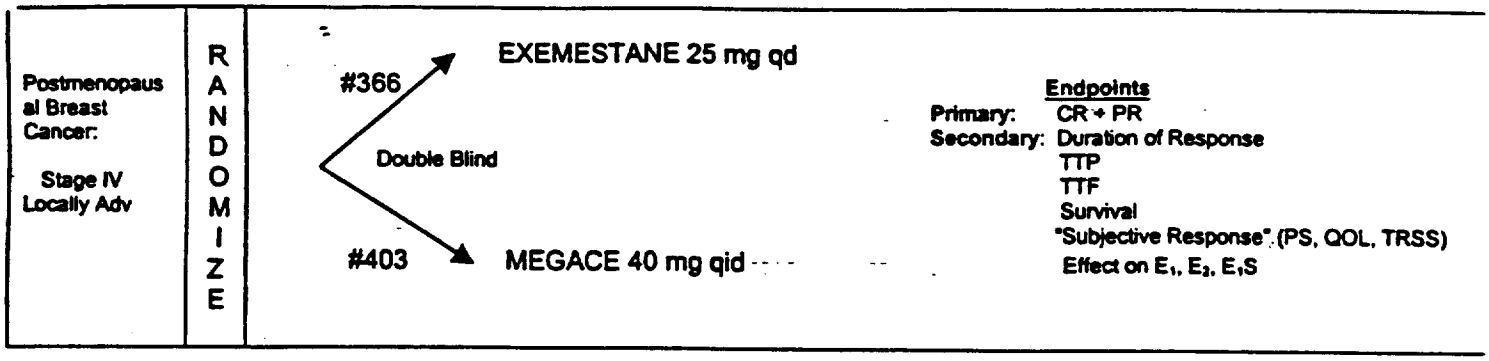
Milestone	Dates	Comments
IND Submission	Jan. 31, 1991	
Amendment #1	July 21, 1995	
Protocol Submission to US FDA	Oct. 4, 1995	
First Patient Randomized	Oct. 27, 1995	
Amendment #2	May 30, 1997	Randomization: Only US patients would be randomized by the US center ; Otherwise, minor changes.
Amendment #3	Feb. 25, 1998	Revision of statistical plan: Sample size of 1480 pts & interim analysis at 750 is replaced with final analysis at 750 patients. *(Replacement text from the amendment is identified by shading. The original text is identified by a strikethrough.)*
Accrual Closed	May 11, 1998	769 patients randomized
Data Cut-off	Aug. 31, 1998	
Database Freeze	Oct. 7, 1998	
NDA Submission	Dec 21. 1998	Non-priority review
SAS Datasets Received	April 23, 1999	

7.1.1 Synopsis

Protocol 018 was a multicenter (144 centers), international (19 countries), controlled, randomized, double-blind, parallel-group phase 3 trial in postmenopausal women with breast cancer progressing despite treatment with tamoxifen. The primary endpoint was demonstration of equivalency in response rate (CR + PR) between exemestane 25 mg q.d. and the control arm, megace 40 mg q.i.d. Secondary endpoints included duration of response, time to progression (TTP), time to treatment failure (TTF), survival, performance status, quality of life, tumor-related signs and symptoms, and effect on circulating estrogens.

Randomization was carried out at two central locations (U.S. and Milan) via minimization (White, 1978).Three stratification factors were used: previous response to tamoxifen (3 levels); site of metastasis (4 levels); and previous chemotherapy (3 levels). Responses, scored by the WHO criteria, were assessed every 8 weeks until week 24 and then every 12 weeks until completion of the second year of treatment; thereafter, every 24 weeks. Patients with a CR, PR or stable disease continue on treatment until progressive disease or unacceptable toxicity. An interim analysis was scheduled when half the patients were entered and target accrual was 1480. Amendment #3 reevaluated sample size based on lower estimates of the response rate in the control arm seen in recent randomized trials and concluded the trial could be closed after accrual of 750 patients. No interim analysis was performed. The primary endpoint would be met if the true RR in the exemestane arm was at least 2% higher in absolute terms than megace's RR; exemestane would be considered at least equivalent to megace, with a power of 80% (alpha = 0.10, one-sided). The upper limit of the 90% CI of the difference between the objective response rate in the two treatment groups (megace RR - exemestane RR) would be calculated and equivalence accepted if it would not exceed 25% of megace's RR.

Protocol #018: Schema



- Central (either Columbus, Ohio or Milan, Italy, depending on country of origin)
- Stratified by Country
- Minimization Procedure for:
  - (i) previous response to TAM:
    - –failure of TAM in advanced disease
    - –progression on TAM after initial response
    - –progression on adjuvant TAM after ≥ 12 months (for unknown receptor status), after ≥ 6 months (for + receptors), or within 12 months of discontinuation of adjuvant TAM
  - (ii) site of metastasis:
    - –viscereral ± others
    - –bone only
    - –bone + soft tissue
    - –soft tissue only
  - (iii) previous chemotherapy:
    - –none
    - –neoadjuvant/adjuvant only
    - –one regimen for metastatic disease ± neoadjuvant/adjuvant

7.1.2 Objectives

Primary:

- Objective response rate (CR + PR)

Secondary:

- Time to event endpoints: duration of response, time to progression, time to treatment failure, survival
- "Subjective response" evaluated by: performance status, quality of life, and tumor related signs and symptoms
- Effect on serum E_1, E_2 and E_1S
- Safety and tolerability

Reviewer Comment: *Overall success rate (and duration of overall success rate) were not protocol-specified endpoints.*

7.1.3 Eligibility Criteria

- Female patients with histologically/cytologically confirmed carcinoma of the breast.
- Postmenopausal status defined as:

  Any age: - bilateral surgical oophorectomy
  - amenorrhea ≥ 5 years (any cause)

  Age ≥ 56 yr.: - natural amenorrhea for ≥ 1 year
  - chemotherapy-induced amenorrhea ≥ 2 years
  - radiation-induced amenorrhea (radiation completed at least 3 months earlier)

Age < 56 yr.: - FSH must be assayed to confirm postmenopausal status (estradiol must be assayed in case of borderline FSH values) if
- amenorrhea < 5 years (any cause)
- hysterectomy without bilateral surgical oophorectomy

- Patients with locally advanced or locally recurrent inoperable or metastatic breast carcinoma with documented disease progression who have:

  - progressed/relapsed under TAM for advanced disease, administered at standard dosage, for at least 8 weeks;
  - progressed under adjuvant TAM given, at standard dosage, for at least 12 months (Estrogen (ER) and/or progesterone (PgR) receptor status : unknown)
  - progressed under adjuvant TAM given, at standard dosage, for at least 6 months (Estrogen (ER) and/or progesterone (PgR) receptor status : positive) ; or
  - progressed within 12 months from the end of adjuvant treatment with TAM.

  Patients may enter the study immediately after discontinuation of TAM.

- Estrogen (ER) and/or progesterone (PgR) receptor status unknown or positive. Patients will be regarded as ER or PgR positive if any assay of primary or secondary tumor tissue is positive. Patients will be regarded as receptor unknown if no assay is known to be positive or negative. Patients with ER negative, but PgR positive status, or vice versa are considered as receptor positive and can enter the trial. In patients previously treated with TAM for advanced disease, unknown ER and PgR receptor status is accepted only if they had responded (CR, PR or NC lasting ≥ 6 months) to TAM therapy.
- At least one bidimensionally measurable or one evaluable bony lesion (see definitions for measurable and evaluable lesions in par. 4.7.1.2).
- Patients taking bisphosphonates are eligible provided that they have bidimensionally measurable lesion(s) outside the bone to be followed for response. They must be kept on bisphosphonates during the trial.
- No more than 1 line of prior chemotherapy (single agent or combination) for advanced metastatic disease. Chemotherapy as the last therapy is allowed. When chemotherapy is the last treatment, patients must be in progression before study entry, the chemotherapy must have been discontinued for ≥ 4 weeks and the patient has recovered from all acute toxicities (except alopecia). A patient may have had adjuvant and/or neoadjuvant chemotherapy.
- ECOG performance status ≤ 2.
- Adequate hematopoietic function as defined by neutrophils ≥ 1500/mm^3 and platelets ≥75000/mm^3.
- Adequate renal and liver function:
  - serum creatinine ≤ 1.5 times the upper normal limit for the laboratory of reference;
  - serum bilirubin level ≤ 1.5 times the upper normal limit for the laboratory of reference (3 times in case of hereditary benign hyperbilirubinemia);
  - transaminases (ALT, AST) ≤ 2.5 times the upper normal limit for the laboratory of reference in patients without liver metastasis or ≤ 5 times the upper normal limit in patients with liver metastasis;
  - alkaline phosphatase ≤ 2.5 times the upper normal limit for the laboratory of reference in patients without bone or liver metastasis.
- Written informed consent or oral witnessed according to local regulations.
- The patient must be able to comply with scheduled visits.

7.1.4 Exclusion Criteria

- Prior treatment with hormonal agents other than TAM.
- High-dose chemotherapy requiring stem cell rescue (bone marrow or peripheral blood cells).
- Prior treatment with strontium 89.

- Conditions where hormonal therapy is not indicated: inflammatory breast carcinoma, or past history or presence of rapidly progressive disease, of massive visceral involvement (more than one-third of the organ), brain metastases or leptomeningeal disease.
- Past history of thromboembolic disease.
- Patients with uncontrolled cardiac disease (e.g. congestive heart failure) and/or uncontrolled diabetes mellitus.
- Concomitant malignancies except for adequately treated carcinoma in situ of the uterine cervix or basal or squamous cell carcinoma of the skin.

Patients with their medical history positive for cancer (i.e. previous cancer other than breast carcinoma) are allowed to enter the study, provided the previous cancer was (i) surgically resected (ii) noninvasive and (iii) DFS was ≥ 10 years.

- Mentally incapacitated patients.

7.1.5 Randomization, Blinding and Treatment

- **Randomization**

Requests for randomization were submitted by FAX to one of two centers–Pharmacia U.S. (Columbus, Ohio) for entry of patients in the U.S., Brazil, Mexico and Argentina (changed by amendment #2 to only the U.S.) or to Pharmacia (Milan) for the other countries. The following passage is excerpted from the sponsor's protocol:

"Each patient will be assigned to one of the two study treatments in a double-blind fashion according to a computer-assisted procedure linking the randomization of a patient with the assignment of a specific medication pack identified by a package number unique for an individual patient. Randomization will be done by country mainly for logistic reasons. In order to ensure that the two treatments are balanced for the major prognostic factors a minimization procedure will be adopted to randomize the patients. The following patient characteristics will be considered:

1) response to TAM
- failure of TAM for advanced disease (best response: NC < 6 months or PD after at least 8 weeks of treatment)
- progression on TAM after initial response (CR, PR, NC ≥ 6 months)
- progression on adjuvant TAM after at least 12 months of treatment (unknown ER and/or PgR receptors) or after at least 6 months of treatment (positive ER and/or PgR receptors) or within 12 months after discontinuation of adjuvant TAM.

2) previous chemotherapy
- no chemotherapy
- neoadjuvant/adjuvant chemotherapy only
- 1 line of chemotherapy (single agent or combination) for advanced metastatic disease ± neo adjuvant/adjuvant chemotherapy.

3) site of metastasis
- visceral ± others
- bone only
- bone + soft tissue
- soft tissue only."

- **Blinding and Treatment** (excerpted from the protocol)

"In order to ensure treatment assignment under blind conditions the clinical supplies will be identified by a package number unique to individual patients. It will consist of two letters identifying the country and four random numbers representing the treatment code. In addition, to ensure administration of the treatment under blind conditions, the double dummy technique will be used. Medication will be given daily to the two treatment groups as follows:

(● = active exemestane, o = placebo exemestane; ⬮ = active MA, 0 = placebo MA)

A. Exemestane group ● 0 0 0 0
one 25 mg sugar-coated tablet of exemestane
four placebos matching MA

B. MA (MA) group o ⬮ ⬮ ⬮ ⬮
one placebo matching exemestane
four 40 mg MA tablets

Two tablets (one exemestane plus one placebo matching MA or one placebo matching exemestane plus one MA) will be taken in the morning after breakfast; each of the three other tablets (MA or placebo matching MA) will be taken after lunch, dinner and at bed time..."

7.1.6 Concomitant Medication and Treatment (excerpted from the protocol)

"No treatment with other anticancer (cytotoxic or endocrine) therapy, immunotherapy, biologic response modifiers are allowed during the study. The administration of any antitumor treatment beyond week 8 will be considered as progression of disease. Exceptions must be cleared with the Study Director of reference.

Corticosteroids. Corticosteroids are allowed during the trial in the following cases:
- Tumor has progressed on long-term corticosteroid therapy prior to the study entry;
- Corticosteroids are given as a short-term course (max. 10 days) for a concomitant condition;
- Corticosteroids are given topically for obstructive airways diseases or non-malignant skin lesion(s).

The use of corticosteroids outside the above conditions will render the patient inevaluable for tumor response. The use of corticosteroids even in the above specified conditions will render the patient not evaluable for estrogen assays.

Palliative surgery/irradiation. Palliative surgery or irradiation to the only evaluable lesion before the first complete on study assessment of tumor response will render the patient non-evaluable for efficacy. Palliative surgery/irradiation of lesions which are progressing or causing symptoms performed beyond week 8 will be considered as progression of disease. Exceptions must be cleared with the Study Director of reference.

Analgesics and adjuvant drugs for pain control. The patient in pain should receive adequate analgesic treatment. It should be adjusted according to the patient's needs before study entry to provide maximum pain relief. Analgesic therapy including adjuvant drugs (non steroidal antinflammatory drugs , bisphosphonates, tricyclic antidepressants and anticonvulsants) will be administered according to the WHO "analgesic ladder."

Strontium 89. Treatment with strontium 89 during the trial is not permitted.

Local analgesic procedures. Local analgesic procedures such as nerve blocks are allowed but will render the patient non-evaluable for assessment of pain.

Bisphosphonates. Chronic treatment with bisphosphonates during the trial is accepted only if the patient has bidimensionally measurable lesion(s) outside the bone which can be followed for response. In this case bone lesions will be considered non-evaluable. A short-term course with bisphosphonates for hypercalcemia is accepted..."

7.1.7 Schedule of Assessments

Sponsor's Table 3:
Patient evaluation schedule

	Baseline	First 24 weeks		Week 25-108		After 108 weeks	Off Treatment[a]	Follow-up every 3 months	Follow-up every 6 months
		week 8, 16	Week 24	Every 12 weeks	Every 24 weeks	Every 24 weeks			
History	X								
Concomitant Medications	X	X	X	X		X	X	X[m]	
Physical examination	X ①	X	X	X		X	X	X[l]	
Hematology, blood chemistry, urinalysis	X ①	X	X	X		X	X	X[m]	Following resolution
FSH (± estradiol)	X ②								
ECG	X ①	If clinically indicated							of toxicities
Adverse events	X	X	X	X		X	X	X[m]	and disease
TRSS, PS, QoL	X	X	X	X		X	X		Progression
E_1, E_2, E_1S assay	X	X[b]	X		X	X	X		or start of new
Chest X-rays	X ③	X[c]	X	X[e]	X	X	X[c]	X[l]	anti-tumoral
Bone scan (scintigraphy)	X ④		X[d]		X[d]	X[d]	X[d]	X[l]	Therapy
Bone X-ray/ CT scan	X[c] ③	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[l]	
Liver ultrasound[g]	X ③	X[c]	X[c, h]	X[c]	X[h]	X[c, h]	X[c]	X[l]	
Liver CT scan/MRI[i]	X ③	X[c]	X[c, j]	X[c]	X[j]	X[c, j]	X[c]	X[l]	
Other tumor evaluations	X ③	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[l]	
Drug compliance[k]		X	X	X		X	X		

Table 3, vol. 3.81

[a] In patients withdrawn from the study for reasons other than PD tumor response will be assessed at treatment discontinuation unless it has been done within the previous 4 weeks (6 months for bone scan).
[b] At week 8 only.
[c] If abnormal at baseline and used to follow up target lesions.
[d] To follow lesions not identifiable by X-ray/CT scan at baseline or for restaging purposes every 24 weeks.
[e] To confirm lesions detected by bone scan.
[f] If abnormal at baseline or to confirm lesions detected by bone scan during the treatment period.
[g] Liver ultrasound accepted at baseline only in case of no liver metastases AND normal LFT. Not required if liver lesions are followed up by CT scan or MRI
[h] For restaging in pts without liver metastases at baseline.
[i] Mandatory at baseline in case of liver metastasis or increased LFT. Any time to confirm objective response and PD detected by ultrasound, or in case of an increase in LFT.
[j] For restaging in patients with liver metastases at baseline.
[k] Will be assessed by tablet counting.
[l] If disease is in response or stable at off treatment visit to follow up tumor response. Tumor assessments to be done as on treatment.
[m] If unresolved toxicity/adverse event observed at off treatment visit

① within 1 week of baseline
② within 6 weeks of baseline; estradiol is required to confirm borderline FSH values
③ within 4 weeks of baseline
④ within 6 weeks of baseline

7.1.8 Efficacy Criteria and Study Endpoints

- **Tumor Response Criteria**

Sites of tumor were classified at baseline as measurable, evaluable or nonevaluable. Criteria were specific to bony or non-bony lesions (Sponsor's Display 2). Although bone disease was not considered measurable, it could count toward response as either evaluable or nonevaluable disease (Sponsor's Display 2).

Sponsor's Display 2: Classification of Lesions at Baseline

Classification	Non-bony lesions	Bony lesions
Measurable	Bidimensional with • at least one diameter ≥ 2 cm OR • at least one diameter ≥ 1 cm for: ◊ photographed skin lesions ◊ lesions on chest-X-ray ◊ liver and extra-abdominal lesions on CT scan	
Evaluable	• bidimensional, but not meeting the criteria for measurable • unidimensional	• lytic lesion on X-ray/CT scan surrounded by calcified bone
Non-measurable- Non-evaluable	• deep palpable mass/node not visualized instrumentally • pleural effusion • atelectasia • pulmonary lymphangitic spread • ascites • skin lymphangitis • previous radiotherapy (RT) unless PD demonstrated after RT	• lytic lesions ◊ not meeting the criteria for evaluable ◊ previous RT unless PD demonstrated ≥ 3 months after RT ◊ chronic bisphosphonates therapy • blastic lesions • mixed lesions

Vol. 3.79, p. 35

Response was evaluated by the modified WHO criteria as described below, excerpted from the sponsor's submission (vol. 3.79, p. 38), which is consistent with the protocol.

"CR was defined as the disappearance of all known disease (measurable, evaluable, and non-evaluable), determined by two consecutive observations not less than 4 weeks apart, and no evidence of new lesions.

PR in measurable disease was defined as a decrease from baseline of at least 50% in the sum of the products of the longest diameter and the greatest perpendicular diameter of all lesions as determined by two observations not less than 4 weeks apart. PR in unidimensional disease or small bidimensional lesions that did not meet the criteria for measurability was characterized by a decrease from baseline of at least 50% in tumor dimension. In the case of bone lesions, PR referred to an estimated decrease in size of at least 50% compared to baseline, or unequivocal radiographic demonstration of recalcification lasting 4 weeks or more. Disease progression in any known lesion (measurable, evaluable, or non-evaluable) and the appearance of new lesions were not allowed. Responses for non-evaluable lesions could not be assessed as PR.

NC was defined as an increase of less than 25% or a decrease of less than 50% in measurable disease or stabilization of evaluable disease compared with baseline for a period of at least 8 weeks from the start of therapy, and no appearance of new lesions. In the case of bone lesions, NC applied if the criteria for CR, PR, or PD were not met.

PD was noted if one or more of the following criteria were met:

(1) An increase of 25% or more in the size of one or more lesions compared with the smallest previous assessment. In the case of lesions with largest diameter ≤ 2.0 cm, any increase of ≥ 25% but < 50% was to be confirmed by the same physician 4 weeks later.

(2) Any unequivocal worsening or clear progression of existing evaluable or non-evaluable bony and non-bony lesions; in the case of bony lesions, an unequivocal worsening of bone scans or x-rays as indicated by an increase in the number of lesions or an increase in the size of lesions, not attributable to tumor flare.

(3) The appearance of any new lesion.

(4) The requirement for RT, surgery, or other antitumor treatment of lesions which were progressing or causing symptoms after 8 weeks on study.

Occurrence of bone compression or fracture and its healing and/or increased radionuclide uptake on bone scan was not used as the sole indicator(s) of progressive disease.

Overall response was determined based on the tumor response criteria for measurable, evaluable, and non-evaluable disease as defined above. Overall response was recorded at each visit.

If both measurable and evaluable disease were monitored in the same patient, the result of each was recorded separately. In patients with multiple measurable lesions, the response for measurable disease was calculated by summing the areas of all lesions of all organs involved.

Response in non-evaluable lesions could influence overall success in the following cases: (1) a CR in non-evaluable lesions had to be observed along with a CR in measurable and evaluable lesions to classify as an overall CR; (2) PD of a non-evaluable lesion classified as an overall PD.

The algorithm for overall response evaluation in patients with measurable, evaluable, and non-evaluable lesions is presented in Display 3."

Sponsor's Display 3: Overall Response Evaluation

Measurable (bidimensional)	Evaluable	Non-Evaluable	Overall
PD	Any	-	PD
Any	PD	-	PD
Any	Any	PD	PD
NC	NC or PR	-	NC
NC	CR	-	PR
PR	NC or PR or CR	-	PR
CR	NC or PR	-	PR
CR	CR	CR	CR

Abbreviations: PD = progressive disease; NC = no change; PR = partial response; CR = complete response

NOTE: The overall response was considered not evaluable for the visit in case the entire extent of the disease was not evaluated according to the schedule of the protocol (see par. 4.7.1.1 in the protocol) unless the patient progressed at that visit.

- **Time to Event Endpoints** (excerpted from protocol)

"**Duration of objective response** (CR+PR) will be calculated from the date the treatment was started and from the date objective response was first documented to the date of PD.

Time to progression (TTP) will be calculated as time between the first day of treatment and the date of documented disease progression or the date of tumor-related death in the absence of previous documented PD. When disease progression is suspected prior to documentation, time to progression will be calculated from the date of treatment start to the day when progression was suspected, provided that progression is later documented and the date of suspected PD is recorded on the CRF.

Time to treatment failure (TTF) will be calculated as time between the day of treatment start to the date of diagnosis of progression, withdrawal from study treatment for any reason, administration of other antitumor treatment or death for any causes, whichever is the earliest event.

Survival
It will be calculated as time between the date of treatment start and the date of death for any reason."

- **Evaluability** (excerpted from the protocol)

"A patient will be considered not evaluable for efficacy if she does not meet the eligibility criteria which define the target population for efficacy evaluation. The evaluability for efficacy of those cases where the entire extent of the disease was not evaluated at each visit as per protocol will be considered on a case by case basis: all cases for whom the assignment of response is controversial will be submitted to the judgement of the Peer Committee in blind condition.

A patient will be considered not evaluable for tumor response if any of the following occurs before the first complete assessment of tumor response:

(1) Withdrawal from the study during the first 8 weeks of therapy for any reason, or after week 8 for any reason other than PD;
(2) Administration of corticosteroids, bisphosphonates, or radiotherapy/surgery to the only lesion monitored for response in the absence of PD (unless it is a condition specified in 4.5.3);
(3) Non compliance with treatment (i.e. < 80% or >120% of the intended dose).

The occurrence of any of the above conditions before completion of 24 weeks of therapy will render the patient not evaluable for the assessment of prolonged disease stabilisation (NC >24 weeks)."

- **Subjective Response**

Performance Status would be graded according to the ECOG scale at baseline and each visit.

Tumor-related signs and symptoms. (excerpted from the protocol) "Pain and other signs and symptoms considered as tumor-related will be followed during therapy to assess subjective response to the drug.

Pain severity will be graded from 0 to 5 according to O. P. Purohit et al.
grade 0 - none,
1 - mild,
2 - moderate,
3 - severe,
4 - very severe, and
5 - intolerable.

In case of pain in multiple sites, the most severe pain will be taken into consideration when scoring severity. The average severity grade over the week prior to the visit will be recorded. In addition, to register serious tumor-related events, the highest pain severity grade since the last visit will be recorded. However, the latter will not be considered for the analysis of subjective response.

If a condition specified below occurs, namely:
- increase in pain is associated with a pathologic fracture of the bone and no signs of PD are observed in this lesion;
- increase in pain is associated with surgery or a concomitant trauma, or exacerbation of chronic disorders of the joints and/or muscoloskeletal disorders;
- clear psychological stress not related to the disease

the effect of the study treatment on tumor related pain will be registered as non-evaluable at this visit and pain will be recorded on the Adverse Event section of the CRF and its most likely cause specified.

TRSS will be graded according to the CTC. For each symptom, at each visit, the average grade of intensity during the last week will be recorded. In addition, to register tumor-related serious events, the highest severity grade since the last visit will be registered, too. However, only the average grade of severity over the last week will be considered for the analysis of subjective response.

In case

- a symptom initially classified as tumor-related is subsequently attributed to a cause other than tumor (e.g. tumor-related nausea followed by nausea due to food poisoning), or
- a tumor-related symptom is masked by a different non-tumor related symptom (e.g. tumor-related anorexia and drug-induced nausea),

the intercurrent symptom will be recorded on the Adverse Event section of the CRF and its most likely cause specified. For this visit, the tumor-related symptom will be registered as non-evaluable."

Quality of life. The EORTC QLQ-C30 questionnaire will be used, which consists of 30 items organized into 5 functional scales (physical, role, emotional, social and cognitive functioning), 3 symptom scales (fatigue, pain and nausea and vomiting), a global health status/QOL scale, and a series of single item measures (dyspnea, sleep disturbance, constipation and diarrhea) and perceived financial impact.

Estrogen assays. (excerpted from the protocol)

"Serum E_1, E_2 and E_1S will be measured in a subset of 200 patients (100 each arm) enrolled at selected centers. Patients taking corticosteroids (topically or systemically) during the 4 weeks before treatment start and/or on study should not be sampled for estrogens assay.

Blood samples (15 ml each) will be taken according to the following schedule:

- at baseline (within 24 hours before treatment is started);
- after 8 and 24 weeks of therapy;
- every 24 weeks thereafter and
- at the time of disease progression or in any case at discontinuation of treatment if it occurs for any reason other than PD (within 24 hours after treatment discontinuation).

Patients should be instructed not to take the assigned drug on the days of sampling until blood is sampled...The samples will be collected by the local Study Monitor and then dispatched according to the procedure described in the appendix..."

7.1.9 Safety Assessments

Safety assessments were based on physical examination, laboratory tests and the reporting of adverse events. Tumor-related signs and symptoms were collected separately on the CRF. Non-tumor related adverse signs and symptoms were collected using a checklist of nine solicited events common to hormonal therapy (nausea, abdominal pain, dizziness, insomnia, anxiety, depression, fatigue, increased sweating and hot flushes) as well as by an open questionnaire. Adverse events were coded by WHO-ART terminology, while severity for both tumor-related and non-tumor related adverse events were graded by the NCI Common Toxicity Criteria (version 1.0). See Section 7.1.7 for test and frequency of assessments.

7.1.10 Withdrawal from Treatment and Conditions for Unblinding

- **Withdrawal**

Patients could be withdrawn from treatment for the following reasons:

(1) Medical necessity;
(2) Patient desire;
(3) Tumor progression;
(4) Unacceptable toxicity precluding further therapy;
(5) Patient is lost to follow-up;
(6) Administration of other systemic antitumor treatment.

- **Unblinding (excerpted from the protocol)**

"The blinding of the trial will be broken at the time of the primary statistical analysis; after that the patients still on therapy will continue treatment in open conditions.

Before the primary statistical analysis is performed, the treatment code will not be broken unless prompt identification of the drug is required , i.e.:

- in case of emergency
- in case a patient with progressive disease might benefit from a further endocrine therapy and it is of importance for choice of further therapy to know which trial treatment the patient received...

...Code breaking should be performed by the local Study Monitor unless a delay in the identification of treatment would endanger the patient. If treatment code is opened at the investigational site the Investigator should immediately inform the local Study Monitor. The reason for and the date of code-breaking should be recorded in the CRF. In the case the code is broken due to a serious event possibly drug related, the patient must be withdrawn from the treatment."

7.1.11 Statistical and Analytical Methods

- **Sample size (excerpted from the protocol)**

The results of this calculation is that if the true RR in exemestane arm is at least 2% higher in absolute terms than megace RR, exemestane will be considered at least equivalent to megace, with a power of 80% (alpha = 0.10, one-sided.

Furthermore, a population of 750 patients also enables to test the hypothesis of equivalence on time to progression, when a hazard ratio < 1.25 is taken as evidence of equivalence. Median time to progression of 5 months in megace group, exponentially distributed survival function, alpha = 0.10 (one-sided) and power = 0.80 are the assumptions used in performing this calculation.

- **Efficacy**

The efficacy analysis will be carried out according to the principles of intent-to-treat- The primary analysis will include patients' data collected for at least 16 weeks since the last patient entered the study.

The upper limit of 90% CI of the difference between the tumor objective response rate in the two treatment groups (megace RR - exemestane RR) will be calculated and the equivalence will be accepted if it will not exceed 25% of megace RR. The proportion of patients with NC or long term stabilisation (NC ≥ 24 weeks) (50-52) out of the total number of patients included in each treatment arm will be compared by Chi square test.

The analysis of the primary end point will be stratified according to the previous response to TAM, previous chemotherapy and site of metastasis. Additionally other baseline characteristics not accounted for by the pre stratification will be evaluated by logistic regression models. Duration of objective response, TTP, TTF and survival in the two treatment groups will be analysed by non-parametric methods for survival analysis (log-rank test, Kaplan-Meier curves) and by Cox model in order to take into consideration covariates of relevance (such as previous response to TAM and site of metastasis). The 90% confidence interval of the observed relative risk will be calculated, as well.

Patients withdrawing from the trial without progressive disease or patients still on treatment at the time of analysis and with no evidence of progression will be censored from the analysis of duration of response and TTP; deaths due to tumor or of unknown cause will be considered progressive disease. TTF will be censored only for patients remaining on trial at the time of the analysis and who have no evidence of progressive disease. Because of the lack of independence among the TTF end points, techniques accounting for competitive risks will be applied...

- **Interim Analysis**

The reported toxicities will be also summarized. All the analyses will be carried out in blind conditions except for the one sided confidence interval of the difference in the objective response rate which will be computed by a statistician external to the study. Results of the analyses and the treatment codes will be provided to an independent Committee who may recommend to stop the trial if equivalence is proven or if

evidence exists that either of the two treatments is causing a high rate of undue toxicity. The interim results are not to be reported publicly or presented at conferences unless the trial is stopped."

Assessment of TRSS

- **Pain** (excerpts from the protocol are within quotation marks)

Baseline and subsequent pain assessments would be scored by a modified O.P. Purohit scale, a composite of (1) pain score assessed by the physician; (2) analgesic consumption score; and, (3) PS. A pain response was defined as an overall score > 20% as compared to baseline on at least two consecutive assessments.

"Patients will be classified as responders if they will have a reduction in the overall pain score greater than 20% as compared to baseline on at least two consecutive assessments. The percentage of responders in the two treatment groups will be analyzed applying a non-parametric method for categorical data and the 95% CI of the difference in the rate of responders will be calculated.

The time pattern of the overall pain score in the two treatment groups will be evaluated by parametric methods and graphically presented."

Quality of Life

See Appendix II for the EORTC QLQ C-30 questionnaire.

Serum estrogen levels (excerpted from the protocol)

"Descriptive summary statistics of the levels of each hormone will be provided. The time pattern of the serum estrogen levels in the two treatment groups will be evaluated by non-parametric methods and graphically presented. In the exemestane group the degree of estrogen suppression will be correlated with tumor response by multivariate analysis."

7.2 Trial Results

7.2.2 Conduct of the Study

- The study was conducted in accordance with the Declaration of Helsinki; patients gave either written or oral witnessed informed consent.

- **Randomization**

(1) Of the 769 patients entered, 366 randomized to exemestane and 403 to megace. The sponsor states that the degree of imbalance is not excessive based on the results of a simulation study they conducted (Appendix 10, vol. 3.85).

Reviewer Comment: The simulation was based on a sample size of 100 patients/country (for 18 countries, Ireland being counted with Great Britain). However, patient numbers/country range from a maximum of 150 for the U.S. to a minimum of 2 for Portugal. Only two had ≥ 100 patients; 14/18 contributed < 60, 10/18 contributed < 25. (See Reviewer Table 3) Thus, n = 100 is not reflective of the trial. However, the sponsor has clarified that minimization was carried out separately within each country and with this procedure, the imbalance becomes plausible. The sponsor acknowledges that empirically a high degree of variability is noted with small sample size (< 30 patients) whereas assignment percentage comes close to 50% for larger sample sizes.

(2) The NDA states "Upon review of the randomization and case report forms, inconsistencies were discovered in the investigators' use of the factors for the randomization procedure. A post-randomization assessment and re-assignment to the three factors was therefore conducted."

Reviewer Comment: The sponsor was requested to provide clarification, including type and frequency of disagreements. A total of 184 patients (23.9%) were reassigned to randomization prognostic factors--94 patients (25.7 %) on exemestane and 90 (22.3%) on megace. The number of reassignment per prognostic category is shown in Reviewer Table 2, below. Note that one patient may have been reassigned in more than one prognostic factor category. The concordance rate per stratification factor ranged from 75-95% per factor (see Appendix III, Sponsor Table 20.2).

Reviewer Table 2*:
Number of Reassignments to Prognostic Factors per Arm

Prognostic Factor	Exemestane	Megace
Response to Prior Tamoxifen	40 (10.9)	36 (8.9)
Prior Hormonal/Chemotherapy	25 (6.8)	23 (5.7)
Site of Metastasis	47 (12.8)	38 (9.4)

Source: Sponsor amendment "BM" dated 9/20/99
*Some patients had more than one reassignment.

The sponsor was also asked to submit frequency of reassignment per country and center. Review revealed no apparent systematic bias. Reassignments were seen in centers located in the U.S. and abroad, as well as in large and small accruing countries .

For purposes of assessment of balance of baseline characteristics, Reviewer Table 4 juxtaposes both investigator and sponsor assignments to these prognostic factors used in randomization.

(3) Two patients (#124002 and #417004) randomized to megace were inadvertently dispensed exemestane.

- **Unblinding**

The precise number of patients that had a treatment code broken during the study depends on the source document, but ranges between 145 and 153 (Source: listing 8.6 and 8.7 of Section 11; MS Access database Treatment_Code_Breaking).

Reviewer Comment: *Approximately 20% of patients had a treatment code break. Review of centers for frequency of unblinding reveals no obvious pattern--countries ranged from no submission of requests for unblinding to requests for unblinding in a third of patients). The predominant reason for unblinding was progressive disease.*

The unblinding during the trial plus the known side effect profile of megace, raises the issue of whether treating physicians were able to discern a patient's treatment. However, efficacy data was reviewed by an Independent Peer Review Committee. The sponsor was asked if and how blinding was preserved for these secondary reviews. Answer: "Both the initial reviewers and the PRC were blinded to treatment. Although the protocol did not formally prohibit the investigator to report the medication the patients had received while on study on the hospital charts, this was specifically requested in the Investigator's Manual: The investigator should record this information on a separate sheet of the hospital chart that would not be disclosed to the Monitor or the source verification, after code breaking, will be done through cross-table verification (sic). To avoid that the monitor have access to the information regarding the treatment, the form received back from the Randomization Office should be filed separately. Furthermore the second, central PRC, that dealt with the discrepancies did not have access to the hospital charts, nor was in direct contact with the investigators."

- **Efficacy Review Committee**

As planned in the protocol, the study report states patients considered to have an objective response underwent peer review. Review was central by "an independent panel consisting of a radiologist and an oncologist" for sites within the US; for countries outside the US, on-site review was conducted by [redacted]. In the case of disagreement with the investigator, data were reviewed by a Peer Review Committee (PRC) composed of two oncologists and two radiologists not affiliated with the [redacted]

- **Protocol Violations**

Violations were classified as either entry criteria violations or as major protocol violations occurring during the study. The percentage of the two kinds of violations summed represents 38% and 39% of patients on exemestane and megace, respectively. The distribution of violations per arm appear balanced.

Violations of Eligibility Criteria. The sponsor's review of the eligibility status of entered patients found a 12.8% ineligibility rate on exemestane and 12.7% on megace (this category is distinct from the 15.3 % ineligible but accepted as exception in patients on exemestane and 15.9% on megace). Reasons for ineligibility are shown in Sponsor Display 8.

Sponsor's Display 8: Number (%) of Patients Classified as Not Eligible according to Final Assessment

Eligibility criteria not fulfilled	Exemestane	Megestrol acetate
All patients randomized	366 (100.0)	403 (100.0)
Any criterion	47 (12.8)	51 (12.7)
Hormonal therapy not indicated: massive visceral disease	8 (2.2)	10 (2.5)
Thromboembolic disease	8 (2.2)	9 (2.2)
No bidimensional measurable or evaluable bone disease	8 (2.2)	7 (1.7)
Patient's informed consent not obtained*	10 (2.7)	2 (0.5)
ER and PgR unknown, and no response to prior hormonal therapy	3 (0.8)	6 (1.5)
Severe cardiac disease	3 (0.8)	4 (1.0)
Diabetes mellitus uncontrolled	1 (0.3)	3 (0.7)
Hematology test(s) <cut-off limits: neutrophils	1 (0.3)	3 (0.7)
Criteria for postmenopausal status not fulfilled	3 (0.8)	1 (0.2)
ER and PgR negative	3 (0.8)	1 (0.2)
Bisphosphonates treatment with only bony lesion	1 (0.3)	3 (0.7)
Other endocrine therapy	4 (1.1)	
Recurrence of disease >12 months since TAM adjuvant discontinued	1 (0.3)	2 (0.5)
>1 chemotherapy for advanced/metastatic disease	1 (0.3)	2 (0.5)
Disease not progressive at entry		3 (0.7)
Hepatic function test(s) >cut-off limits: alkaline phosphatase	1 (0.3)	1 (0.2)
Hormonal therapy not indicated: inflammatory breast carcinoma	2 (0.5)	
Hormonal therapy not indicated: brain metastases		2 (0.5)
Other cancer except uterine cervix or basal or squamous cell cancer		2 (0.5)
No microscopic confirmation of breast cancer	1 (0.3)	
Progression on TAM <8 weeks (metastatic disease)	1 (0.3)	
Hepatic function test(s) >cut-off limits: bilirubin	1 (0.3)	
Hepatic function test(s) >cut-off limits: SGOT (AST)	1 (0.3)	
No measurable or evaluable disease**	1 (0.3)	
ER and PgR unknown with short duration of TAM in adjuvant setting	1 (0.3)	
Progression after short duration of adjuvant TAM		1 (0.2)
No locally advanced or metastatic disease		1 (0.2)

*2 patients were never treated (pts 048007 and 152002); the remaining 10 patients had a study procedure performed (blood drawn) before informed consent obtained, but informed consent was obtained before treatment started

**incorrectly reported and is being corrected to be "no bidimensional measurable or evaluable bone disease" and "disease not progressive at entry" (pt 089001)

Major Protocol Violations. The following Sponsor Display 9 presents the frequency and type of violation of protocol during the conduct of the trial. The sponsor states that, "These protocol violations were not considered to have affected the study results."

Reviewer Comment: *Support for this conclusion is not offered. It is noted that frequency and type of violation is balanced between the arms. The following comments address the three most common violations and are based on review of Appendix 14, listing 5:*

(1) The sponsor distinguishes between incomplete tumor assessments during the trial that did not affect assignment of best response (e.g., routine imaging studies of sites not known to have disease) and those that did (failure to assess all known sites of disease). Patients with insufficient data to assess response would be assigned NE; however, may have been able to be assigned a category at a later date. These types of violations appear evenly distributed, at least with regard to frequency, but the effect on a time to event endpoint, such as PD which might be delayed, is unassessed.

It is noted that the number of patients in this category (based on listing 5 in Appendix 14) does not precisely match the number considered inevaluable for best tumor response by the PRC (see Reviewer Table 5). The drift is toward greater conservatism with the PRC listing 23 patients (7.9%) on exemestane and 37 (9.2%) on megace. The difference between the arms remains about 1%.

(2) *Noncompliance with treatment includes failure to assess compliance and does not necessarily mean that the patient did not take the medication.*

(3) *The use of prohibited medications consisted primarily of steroids for a variety of conditions, including uveitis, pain, asthma, etc. Steroids account for 9/12 violations on exemestane and 20/25 on megace and this reviewer agrees that this should not be confounding for objective response determination in breast cancer (although it might affect pain assessments). Three patients on exemestane did receive medication which could be confounding (bisphosphonates - 2, estrogen - 1) and 2 on megace (bisphosphonates). One patient on exemestane (#41400200) had no other lesions outside bone to evaluate for response*

Sponsor's Display 9: No. (%) of Patients with Major Protocol Violations during Conduct of the Study (vol. 3.79, p. 54)

Violation	Exemestane (N=366)	Megace (N=403)
Any major violation	91 (24.9)	106 (26.3)
Incomplete tumor assessment during treatment preventing assignment of best response or its duration	24 (6.6)	31 (7.7)
Noncompliance with treatment for the whole treatment period	18 (4.9)	20 (5.0)
Treatment with concomitant medications not allowed	12 (3.3)	25 (6.2)
Noncompliance with treatment before the first complete assessment of tumor response	15 (4.1)	21 (5.2)
Incomplete tumor assessment not affecting assignment of best response or its duration	9 (2.5)	13 (3.2)
Tumor lesions assessed by method other than used at baseline	11 (3.0)	8 (2.0)
Baseline assessment performed out of interval foreseen by the protocol	7 (1.9)	10 (2.5)
Noncompliance with treatment during part of the treatment period	3 (0.8)	9 (2.2)
Incomplete tumor assessment at baseline	4 (1.1)	7 (1.7)
Concomitant radiotherapy and/or surgery and/or drainage on the only lesions in absence of PD	3 (0.8)	1 (0.2)
Compliance with treatment and drug accountability	1 (0.3)	1 (0.2)
Treatment with expired drug*	1 (0.3)	0

7.2.2 Enrollment, Disposition, Demographics and Baseline Characteristics

- **Enrollment:** A total of 769 patients were randomized to treatment in 19 countries at 144 centers. "Center" may, in this NDA, represent multiple sites. Recruitment by country is shown in Reviewer Table 3.

Reviewer Table 3:
Enrollment by Country

Country	# Centers	# Pts
U. S.	37	150
Belgium	14	134
Argentina	7	83
Netherlands	12	62
Italy	3	56
U.K.	13	54
Germany	15	52
Spain	11	25
Slovenia	1	22
Turkey	6	22
Australia	5	20
Mexico	3	20
France	4	19
Brazil	3	17
Poland	3	12
South Africa	4	11
Austria	2	8
Portugal	1	2
Ireland	2	–
Total: 19	144	769

Composite table derived from Sponsor's Tables 1 and 1.1 from vol. 3.79 and List of Investigators contained in Appendix 5, vol. 3.82 and Appendix 8, vol. 3.85.

There were 37 sites accruing 150 patients in the U.S; the single site with the greatest accrual in the U.S. entered 9 patients.

- **Disposition:**

The median duration of follow-up was 55.4 weeks for patients receiving exemestane vs. 44.1 weeks for patients randomized to megace. Information on disposition is derived from the Off Study form of the CRF. This form provided the investigator with 7 categories of reasons, including "other" (see Sponsor's Display 6). The reasons for withdrawal appear to be balanced across the arms with the exception that 5.0% of patients receiving megace were withdrawn for an adverse event compared to 1.6% on exemestane.

The reasons that 6 randomized patients did not receive treatment are: #048007 and #060003 – informed consent not given; #087004 and #152002 – patient refusal although informed consent had been given; #436003 and #033002 – investigator decision.

Sponsor Display 6*: Disposition (Abridged)

Reasons for Withdrawal After Start of Rx	Exemestane		Megace	
	No.	%	No.	%
Progressive disease	252	68.9	281	69.7
Adverse Event	6	1.6	20	5.0
Patient Refusal	9	2.5	14	3.5
Protocol Violation	1	0.3	0	0
Death	6	1.6	10	2.5
Lost to follow-up	3	0.8	1	0.2
Other	8	2.2	9	2.2
Subtotal	**285**	**77.8**	**335**	**83.1**
Randomized but not Rx'd	5	1.4	1	0.2
Still on Rx as of 8/31/98	76	20.8	67	16.6
Total Randomized	**366**	**100**	**403**	**100**

*Modified from Sponsor's Display 6, vol. 3.79, p. 51.

Reviewer Comment: *The adverse event category appears to have been interpreted as drug-related toxicity rather than as the broader category of treatment emergent signs and symptoms. Review of the reasons for patient refusal and death are discussed in further detail in Section 7.2.4, Safety Profile.*

- **Demographics and Baseline Characteristics**

The following table, Sponsor's Display 10, presents demographics of the study by arm. The median age for patients receiving either exemestane or megace was 65. Greater than 90% of patients on the study were caucasian. Approximately 50% of patients on both arms were considered overweight. No significant difference was apparent with regard to performance status, years from menopause or type of menopause.

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Sponsor's Display 10*:
General Baseline Characteristics across Treatment Groups

Characteristic	Exemestane (N=366)	Megace (N=403)
Age (years)		
Median	65	65
Min	35	30
Max	89	91
Mean	64	65
SD	10	10
Number (%) of patients by age category		
<50 years	29 (7.9)	24 (6.0)
50-64 years	150 (41.0)	159 (39.5)
65-79 years	163 (44.5)	188 (46.7)
80 years	24 (6.6)	32 (7.9)
Number (%) of patients by race		
White caucasian	336 (91.8)	376 (93.3)
Black	11 (3.0)	9 (2.2)
Asian	5 (1.4)	3 (0.7)
Other race	14 (3.8)	15 (3.7)
Number (%) of patients by body mass index		
Underweight (<20 kg/m^2)	15 (4.1)	18 (4.5)
Normal (20-25 kg/m^2)	116 (31.7)	117 (29.0)
Overweight (>25 kg/m^2)	194 (53.0)	224 (55.6)
Unknown	41 (11.2)	44 (10.9)
Number (%) of patients by performance status		
0	167 (45.6)	187 (46.4)
1	162 (44.3)	172 (42.7)
2	34 (9.3)	42 (10.4)
Unknown	3 (0.8)	2 (0.5)
Postmenopausal status		
Number (%) of patients	366 (100.0)	403 (100.0)
Years from menopause		
Median	15	17
Min	0	1
Max	55	50
Mean	16	17
N	364	398
Number (%) of patients by type of menopause		
Natural	258 (70.5)	293 (72.7)
Surgical	43 (11.7)	43 (10.7)
Radiotherapy	4 (1.1)	10 (2.5)
Chemical	32 (8.7)	24 (6.0)
Other	29 (7.9)	33 (8.2)

*Abridged from Sponsor's Display 10, vol. 3.79, p. 55

The study attempted to control for prognostic factors of potential clinical importance by stratification/minimization; however, as discussed previously, 23.9% of patients were reassigned. Reviewer Table 4 juxtaposes sponsor's reassignment to factors next to the investigator's initial assignment.

Reviewer Comment: *Reassignment has not made a major impact on the degree of balance between the arms. With either the sponsor's or investigator's assessments, the trend toward a better patient population is seen in the exemestane arm with regard to site of metastasis (greater number of patients with soft tissue only disease; fewer with bone only or visceral disease). This advantage is possibly underscored by whether of not the disease was measurable. More patients with soft tissue disease and fewer patients with visceral disease were considered to have measurable disease on exemestane.*

Reviewer Table 4:
Baseline Characteristics of Potential Prognostic Value

	Exemestane N = 366		Megace N = 403	
Randomization Characteristic	**Investigator**	**Sponsor**	**Investigator**	**Sponsor**
Response to prior TAM				
(Neo)Adjuvant	143 (39.0)	145 (39.6)	149 (40.0)	152 (37.7)
CR, PR, or NC ≥6 months	193 (52.7)	179 (48.9)	225 (55.8)	210 (52.1)
NC < 6 months, PD, or NE	30 (8.2)	42 (11.5)	29 (7.2)	41 (10.2)
Prior Chemotherapy				
No chemotherapy	213 (58.1)	203 (55.5)	235 (58.3)	226 (56.1)
Adjuvant chemorx only	94 (25.7)	104 (28.4)	102 (25.3)	108 (26.8)
Chemorx for advanced disease +/- adjuvant	59 (16.1)	58 (15.8)	66 (16.4)	67 (16.6)
Site of Metastasis				
Soft tissue only	48 (13.1)	54 (14.8)	45 (11.2)	51 (12.6)
Bone only	69 (18.8)	61 (16.7)	77 (19.1)	73 (18.1)
Bone + soft tissue	36 (9.8)	43 (11.7)	38 (9.4)	38 (9.4)
Visceral +/- other sites	213 (58.2)	207 (56.6)	243 (60.3)	239 (59.3)
Other Characteristics				
Number (%) of pts by duration of first disease free interval				
<2 years	55 (15.0)		56 (13.9)	
2-< 5 years	130 (35.5)		142 (35.2)	
≥ 5 years	114 (31.1)		134 (33.3)	
NA (M=1)	43 (11.7)		52 (12.9)	
NA (no surgery)	23 (6.3)		19 (4.7)	
NA (surgery date after date of PD)	1 (0.3)			
Number (%) of pts by washout from last hormonal rx				
< 4 weeks	260 (71.0)		299 (74.2)	
4 - < 9 weeks	54 (14.8)		54 (13.4)	
9 - 52 week	30 (8.2)		37 (9.2)	
>52 weeks	18 (4.9)		12 (3.0)	
Unknown	4 (1.1)		1 (0.2)	
Number (%) of pts by site of disease (pts with only 1 site)				
Soft tissue only	54 (14.8)		51 (12.7)	
Bone only	61 (16.7)		73 (18.1)	
Visceral only	46 (12.6)		69 (17.1)	
Receptor status (either at first dx or recurrence)				
ER and/or PR +	246 (67.2)		274 (68.0)	
ER and PR unknown	116 (31.7)		128 (31.8)	
Responders to prior hormonal therapy	68 (18.6)		85 (21.1)	
Nonresponders to prior hormonal therapy	2 (0.5)		2 (0.5)	
Nonevaluable for response to prior hormonal therapy	46 (12.6)		41 (10.2)	
Measurability vs. Evaluability				
≥ 1 measurable lesions				
Any site	287 (78.4)		314 (77.9)	
Soft tissue	165 (45.1)		156 (38.7)	
Bone	1 (0.3)		0 (0)	
Visceral	168 (45.9)		200 (49.6)	
Lung	73 (19.9)		94 (23.3)	
Liver	79 (21.6)		105 (26.1)	
Other	38 (10.4)		34 (8.4)	
Evaluable lesions only	75 (20.5)		82 (20.3)	
Nonevaluable lesions only	3 (0.8)		5 (1.2)	
N/A	1 (0.3)		2 (0.5)	

Data derived from Sponsor's Display 11, vol. 3.79, pp. 57-60, Display 12, vol. 3.79, p. 60 and Table 20.2 (submitted as correspondence–see Appendix III).

Presence of comorbid conditions appears to be balanced between the arms (see Sponsor's Display 13, included in Appendix III).

7.2.3 Efficacy Results

7.2.3.1 Primary: Response Rate

Investigator vs. Peer Review Committee.

All objective responses were to be reviewed by an oncologist and radiologist either on site or centrally. The investigators claimed a total of 129 responses. Records on 6 patients (3 on exemestane and 3 on megace) were unavailable for review. Fifty one discrepancies (for response, TTP or both) of the 123 cases reviewed were forwarded to a Peer Review Committee consisting of 2 oncologists and 2 radiologists. Patients assigned the response category of "no change" (NC) were not peer reviewed.

The following excerpt from the study report describes how the final designation of response was chosen in the event of disagreement:

- "The best tumor response assigned by the investigator was considered final for patients not submitted to peer review for any reason.
- Response assigned by the reviewers was considered final for patients who were submitted for such review.
- Response assigned by the PRC was considered final for patients who were submitted for such review.
- Response assigned by the reviewers when the PRC session had already taken place, in agreement with decision of the PRC which stated that in the cases reviewed after the PRC session the worst judgment, investigator's or reviewer's, will be quoted."

Reviewer Table 5*:
Responses according to the Investigator and PRC

Response	Exemestane N = 366		Megace N = 403	
	Investigator	PRC	Investigator	PRC
Objective Response (CR + PR) 95% C.I.	70 (19.1) 15.2-23.5	55 (15.0) 11.5-19.1	59 (14.6) 11.3- 8.5	50 (12.4) 9.4-16.0
Complete Response (CR)	11 (3.0)	8 (2.2)	6 (1.5)	5 (1.2)
Partial Response (PR)	59 (16.1)	47 (12.8)	53 (13.2)	45 (11.2)
Stable Disease > 24 weeks†	70 (19.1)	78 (21.3)	83 (20.6)	85 (21.1)
Not evaluable for best tumor response	26 (7.1)	29 (7.9)	33 (8.2)	37 (9.2)
Not treated	5 (1.4)	5 (1.4)	1 (0.2)	1 (0.2)
Median time to objective response (wks) 95% C.I.	16.1 15.7-23.1	16.7 15.9-23.9	15.0 8.7-16.1	15.8 8.7-16.7
Median duration of objective response (wks) 95% C.I.	82.1 59.7-110.0	76.1 60.4-130.9	60.0 49.7-107.1	71.0 51.6-84.0
Median duration of SD ≥ 24 wks (wks) 95% C.I.	48.0 45.0-60.1	48.0 46.6-60.1	46.6 37.4-56.6	46.6 36.7-55.7

*Data derived from Sponsor's Display 15, 16, 17 and 18
†Not a prospectively defined category of interest but appears in the label

The criteria for equivalence between the treatments is met by either the investigator's or the PRC's response rate. There is no difference in median time to response or of durations of response.

Testing the Equivalency Hypothesis (ICH E9).

ICH E9 raises the issue of that an intent-to-treat analysis is not conservative when testing for noninferiority. Since the sponsor had prospectively defined an evaluable population (see Section 7.1.8 of the protocol review), they were requested to provide the response rate for this population. The analysis

provided by the sponsor supported the ITT analysis (18.2% (8 CR's and 47 PR's) for Exemestane vs.14.9% (4 CR's and 43 PR's) for Megestrol Acetate; Δ = -3.3%, 95% CI for Δ: -2.6%, +9.2%).

Reviewer Comment: *The definition for the evaluable patient population was not the one in the protocol and the criteria appear to have been applied inconsistently. For instance, patients who violated the eligibility criteria for massive visceral disease, or for unknown receptor status in patients without a prior response to tamoxifen, were inconsistently excluded from the evaluable patient population. This analysis is not reliable.*

Complete Responders.

Case report forms (CRFs) for complete responders were reviewed and response status was confirmed. None of the eight had major protocol violations preventing assessment of response. Four patients had a single lesion--in skin (2) or in a lymph node (2). Six of the eight patients had a single organ involved with disease--2 patients had disease confined to skin, 2 to lymph nodes and 2 to the lungs. Six patients had relapsed on tamoxifen, either as adjuvant therapy or treatment for metastatic disease.

Reviewer Comment: *A random sample of CRFs of patients who were assigned a PR were also reviewed. There were no disagreements with assignment of response category.*

Response by Country.

Response rate by country is presented in Sponsor's Display 30. Of the 18 countries (Ireland was counted with the U.K.), 5 trended in favor of megace, 6 in favor of exemestane; the remaining 5 countries had nearly identical response rates in the two arms. Four countries had a notable difference between the arms--Australia, the Netherlands, United Kingdom and Turkey; however, these countries were not the largest accruers and their results did not drive the overall response rate of protocol #018. The largest accruers, USA (150 patients) and Belgium (134 patients), showed no difference between the arms.

Sponsor's Display 30:
Number (%) of Patients with Objective Tumor Response by Country

			Objective response rate	
Country	**Number of Centers**	**Number of patients (exemestane/ megestrol acetate)**	**Exemestane**	**Megestrol Acetate**
Argentina	7	44/39	6 (13.6)	4 (10.3)
Australia	5	8/12	4 (50.0)	-
Austria	2	4/4	-	-
Belgium	14	66/68	9 (13.6)	9 (13.2)
Brazil	3	6/11	-	-
France	4	9/10	1 (11.1)	-
Germany	15	24/28	2 (8.3)	3 (10.7)
Italy	3	25/31	4 (16.0)	3 (9.7)
Mexico	3	10/10	4 (40.0)	4 (40.0)
Poland	3	6/6	1 (16.7)	1 (16.7)
Portugal	1	1/1	-	1 (100)
Slovene	1	11/11	2 (18.2)	2 (18.2)
South Africa	4	6/5	-	2 (40.0)
Spain	11	11/14	2 (18.2)	3 (21.4)
The Netherlands	12	24/38	4 (16.7)	3 (7.9)
Turkey	6	12/10	1 (8.3)	2 (20.0)
United Kingdom •	13	24/30	4 (16.7)	2 (6.7)
USA	37	75/75	11 (14.7)	11 (14.7)

- includes Ireland
- Vol. 3.79, p. 92

Potential Effect of Bisphosphonates.

According to Sponsor's Table 15: Concomitant medications: Analgesic Use (vol. 3.79) a total of 37 patients received a bisphosphonate, 16 on exemestane and 21 on megace.

Reviewer Comment: *(The number of patients in Sponsor's Table 15 on bisphosphonates and megace actually tally 17, for a total of 22 patients.) None of the patients listed in the Table had bone-only disease, as had been intended by protocol inclusion criteria, and therefore should not have prohibited assessment of other sites of disease. One patient, #06900500 from Appendix 15, Listing 5: Major protocol violations, did have bone only disease and received bisphosphonates. Only one of the 33 patients (#06500100) had an objective response (randomized to exemestane). The response designation of PR was based on a supraclavicular lymph node meeting bidimensional criteria for a PR accompanied by a CR in bone.*

New bone lesions were seen at week 48 in the right scapula and sternum; however, bone lesions were considered inevaluable because of administration of bisphosphonates. She is listed as having progressive disease at week 84 when she had PD in the lymph node (also accompanied by additional new bone lesions).

Effect of Tamoxifen Withdrawal Phenomenon.

***Reviewer Comment:** The issue of whether efficacy results in trials of second-line hormonal treatments can be biased by a "tamoxifen withdrawal phenomenon" was discussed at the December 1996 ODAC when Femara™ (letrozole tablets) was presented. The pivotal trials with Femara, as with exemestane, allowed patients onto study without a washout period after treatment with tamoxifen.*

Objective responses due to tamoxifen withdrawal has been reported in ≤ 8% of patients, primarily those with soft tissue disease who have demonstrated a response to tamoxifen. It generally occurs within 1-2 months of cessation of therapy. If stable disease is included with objective response, the rate of response to tamoxifen withdrawal can rise to 30%.

ODAC unanimously agreed (11 to 0) that although a withdrawal phenomenon might cause a modest inflation of results, it should not bias results in favor of either arm in a randomized trial so long as prognostic factors are balanced. The committee was split (6 to 5) as to whether trials ought to require a washout period before initiating treatment with a study drug. Distribution of patients by response to prior tamoxifen and presence of soft tissue disease as the only site of disease can be seen in Reviewer Table 4. There are 2% more patients on megace who had a prior response to tamoxifen but 2% fewer patients on megace with soft tissue only disease.

Prognostic Factors. Site of metastasis was found to be strongly correlate with outcome ($p<0.0001$) whereas previous response to tamoxifen ($p=0.09$) and prior chemotherapy ($p=0.33$).

7.2.3.2 Secondary Endpoints

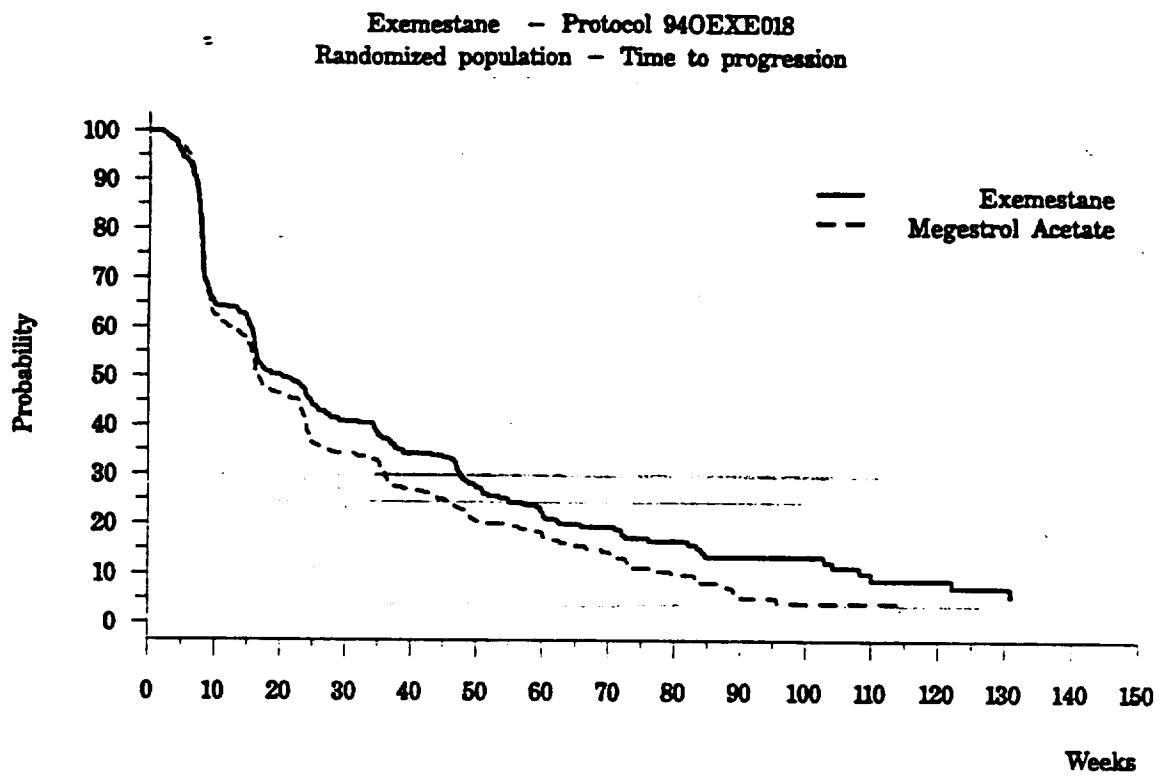
***Reviewer Comments: Multiplicity / False Positive Error Inflation.** There are a very large number of secondary endpoints including several time to event measures (TTP, TTF, time to response, response duration, duration of success, survival), TRSS, Purohit overall pain score, and a large number of QOL measures (15). Thus, there is a major false positive error inflation issue which cannot be ignored. When making claims of statistically significant improvement for some of these endpoints, the sponsor has not adjusted the statistical significance level to account for multiplicities. Thus, any major claims made for the secondary endpoints should be interpreted in this light.*

- **Time to Progression**

The protocol did not specify whether an adjusted or nonadjusted analysis would be primary for TTP. The sponsor undertook both logrank testing and a Cox proportional hazards regression model incorporating the three randomization stratification factors. Logrank analysis yielded a statistically significant finding in favor of exemestane (medians of 20.3 weeks vs. 16.6 weeks, $p=0.037$). The Cox model also yielded a significant treatment effect coefficient in favor of Exemestane ($p=0.023$, hazard ratio=0.82, 95% CI: 0.70, 0.97). TTP data was mature; the percentages of censored observations were 26.2% and 24.3% for exemestane and megace respectively. The Kaplan-Meier plots from the sponsor's univariate TTP analysis is shown on the following page.

The statistical amendment to the protocol specified a hazard ratio (HR) ≤ 1.25 would be taken as evidence of equivalence. The HR of exemestane/megace (unadjusted for prognostic factors) is 0.84; the 95% confidence interval for the HR is (0.71 and 0.99).

Sponsor's Figure 1: Time to Progression



Reviewer Comment: *The reviewers undertook an exploratory analysis to examine the potential impact of geography (U.S. vs. non-U.S. centers) and center size (large contributors vs. small contributors, i.e. ≤ 25 patients) on the robustness of TTP findings. Reviewer Tables 6 and 7 summarize their findings.*

Reviewer Table 6:
TTP by Geographic Location

TREATMENT	N	Median (wks)	% Censored	Logrank
U.S. CENTERS				
Exemestane	75	15.7	29.3	P = 0.95
Megace	75	23.1	26.7	
NON – U.S. CENTERS				
Exemestane	291	21.7	25.4	P = 0.016
Megace	328	16.1	23.8	

Reviewer Table 7
TTP by Center Size

TREATMENT	N	Median (wks)	% Censored	Logrank
LOW CONTRIBUTING COUNTRIES (≤ 25 Patients)				
Exemestane	84	24.7	33.3	P = 0.113
Megace	94	16.7	33.0	
HIGHER CONTRIBUTING COUNTRIES (> 25 Patients)				
Exemestane	281	17.7	23.8	P = 0.102
Megace	306	16.1	21.2	

These exploratory findings indicate a more robust pattern for the Megace treatment arm in terms of median TTP. Superiority is not seen in the U.S. centers.

- **Time to Treatment Failure (TTF)**

Independent Peer Reviewers' Assessement: TTF for patients receiving exemestane was 16.3 weeks (95% CI 15.4 - 21.1) and 15.7 weeks (95% CI 13.7 - 16.7) for megace (p = 0.042).

Investigator Assessment: TTF for patients receiving exemestane was 15.4 weeks (95% CI 15.6 - 22.7) and 16.0 (95% CI 14.0 - 16.9) for megace.

- **Survival**

The sponsor reports a significant logrank test result (p=0.039) favoring exemestane (inestimable vs. 123.4 weeks).

Reviewer Comment: *These data are too immature to draw strong conclusions bearing on a survival advantage. There are 73% censored observations on the Exemestane arm and 68% on the megace arm. The same comment applies to the adjusted Cox regression model for survival.*

At the November 25, 1998 pre-NDA meeting, the sponsor was asked to explain the early separation in survival curves (also seen with TTP and TTF). The sponsor's submission "NC" dated 3/3/99 provides exploratory analyses to address these questions. Early deaths, defined as those which occurred within 15 weeks of the start of treatment were analyzed (reason for censoring at 15 weeks is not explicitly stated). The cumulative probability of death within 15 weeks of starting treatment was 4.4% in the exemestane arm and 7.4% for patients receiving megace. The sponsor identifies disease progression as the cause in 3.8% on exemestane and 5.2% on megace and postulates that they "might be a consequence of treatment failure." The other deaths were due to adverse events or worsening of baseline conditions.

- **Overall Success Rate**

The sponsor presents data as an "overall success rate," defined as the "proportion of patients who achieved a CR, PR or NC of at least 24 weeks' duration." "Overall success duration" for this population is calculated from the first day of treatment to the day of PD. However, this endpoint was not prospectively defined and, as a composite category, arguably adds anything in addition to its component parts. In fact, the results in this category parallel the findings in the other endpoints. No significant difference was seen between the arms with regard to "success rate"; however, the median duration of "overall success" was 60.1 weeks (50.7 - 72.0) for patients on exemestane and 49.1 weeks (45.4 - 61.0) for patients on megace (Log-rank 5.02, p = 0.025).

- **Sponsor's Responder Analyses for Pain Control and Tumor Related Signs and Symptoms (TRSS)**

The sponsor makes the following claims: "In patients with a complete or partial response, a greater percentage of exemestane-treated patients experienced an improvement in overall pain score (51.4% exemestane vs. 46.2% megestrol acetate). Overall, a greater percentage of patients treated with exemestane showed an improvement in tumor-related signs and symptoms compared with megestrol (12.1% exemestane vs. 7.5% megestrol acetate; x^2 ((1df)=2.98, p=.084), with the greatest number of patients showing improvement who had experienced a complete or partial tumor response."

Reviewer Comments: *(1) No attempt was made in the protocol to pre-specify or rank order the major TRSS nor to formulate key hypotheses bearing on TRSS. The protocol only states that data for each TRSS will be tabulated and summarized in frequency tables and that multivariate exploratory methods will be used to characterize distributio.. pattern and relationship to tumor response and QOL outcome. Thus, the findings should be reported in a descriptive manner only. (2) The responder analyses undertaken do not have statistical validity since they involve comparing nonrandomized groups and there is also a lead time bias issue. Such analyses should be used for descriptive purposes only, not inference.*

- **Purohit Pain Score Analysis**

For baseline and each subsequent visit, an overall pain score was derived using a procedure modified from that of Purohit (Br. J. Cancer, 1994). This score is a composite obtained by summing the following three parameters: [a] pain score as assessed by physician on a scale from 0 (none) to 5 (intolerable) [b] analgesic consumption score on a scale from 0 (none) to 6 (oral morphine > 100 mg/day) and [c] ECOG performance status on a scale from 0 (normal) to 4 (completely bed-bound). For statistical analysis the protocol states: "The overall pain score will be standardized over the maximum score possible. Patients will be classified as responders if they have a reduction in the overall pain score greater than 20% as compared to baseline on at least two consecutive assessments. The percentage of responders in the two treatment groups will be analyzed applying a non-parametric method for categorical data and the 95% CI of the difference in the rate of responders will be calculated. The time pattern of the overall pain score in the two treatment groups will be evaluated by parametric methods and graphically presented." A total of 363 Exemestane patients (99.2%) and 399 (99.0%) Megace patients were analyzed. Univariate summary statistics reveal very similar distribution patterns:

Excerpt from Sponsor's Table 8:
Descriptive Statistics for Purohit Pain Score at Baseline

Treatment	Exemestane	Megestrol Acetate
Median	13	13
Minimum	0	0
Maximum	67	73
Mean	16	15
Standard Deviation	16	15
Sample Size	363/366 (99.2%)	399/403 (99.0%)

Of those patients assessed on Purohit pain score, 103 Exemestane patients (28.4%) and 118 Megace patients (29.6%) were considered nonevaluable for this measure (reasons not stated). As previously mentioned, the sponsor's analysis was overall pain score by tumor response which is invalid. Only the following comparison by randomized groups yields meaningful inference:

Reviewer Table 8*:
Purohit Pain Response Analysis

Treatment	Pain Responder	Non-Responder	Total
Exemestane	65 (24.7%)	198 (75.3%)	263
Megace	69 (24.2%)	216 (75.8%)	285
Total	134	414	548

*Data derived from Sponsor's Display 19, vol. 3.79

Chi-square analysis of the responder proportions in this table yields a nonsignificant p-value of 0.89.

- **QOL Analysis**

The European Organization on Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument was utilized. The 30 questions in the instrument were converted into 15 subscales. All patients completing the questionnaire at baseline and at least once during treatment were included in the following analyses: (a) Endpoint analysis utilizing baseline value and last recorded value yielded individual tests for 15 QOL scale/items and associated p-values for testing the difference (Baseline – Last) for Exemestane vs. Megestrol Acetate and (b) Longitudinal analysis via plots of mean change over time and individual ANOVA's to test the Treatment x Time interaction for each QOL scale/item. In their proposed package insert the sponsor makes the following QOL claims: "Patients receiving AROMASIN reported significantly better results than those receiving megestrol acetate for global health status ($p<.001$), two of five functional scales (physical, role; $p<.001$), and three of nine symptom scales (fatigue, dyspnea, and constipation; $p=.001$). Patients receiving megestrol acetate noted significantly better results than patients receiving AROMASIN for one functional scale (emotional; $p=0.01$) and one

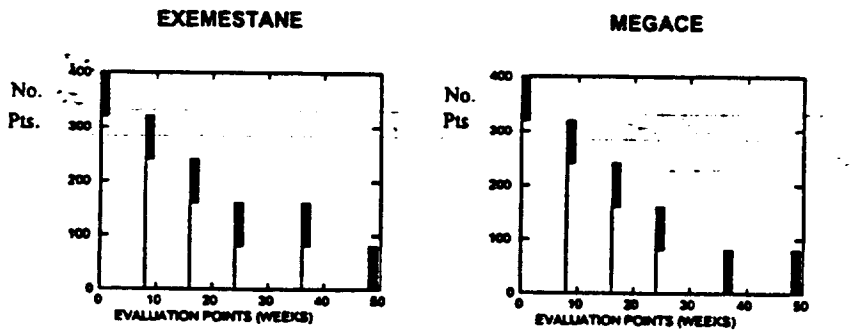
symptom scale (appetite loss; p<0.007). An improvement in pain on both symptom scales was observed for both treatments, but was significantly improved for megestrol acetate (p<0.007). No significant differences were noted for the other subscales."

Reviewer Comments: *(1) As previously noted, no key QOL hypotheses were prospectively identified. (2) There is a huge false positive error inflation problem as 15 unadjusted p-values are reported based on endpoint analyses and 15 additional sets of unadjusted p-values are reported for the ANOVA's. No α-adjustment of any kind was imposed. Given the high degree of multiplicity only descriptive statements about trends toward improvement or worsening are warranted, not inferential claims. (3) The sponsor has provided no analysis to investigate the type of missing data mechanism, i.e., whether informative or noninformative. If the missing data mechanism is informative, then both the endpoint analysis and ANOVA approaches have a high potential for yielding biased results.*

QOL Pain Assessment: The following Reviewer Plot 1 displays the observed missing data pattern for the QOL instrument Pain Question. The other QOL instrument domains and elements reveal a very similar pattern in terms of sample size attrition over time. It can be seen that by Week 16 almost half of the patients on each treatment arm have dropped out of the QOL assessment. By Week 36 the droput proportions show a differential effect, viz., 73% for Exemestane and 84% for Megestrol Acetate. This observation is roughly confirmed by the estimated TTP medians, viz., 20.3 weeks for Exemestane and 16.6 weeks for Megestrol Acetate. Thus, any inferential claims based on data beyond Week 24 are far from robust.

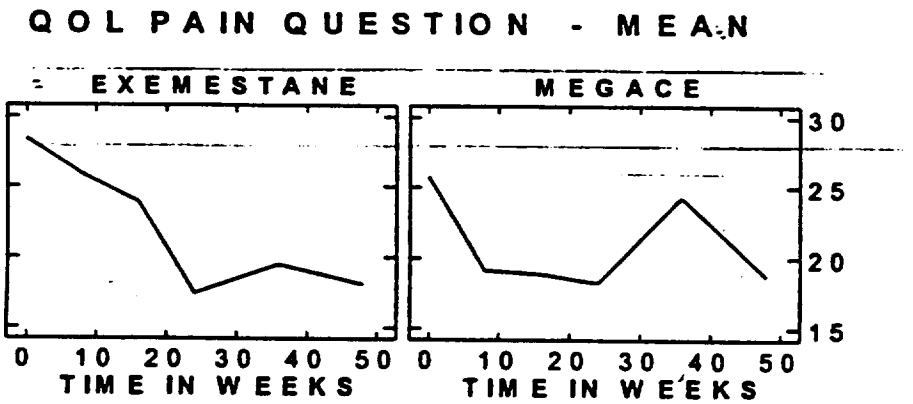
Reviewer Plot 1

MISSING DATA PATTERN / QOL PAIN QUESTION



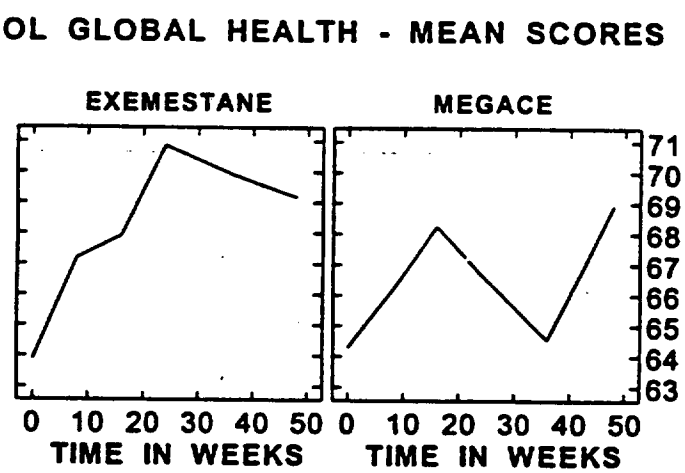
The sponsor claims a highly statistically significant ANOVA Treatment x Time interaction test result for this measure (p=0.0001). The following Reviewer Plot 2 of mean QOL pain scores over time indicates a profile where the exemestane group had a worse QOL pain score at Baseline which trended toward a slight improvement over megace at Week 24. At that point there was a trend toward increasing pain for both with a more marked increase for Megace at Week 36. After this point both decreased to about the same level. Given the attrition pattern after Week 24 and the major multiplicity of endpoints issue, only general statements regarding trends are warranted.

Reviewer Plot 2



QOL Global Health Status Assessment: For the patient assessed QOL instrument Global Health element the sponsor claims a statistically significant (p=0.0069) Treatment x Time interaction effect favoring Exemestane. The missing data attrition pattern is almost identical to that already presented for the QOL Pain Question in the histogram in Reviewer Plot 1. Reviewer Plot 3 of the mean global health scores over time indicates a profile of similar improvement for the two treatment groups until Week 24. At Week 36 there is a more pronounced deterioration for Megace. However, sample size losses at this point in time due to attrition render any inferential claims highly questionable. Again, given the degree of attrition and the major multiplicity issue, only descriptive statements regarding trends are warranted, certainly not inferential claims.

Reviewer Plot 3:



Reviewer's Comments on the Sponsor's QOL Analytic Approach: *To adequately assess the validity of the sponsor's performing endpoint analyses (involving 15 baseline to endpoint comparisons for the QOL scales/elements) and the 15 ANOVA analyses (with missing data imputation) one would need to undertake formal longitudinal modeling to ascertain the pattern mixtures for completers and dropouts. Only if these are similar, indicating a noninformative missing data mechanism, can one justify the validity of their approach. Given the huge multiplicity of endpoints issue only descriptive statements on trends would be warranted even if a full longitudinal analysis were also to be undertaken in the present case.*

- **Estrogen Suppression**

Samples were to be drawn in a subset of 100 patients per arm in 41 selected centers at the following timepoints: baseline, week 8, 24, 48 and at time of progressive disease. Samples were frozen and analyzed centrally in the Laboratory of Endocrinology/Oncology Research at Pharmacia & Upjohn, Nerviano, Italy. Samples were measured by[ ]

Serum samples were received for 168 patients. A total of 126 patients had serum samples drawn at baseline and at least once during treatment and were therefore considered evaluable. Sixty-one patients (48%) were receiving exemestane and 65 (52%) with megace.

Both treatments caused a reduction in serum estradiol, estrone and estrone sulfate. Few conclusions can be drawn past week 8 since fewer than 50% of patients had samples beyond that point.

For details, see Sponsor's Displays 20 and 21 in Appendix III.

The sponsor states that analyses of correlation of degree of estrogen suppression to tumor response were not performed since data indicated that estrogen was completely suppressed. However, there was no evidence of escape from estrogen suppression at time of PD (4 patients on each arm).

7.2.4 Safety Profile

Of the 769 patients randomized, 6 (5 randomized to exemestane, 1 to megace) did not receive study drug and 5 (3 randomized to exemestane and 2 to megace) were not assessed for safety. A total of 758 patients are therefore evaluable for safety, 358 randomized to exemestane and 400 to megace.

7.2.4.1 Extent of Exposure

Data on extent of exposure is available for the 763 patients who were randomized and did receive drug. Compliance was assessed on site by counting tablets returned in blister packs. While only 10% of patients on either arm took 100% of their assigned treatment, 83% on the exemestane arm and 75% on megace were assessed as taking between 80% and 120% of assigned treatment.

Reviewer Table 9:
Extent of Exposure

	Exemestane (N=361)	Megace (N=402)
Mean duration of treatment (weeks)	30.4	25.4
Median duration of treatment (weeks) (range)	17 (0.1 - 133)	16.6 (0.1 - 114.1)
Median time to response (CR+PR, weeks) (range)	16.7 (7.7 - 51)	16.8 (7.4 - 50)

Data derived from sponsor's Displays 31 and 17, vol. 3.79; Appendix 10; pertinent CRFs.

7.2.4.2 Overall Incidence and Severity of Adverse Events

For purposes of an overview, the following Reviewer Table 10 presents incidence of adverse events of any cause and due to study drugs by CTC grade. For CTC grade 3 and 4, types of toxicity are included.

Reviewer Table 10:
Incidence and Severity of Adverse Events

	Exemestane N = 358 No. of Patients (%)	Megace N = 400 No. of Patients (%)
All Adverse Events, any cause	284 (79.3)	320 (80.0)
Adverse Events, related to rx or indeterminate	140 (39.1)	183 (45.8)
Adverse Events, related to rx or indeterminate, Gr 1	84 (23.5)	112 (28.0)
Adverse Events, related to rx or indeterminate, Gr 2	39 (10.9)	41 (10.3)
Adverse Events, related to rx or indeterminate, Gr 3	16 (4.5) • Increased sweating • Hot flushes • Carpal Tunnel • Pain, tumor site • HTN • Dizziness • Headache • Nausea +/- Vomiting • Esophagitis • Erythema multiforme • Cerebral ischemia	26 (6.5) • Increased sweating • Fatigue • Edema, legs • Pain • Pain, tumor site • HTN • Dementia • Hoarseness • Abdominal pain • Anorexia • Constipation • Diarrhea • Dysphagia • Dry mouth • Vomiting • Hyperglycemia • Depression • Insomnia • Lethargy • Sleepiness • Vaginal Haemorrhage • Shortness of Breath • DVT
Adverse Events, related to rx or indeterminate, Gr 4	1 (0.3) • Nausea	4 (1.0) • Pulmonary edema • Colitis/melena • Hepatitis/jaundice • Shortness of breath

Data derived from sponsor's Table 26.1,26.2 and 26.3, vol. 3.80

7.2.4.3 Deaths

A total of 55 patients died on study or within 30 days of receiving study drug: 19 (5.3%) on exemestane and 36 (8.9%) on megace. On both arms, the majority of deaths occurring on treatment were due to adverse events (4 on each arm) which may or may not have been drug-related, while the majority of deaths occurring within 30 days of treatment were due to progressive disease.

The CRF provided four categories for explanation of cause of death: progressive disease, adverse event, worsening of baseline condition and "other, specify." Review of the CRFs led to 12 reclassifications. Details are provided below in Reviewer Table 11 and comments following the table. Relationship of death to drug could be assessed as definite, probably, possible, doubtful, of no relationship or of an indeterminate relationship. Thirteen deaths might have had a relationship to study drug (pt ID numbers in bold in Reviewer Table 11). Six deaths on exemestane were considered to have a "doubtful" relationship, but this could not be excluded. Four deaths on megace were considered to have a "doubtful" relationship, 2 "probably" related and 1 "possibly" related.