

**Reviewer Table 11:  
Deaths On or Within 30 Days of Treatment**

EXEMESTANE Cause of Death	Patient Number	MEGACE Cause of Death	Patient Number
<b>ON TREATMENT - Reviewer: 6 (Sponsor: 3)</b>		<b>ON TREATMENT - Reviewer: 9 (Sponsor: 5)</b>	
Progressive Disease - 2	#06500200, #60300500,	Progressive Disease - 3	#04200500, #05600600, #60400900
Adverse Event - 4 MI - 3	#04100300, #43400200, #06000200	Adverse Event - 4 CVA	#09300300
Fever, dehydration (r/o ↑ TFTs) - 1	#05900200	Dyspnea	#00400400
Worsening Baseline Condition - 0		MI	#04000300
"Other" - 0		Unexpected death	#13600100
		Pneumonia/sepsis	#04800200
		Worsening Baseline Condition - 1 ( ↓TFTs only stated baseline condition)	#0880200
		"Other" - unknown - 1	#00800600
<b>WITHIN 30 DAYS - Reviewer: 13 (Sponsor: 16)</b>		<b>WITHIN 30 DAYS - Reviewer: 27 (Sponsor: 31)</b>	
Progressive Disease - 12	#05500200, #60700700, #01200100, #03200100, #05300900, #13200200, #13300700, #40600400, #40700100, #41100100, #44600500, #60700600	18	#60300800, #60200500, #60200300, #45500300, #43600200, #41000100, #12100500, #00900300, #01800600, #01900100, #02702000, #41008000, #04600100, #06300300, #06900100, #09601400, #11000800, #13200100
Adverse Event - 1 Perforated bowel due to peg tube	#45500100	Adverse Event - 7 Cardiac	#09604500
Worsening Baseline Condition - 0		Neutropenia 2° Chemorx	#05400600
"Other" - 0		GI Bleeding 2° NSAIDs	#08700200
		Colitis	#60700800
		Perforated Bowel	#42800200
		PE	#12400100
		Worsening Baseline Condition - 1 Valvuloplasty for As	#41701300
		"Other" - 1 Sepsis 2° Decubitus 2° cord compression	#01300100

Data derived from Sponsor's Displays 34 and 35, vol. 3.79, listing 30, and review of CRFs.

**Reviewer Comment: Reasons for reclassifications are detailed below:**

1. The following patients were coded as "other" in the NDA, but as an AE in the review. Patient #43400200 had a MI with arrhythmia while on treatment. Patient #13600100 was unexpectedly found dead at home.
2. The following patient(s) were reclassified from "worsening baseline condition" to adverse event in this review: #06000200 with known baseline cardiac disease died of a MI on study. Since a contribution from study medication cannot be ruled out as contributory, she is coded as an AE.
3. The sponsor coded patients #06500200, #06000200, #00400400, #04000300, #00800600, #60300500, #60400900, #04800200 as deaths within 30 days of receiving study. This review codes these patients as deaths on study as the investigator coded "Death" as the "Reason for Stopping Treatment" on the CRF.

4. #42800200 was miscoded and moved from death due to perforated bowel on treatment to same cause of death but within 30 day of study drug.
5. #12400100 is correctly listed as death within 30 days, but the CRF lists the cause as secondary to a PE, rather than PD.

#### 7.2.4.4 Premature Withdrawals

Investigators could choose from the following categories for reason for stopping therapy: progressive disease, adverse event, patient refusal, protocol violation, death, lost to follow-up and "other, specify." CRFs were reviewed for the categories of patient refusal, protocol violation, death, lost to follow-up and other. In Reviewer Table 12, reviewer disagreement is identified by bold type—7 additional patients would be counted as withdrawn for adverse event for a total of 13 on exemestane. Similarly, 7 additional patients on megestrol would be counted withdrawn for adverse events for a total of 27.

Reviewer Table 12:  
Reasons for Premature Withdrawal

Sponsor's Reason for Withdrawal	PL ID	Age	Weeks on Rx	Best Response	Reviewer Comment
<b>Exemestane</b>					
Adverse event	#02100100	63	1.3	NE	N & V (gr 2)
	#02700299	56	1.9	NE	Abd. pain (gr 3), malaise, aches, N & V, pm bldg
	#06600300	49	2.4	NE	Vomiting
	#41400200	49	3.9	NE	Allergic rx—erythema multiforme
	#42800700	66	8.6	NC	Malaise, H/A, abd. pain
	#45500100	74	4.1	NE	Perforated bowel 2 <sup>nd</sup> peg tube
Patient refusal	#05700100	63	16.4	NC	Nausea
	#06100500	73	2.0	NC	N & V
	#06100800	52	9.9	NC	N & V (2 wks later, dx of meningeal ca)
	#06900900	74	4.0	PD	Headache
	#11000600	82	4.0	NE	"Pt doesn't want to go on with rx"
	#40500300	69	2.1	NE	Chooses chemorx to get quicker response
	#40600200	71	9.0	NE	Unwilling to travel to office
	#60600300	48	15.9	NC	Started chemorx at another institution despite SD
	#13000300	60	13.1	NC	"No further will for antitumor rx"
Protocol violation	#13400100	49	9.0	NE	Excision of the measurable disease
Death	#04100300	70	56.9	PR	MI
	#05900200	82	22.7	NE	Fever, dehydration, ? TTFTs
	#06000200	75	3.6	NE	MI
	#06500200	63	21.0	NC	PD
	#43400200	63	46.7	NC	MI
	#60300500	73	2.9	NE	PD
Lost to follow-up	#01100200	85	24.4	NC	-
	#09000200	45	0.1	NE	-
	#60201700	55	0.1	NE	-
Other	#01800100	86	77.7	PR	TESS—worsening CHF prevents compliance
	#01800200	87	64.0	PR	"Inability to comply with visits" — 7 reason
	#04101900	66	15.7	PD	Withdrawn for PD, although not confirmed on scans
	#04201100	48	17.9	NC	PD by Hypercalcemia
	#05400800	47	25.1	NC	PD by bone pain, alk phos, hypercalcemia
	#07300100	71	50.3	PR	Pt was poorly compliant to scheduled visits
	#41800300	74	108.1	CR	Prob. Related AE: SOB, pedal edema, fatigue
	#60300600	60	9.3	NC	↑ Pain in shoulder/arm

Reviewer Table (continued)

Sponsor's Reason for Withdrawal	PL ID	Age	Weeks on Rx	Best Response	Reviewer Comment
<b>Megace</b>					
Adverse event	#01300100	63	14.0	NC	Hepatitis
	#02600100	58	4.1	NE	Lethargy
	#04700100	65	3.7	NE	CVA
	#04900200	56	3.4	NE	Suspected PE
	#05401000	78	26.4	PR	HTN
	#05800300	87	19.1	NC	Tremulous
	#06100600	70	37.3	NC	"Heart failure"
	#06102100	71	8.6	NC	DVT
	#08000200	80	23.1	NC	Neurologic
	#08700200	68	4.3	PD	GI bleeding
	#08900300	62	28.0	PR	"Overweight"
	#09604500	65	19.9	NC	Stupor
	#13200100	66	16.0	NC	"Heart problems"
	#15200100	63	5.0	NC	Malignant hypercalcemia
	#41200300	62	8.1	NE	DOE
#41400400	66	12.1	NC	SOB	
#43300300	83	95.7	NC	Biliary obstr. prob 2o to stone-doubtful relationship	
#60700800	56	4.7	NE	Colitis	
#80400300	59	9.9	NC	Cardiomyopathy	
#12400100	83	55.3	PD	PE	
Patient refusal	#04100100	39	9.1	NC	"Increasing symptoms"
	#04104100	76	15.3	NC	"Insufficient cooperation"
	#05400100	71	10.1	NC	-
	#06000500	69	7.9	NE	"Unacceptable adverse events"
	#09200500	58	15.0	NC	"Gastric discomfort"
	#09603600	74	3.0	PR	-
	#11800300	73	47.7	NE	Can't comply with appts
	#12100400	52	8.0	PR	Hot flushes, insomnia
	#13300300	60	27.1	PD	"Intolerant"
	#41800600	79	12.7	PR	Weight gain
	#44300500	73	0.4	NC	Excessive diaphoresis
	#60200900	76	2.1	NE	"Digestive intolerance"
#60201100	69	14.0	NE	"Pt's own decision"	
#60400100	76	97.6	NC	"She retired the informed consent"	
Protocol violation					
Death	#00400400	70	15.7	NE	Dyspnea
	#00800600	65	0.1	NE	Unknown
	#04000300	74	30.1	NC	MI
	#04800200	53	9.9	PD	Pneumonia/sepsis
	#05600600	77	19.0	PD	PD
	#08800200	80	6.1	NE	"Worsening of baseline condition"
	#09300300	83	13.7	NE	CVA
	#13600100	64	42.7	PR	Unexpected death - ?reason
	#41201300	76	4.0	NE	During valvuloplasty operation
#60400900	72	35.0	NC	PD	
Lost to follow-up	#60400300	56	16.1	NC	-
Other	#01800600		6.7	PD	Hospice/PD
	#33300100	8474	91.0	NC	Noncompliant
	#03300400	82	35	NC	Anxiety; poor diabetic control
	#04102200	68	1.6	NE	"Decision of GP"
	#04600100	82	6.6	PD	PD/Aggravation of general status"
	#04800100	62	9.4	NE	Esophageal stenosis
	#41701800	61	8.4	NE	No known disease
	#42400200	76	50.7	CR	Inadequate drug compliance
#80501100	77	8.0	NC	Noncompliant to appts	

Data derived from Sponsor's Display 6, vol. 3.79, p.51; Appendix 13, Listing 2; relevant CRFs and listings in Section 11

#### 7.2.4.5 Treatment Emergent Adverse Events

Sponsor's Display 33 presents adverse events considered drug related or of indeterminate cause in  $\geq 2\%$  patients. Overall, more adverse events were reported for megace, a pattern also seen with adverse events due to any cause (see Sponsor's Display 32, Appendix III).

Items that are asterisked were the prospectively identified events thought to be associated with hormonal treatment and which were specifically solicited during the trial. Of the 9 items, 7 had an incidence of  $\geq 2\%$  when considering whether the cause was drug related or indeterminate. Nausea (as well as the unsolicited event of vomiting) and hot flushes were more common in patients taking exemestane while fatigue and increased sweating were more common in patients on megace. Insomnia, dizziness and abdominal pain was equally prevalent in either arm. The 95% confidence intervals for the odds ratio excluded one for nausea, vomiting and hot flushes.

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Sponsor's Display 33: Number (%) of patients reporting treatment emergent adverse events of all CTC Grades, considered to be drug related or of indeterminate cause, and occurring in  $\geq 2\%$  of treated patients

Event	Exemestane (N=358)	Megestrol acetate (N=400)	Odds Ratio (E/M)	95% OR CI
Any adverse event	140 (39.1)	183 (45.8)	0.76	0.57 - 1.02
Any autonomic nervous system event	17 (4.7)	30 (7.5)	0.61	0.33 - 1.13
*Increased sweating	16 (4.5)	30 (7.5)	0.58	0.31 - 1.08
Any body as a whole event	74 (20.7)	84 (21.0)	0.98	0.69 - 1.39
*Fatigue	27 (7.5)	41 (10.3)	0.71	0.43 - 1.19
*Hot flushes	45 (12.6)	20 (5.0)	2.73	1.58 - 4.72†
Edema legs	5 (1.4)	11 (2.8)	0.50	0.17 - 1.46
Pain	10 (2.8)	11 (2.8)	1.02	0.43 - 2.42
Any cardiovascular event, general	7 (2.0)	18 (4.5)	0.42	0.17 - 1.03
Hypertension	6 (1.7)	13 (3.3)	0.51	0.19 - 1.35
Any central & peripheral nervous system event	25 (7.0)	35 (8.8)	0.78	0.46 - 1.34
*Dizziness	12 (3.4)	12 (3.0)	1.12	0.50 - 2.53
Headache	9 (2.5)	6 (1.5)	1.69	0.60 - 4.81
Any gastrointestinal system event	65 (18.2)	86 (21.5)	0.81	0.57 - 1.16
*Abdominal pain	10 (2.8)	17 (4.3)	0.65	0.29 - 1.43
*Nausea	33 (9.2)	20 (5.0)	1.93	1.09 - 3.43†
Appetite increased	10 (2.8)	23 (5.8)	0.47	0.22 - 1.00
Constipation	3 (0.8)	10 (2.5)	0.33	0.09 - 1.21
Vomiting	10 (2.8)	3 (0.8)	3.80	1.04 - 13.93†
Any psychiatric event	26 (7.3)	26 (6.5)	1.13	0.64 - 1.98
*Insomnia	13 (3.6)	13 (3.3)	1.12	0.51 - 2.45
Any reproductive event, female	7 (2.0)	14 (3.5)	0.55	0.22 - 1.38
Vaginal hemorrhage	2 (0.6)	10 (2.5)	0.22	0.05 - 1.01
Any respiratory system event	8 (2.2)	22 (5.5)	0.39	0.17 - 0.89†
Dyspnea	1 (0.3)	12 (3.0)	0.09	0.01 - 0.70†
Any skin and appendages event	25 (7.0)	12 (3.0)	2.43	1.20 - 4.91†
Rash	7 (2.0)	0	Inestimable	Inestimable

Source: Table 26.3

\* elicited adverse events (patients specifically asked about these adverse events)

† interval does not include 1

**Reviewer Comment:** Reviewer queries to the MS Access database collapsed related terms to verify incidence. It appears that items 1-4 below should also be included in Display 33 for completeness.

(1) The incidence of the solicited event "depression" considered "probably" or "possibly" related to study drug or of "doubtful" relationship (i.e., not "none" for assessment of drug relationship) was 3.6% in patients receiving exemestane (#13) and 2.5% in patients on megace (#10).

- (2) Paresthesias were included in the table of adverse events of all causes, but did not convey to Display 33. The search for paresthesia, nerve pain, localized numbness, dysaesthesia (considered probably, possibly related to study drug or of doubtful relationship) identified 8 patients (2.2%) on exemestane and 5 patients (1.2%) on megestrol.
- (3) Queries re. Itching/pruritis (considered probably, possibly related to study drug or of doubtful relationship) was 2.2% (8 patients) on exemestane and 1.2% (5 patients) on megestrol.
- (4) Expanding the category of edema legs to include the related categories of edema limb, edema arm, edema, fluid retention in tissues and water retention in tissues (but excluding ascites, pleural effusion and pulmonary edema), gave frequencies of 3.9% for patients on exemestane and 5% for patients on megestrol.
- (5) "Hypertrichosis" or "facial hair" was searched since androgenic effects have been seen at higher doses. This event was reported in 3 patients on exemestane (0.8%) and 1 on megestrol (0.2%). All were grade 1 and considered "possibly" related to study drugs. The search for "acne" was negative.

For previously approved aromatase inhibitors, labels have displayed adverse events regardless of causality. A similar table is included in Appendix IV and will be considered for the label. The discrepancies noted above may in part be due to attribution of cause, which will be less of an issue if such a table is used.

#### 7.2.4.6 Laboratory Findings

The 95% confidence interval for the odds ratio excluded one for the following five laboratory abnormalities: WBC (↓), lymphocytes (↓), SGPT, alkaline phosphatase and glucose (either increased or decreased). The abnormalities in these parameters, as well as in related liver function tests, are presented by frequency of all grades and grades 3-4 (Reviewer Table 13). The sponsor notes that of the 24 patients on exemestane with grade 3-4 treatment emergent increases in gamma-GT, 12 had hepatic metastases, 4 had other liver disease, and 8 had no known liver disease. Of the 17 patients on megestrol with grade 3-4 elevations in gamma-GT, 10 had liver metastases, 1 had tumor-related ascites and 6 had no concurrent hepatic disease.

Reviewer Table 13.  
Laboratory findings, all causes, by CTC grade

Parameter	EXEMESTANE			Megestrol		
	No. Eval Pts	Gr 1-4	Gr 3-4	No. Eval Pts	Gr 1-4	Gr 3-4
WBC	342	34 (9.9%)	1 (0.3%)	386	16 (4.1%)	0 (0%)
Lymphocytes	318	147 (46.2%)	55 (17.3%)	370	67 (18.1%)	20 (5.4%)
SGPT	316	62 (19.6%)	1 (0.3%)	368	45 (12.2%)	1 (0.3%)
SGOT	315	49 (15.6%)	3 (1.0%)	366	52 (14.2%)	5 (1.4%)
Gamma-GT	301	77 (25.6%)	24 (8.0%)	337	82 (24.3%)	17 (5.0%)
BR	312	21 (6.7%)	5 (1.6%)	357	29 (8.1%)	11 (3.1%)
Alk Phos	318	77 (24.2%)	4 (1.3%)	367	58 (15.8%)	6 (1.6%)
Glucose	291	88 (30.2%)	9 (3.1%)	337	63 (18.7%)	16 (4.7%)

Source: Table 31.2, vol. 3.80.

**Reviewer Comment:** Elevation of a transaminase and bilirubin. Nineteen patients, 9 on exemestane and 10 on megestrol, had an elevation of both a transaminase and bilirubin. The investigator coded 7 of the 9 on exemestane and 4 of the 10 on megestrol as due to tumor. Eight of the 9 patients on exemestane were withdrawn from the study for PD with the remaining patient continuing treatment at the time of data cutoff. Nine of the patients on megestrol were withdrawn for PD. The one remaining patient (#08700200) died secondary to "GI bleeding" while taking nonsteroidal antiinflammatory agents. Eight patients (5 on exemestane and 3 on megestrol) were listed in the MS Access database as having an adverse event pertaining to the liver. Of these, only one was coded as related to study drug which was megestrol. The

events were hepatitis (2-both on megace; one of these was #08700200)); hepatic failure (1-a patient with baseline hepatic metastases on megace and two medications containing acetaminophen; withdrawn from study at 7.2 weeks for PD); liver tender (1-on exemestane; considered tumor related); LFT abnormality (2-one on megace and the other on exemestane, both considered tumor related); and hepatomegaly (2-one on megace and the other on exemestane, both considered tumor related). Study #018 does not suggest an increased risk of liver toxicity with exemestane compared to megace treatment. (Sources of data: listing 31, vol. 3.89; listing 24.1, Section 11; MS Access database of adverse events).

Lymphopenia. The decrease in WBC was primarily due to a decrease in lymphocytes; 17.3% of evaluable patients had grade 3-4 lymphopenia. The sponsor notes that there was no increase in infection although a mechanism for this effect is not suggested. Abnormalities in glucose went in both directions; however, it is not clear to this reviewer that there was control over the timing of sampling to food and therefore this finding is uninterpretable.

Cholesterol and Triglycerides. A formal study with controlled blood sampling and processing was not conducted. No significant increases in mean or median cholesterol, HDL-cholesterol and triglycerides were seen in the random sampling of patients receiving exemestane.

No strong time trends for any of the laboratory parameters were seen.

#### 7.2.4.7 Other Potential Safety Issues

Bone Fractures. The Division has requested that sponsors of marketed aromatase inhibitors search their databases for evidence of an increased incidence of bone fractures. A search of this NDA's MS Access database, using the recommended search words, revealed 20 cases of fractures, 10 in patients receiving exemestane and 10 megace. Therefore, it is concluded that there is no evidence for an increase in bone fractures for the extent of exposure and patient population represented in this NDA.

Tumor Flare. No cases were reported for #018 as such, or identified in the MS Access database of adverse events. Two cases of hypercalcemia were reported on each arm, each considered related to tumor.

Seizures. In mice and dogs, seizures were noted after single doses approximately 80 and 4000 times the recommended human dose. The ISS notes 1 patient with convulsions. No further cases are found by a search of the MS Access database of adverse events. In the high dose phase 2 study (#009) which gave exemestane at 200 mg daily, the sponsor notes only one toxicity greater than grade 2 which was considered related to study drug--akathisia, which led to discontinuation of drug. The toxicity resolved without sequelae.

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## 8.0 Supportive Uncontrolled Trials

### 8.1 Protocol # 93 OEXE 010: Antitumor efficacy of exemestane in postmenopausal patients with metastatic breast cancer, failing to tamoxifen

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#### Protocol Milestones:

Reviewer Table 14:  
Protocol #010 Milestones

Milestone	Date	Comments
Amendment #1	May 12, 1993	All patients entered after amendment. Protocol review below incorporates this amendment.
Amendment #2	July 1996	Pertinent only to center 002 in Norway.
First patient entered	June 18, 1993	
Last patient enrolled	July 1996	
Data Cutoff	February 28, 1998	

**Study Design:** This study was an open label, uncontrolled two-step phase 2 trial of exemestane 25 mg (hard gelatin capsule) daily. Response rate, which included the category of "no change" or stable disease, was determined for each of 3 strata based on response to prior tamoxifen: (a) patients who received tamoxifen for metastatic disease whose best response was progressed disease or disease stabilization lasting < 6 months; (b) patients who received tamoxifen for metastatic disease who had an objective response or disease stabilization lasting > 6 months; and (c) patients who received adjuvant tamoxifen but recurred with metastatic disease during treatment or within 12 months since discontinuation of adjuvant tamoxifen. A total of 140 patients were entered from 26 European countries as well as from South Africa.

#### 8.1.1 Protocol Review

**Objectives:** "To evaluate the antitumoral efficacy (in terms of response rate, duration of response and time to progression)..."

**Reviewer Comment:** Although a single primary endpoint was not specified as an objective, the statistical section is based on "success rate" defined as a CR, PR or SD.

#### Eligibility Criteria:

- Histologically/cytologically confirmed breast cancer at original diagnosis
- Metastatic disease
- Tamoxifen failure
- At least one measurable bidimensional lesion or lytic bone lesion quantifiable by x-ray
- ER or PR positive at initial diagnosis or subsequently at a metastatic site OR unknown receptor status if patients have shown response or disease stabilization lasting  $\geq 6$  months

(Positivity is defined as  $> 10$  fmol of  $H^2$ -estrogen or  $> 20$  fmol of  $H^2$ -progesterone binding/mg cytosol protein for DCC and sucrose density methods;  $\geq 0.10$  fmol of  $H^2$ -estrogen or  $\geq 0.20$  fmol of  $H^2$ -progesterone binding/ $\mu$ g of DNA of IF/EIA or positive staining ( $>0$ ) for the immunocytochemical method)

- Postmenopausal status

(Defined as natural menopause with >1 year since last menses; surgery or radiation-induced oophorectomy; LHRH analogs or chemotherapy-induced menopause with ≥ 3 years since last menses, and serum FSH and LH levels clearly in the postmenopausal range for institution, in the presence of low plasma estradiol concentrations. Patients who are less than 56 and (a) underwent hysterectomy without BSO or (b) with a tamoxifen-induced amenorrhea and < 3 months since tamoxifen discontinuation are excluded unless the serum FSH and LH levels meet criteria for postmenopausal status in the presence of low plasma estradiol, as defined by the institution.)

- At least 4 weeks off tamoxifen
- Maximum of 2 prior therapies for metastatic breast cancer, provided that one was chemotherapy
- ECOG PS ≤ 2 and a life expectancy ≥ 3 months
- Adequate hematologic parameters (WBC ≥ 4000/mm<sup>3</sup>, neutrophils ≥ 2000/mm<sup>3</sup>, platelets ≥ 100,000/mm<sup>3</sup>)
- Adequate renal and hepatic function (creatinine and BR < 1.5 X ULN for the institution; SGPT ≤ 3 X ULN)

**Exclusion Criteria:**

- No prior exposure to tamoxifen
- Male patients
- Inflammatory breast cancer or rapidly progressive disease where hormonal therapy is not indicated, and/or presence of massive visceral disease, and/or brain metastases
- Nonevaluable disease only, e.g., lymphangitic spread, ascites, blastic bone lesions
- Treatment with bisphosphonates in the 8 weeks prior to entry
- Treatment with LHRH analogs within 3 months prior to entry (4 months for depot therapy)
- Other malignancies excepting adequately treated in situ carcinoma of the cervix, uterus, basal or SCC of the skin

**Concomitant Therapy:** Treatment with bisphosphonates is permitted only for ≤ 7 days in case of hypercalcemia or tumor flare.

**Schedule of Assessment:** Patients were evaluated every 4 weeks for 4 months and then every 8 weeks for the first year. Response to treatment was assessed every 8 weeks. The second year, the patient was evaluated every 12 weeks.

**Criteria for Patient Evaluability:**

- A patient who requires palliative XRT during the first 8 weeks, and if there is no other measurable or quantifiable bone lesion, will be considered inevaluable for efficacy. Any patient requiring palliative XRT after week 8 will be considered as having PD.
- Patients who have taken less than 80% or more than 120% of the intended dose during the first 8 weeks of treatment will be considered inevaluable for efficacy.
- Patients withdrawn for causes other than disease progression or death due to progressive disease during the initial 8 weeks will be considered inevaluable for efficacy.

**Statistical Considerations:** A two-stage design, according to Gehan's method, was applied to each of the three patient categories. Success was defined as CR, PR or NC. Assuming a 30% response rate of interest, if at least 1 in the first 9 patients had a CR, PR or NC within 8 weeks, 16 additional patients per category would be entered. Otherwise, the drug would be rejected with a type II error  $\beta < 0.05$ .

For the efficacy analysis, NC was divided into two categories: (a) NC lasting ≥ 8 weeks and < 6 months ("short-term" stabilization); and (b) NC lasting for at least 6 months ("long-term" or "real stabilization"). In patients with PR or CR who have "predominant" (not further defined) nonmeasurable disease, "the overall response will be evaluated both in measurable disease only, and taking into consideration all types of disease" (no algorithm provided).

Efficacy analyses would be performed on "evaluable" patients only.

### 8.1.2 Results

**Conduct of the Study:** The protocol was approved by the institution's Ethics Committee. The protocol stipulated that the investigator must adhere to the 1989 Declaration of Helsinki or to national regulations, whichever provided greater protection for the individual. The patient was to give written or oral witnessed consent.

- **Registration:** Treatment was started in 16 patients without formal registration. A total of 140, rather than the protocol-specified 90 patients, were entered. The distribution of patients per stratum was determined retrospectively.
- **Eligibility criteria violations:** 105 patients (76.6%) were eligible (9 as exceptions); 32 were considered ineligible.
- 34 patients did not fit any of the 3 strata.
- 82 patients (59.9%) had major protocol violations during the study.
- 97 of 137 patients were considered evaluable for objective tumor response.
- There were 14 discrepancies in overall response between sponsor and investigator.

#### Enrollment:

Twenty seven of 33 centers entered 140 patients. Three of the 140 patients registered never received treatment.

#### Disposition:

Disposition of the 137 treated patients is presented in Reviewer Table 15.

**Reviewer Table 15: Disposition of Treated Patients\***

Reasons	No. Patients
Progressive disease	117
Patient refusal	2
Adverse event	4
Death	0
Other	6
Protocol violation	2
Still on treatment	6
Total	137

\*Data derived from Table 3, vol. 3.55

- **Demographics**

The median age was 64 (range 42 - 99). The majority of patients, 134 (97.8%), were caucasian. The median PS was 1 (range 0 - 2). The median number of years from menopause was 15 (range 1 - 49).

#### Primary Endpoint: Response Rate

Response rate according to investigator assessments was 24.8% (4 CR, 30 PR). CRFs (not radiographs) were reviewed by physicians at Pharmacia and Upjohn. The internal review by the sponsor changed 4 assessments of objective response (3 PRs were downgraded to 1 SD and 2 NE; 1 NC was upgraded to 1 PR) for a final response rate of 23.4% (CR 4, PR 28).

**Reviewer Comment:** FDA review of the CRFs of the 4 reassessments agrees with the sponsor and therefore further analyses will be based on their, rather than the investigator's assessment of response.

**Tumor Response by Stratum and Other Baseline Characteristics**

**Reviewer Table 16:  
Tumor Responses According to Stratum and Other Baseline Characteristics**

Baseline Characteristic	No. Treated (N = 137)	CR + PR (%)
<b>Stratum</b>		
TAM nonresponders	12	12 (25.0)
TAM responders	55	15 (27.3)
Adjuvant TAM	36	9 (25.0)
Stratum not Applicable	34	5 (14.7)
<b>Receptor Status</b>		
ER and/or PR +	87	22 (25.3)
ER and PR unknown	46	8 (22.2)
ER and PR negative	4	2 (22.2)
<b>Washout from TAM (weeks)</b>		
< 4	21	5 (23.8)
4 - 8	79	17 (21.5)
>8 - 52	24	7 (29.2)
>52	13	3 (23.1)
<b>Predominant Site of Disease</b>		
Soft tissue only	22	7 (31.8)
Bone +/- soft tissue	52	9 (17.3)
Visceral +/- others	63	16 (25.4)

Data derived from Sponsor's Tables 16, 26, 28, 30 and 34.

Median duration of response was 69.4 weeks (95% C.I. 58 - 79.7) according to the reviewers and 74 weeks (95% C.I. 61.9-96.7) according to the investigators.

**Safety Results:**

**Extent of Exposure**

The median duration of exposure was 31.9 weeks (range 2.1 - 182.4). The mean duration was 45.7 weeks.

**Deaths on Study or within 30 Days of Treatment**

No patient died while on study. Four patients died within 30 days of the last dose of exemestane. A 63 year old patient (#01301501) with a history of dysphagia and esophageal stenosis, died of aspiration pneumonia after two weeks of treatment.

**Reviewer Table 17  
Deaths on Study or within 30 days of Treatment Cessation\*  
(N = 9)**

Cause of Death	Number of Patients	Patient ID
Patients Treated	137	
Deaths During Treatment	0	
Deaths Within 30 Days	4	
Progressive Disease	3	#00504102, #01000101, #02503902
Due to Adverse Event	1	#01301501

- **Premature Withdrawals due to TESS**

Three patients were withdrawn for treatment emergent adverse events; however, only one was considered related to study drug (Reviewer Table 18).

**Reviewer Table 18\***  
Discontinuations Due to Treatment-Emergent Signs and Symptoms\*

Patient ID	Weeks on Treatment	Event	Causality
#00101002	2	Exanthema, gr 3	Prob. study drug
#01301501	0	Dyspnea, gr 3 and Dysphagia, gr 3	H/o esophageal stricture
#02800300	9	Cardiac insufficiency, gr 2	Prev. tumor treatment

\*Data derived from Lisint 14, vol. 3.57

- **Drug-Related or Indeterminate TESS**

Fifty nine patients (43.0%) of patients experienced at least one drug-related or cause indeterminate TESS. Reviewer Table 19 presents the events reported in  $\geq 5\%$  of patients. There were five grade 3 events: pruritis, rash, headache, cholecystitis ("cause indeterminate" but "no relationship to drug"), hypoglycemia and hypertension. There were no grade 4 adverse events.

**Reviewer Table 19\*:**  
Drug-Related or Indeterminate Signs and Symptoms  
Reported in  $\geq 5\%$  of 137 Patients Treated with Exemestane

Body System/Event	Treated N = 128		CTC Grade			
	No.	%	1 No.	2 No.	3 No.	4 No.
Gastrointestinal Nausea	11	8.0	11	-	-	-
Body as a whole Hot flushes Pain	19 12	13.9 8.8	14 10	5 1	- 1	- -
Nervous System Dizziness	12	8.8	11	1	-	-
Autonomic system Incr. Sweating	7	5.1	5	2	-	-

\*Data derived from Sponsor's Table 46

- **Serious Adverse Events**

Of the 26 serious adverse events, none were considered to be definitely, probably or possibly related to study drug. Five were considered of doubtful relationship: grade 2 vomiting (#00500801), grade 2-3 nausea, vomiting, diarrhea and abdominal pain (#00504102), grade 1 CVA (#01702603), grade 3-4 cardiac insufficiency, dyspnea and DIC (#02800300), and grade 1 cold agglutinin syndrome (#01301801). Source: Listing 15, vol. 3.57.

**8.2 Protocol #120002-999: Efficacy trial of FCE 24304 (Exemestane, 6-methylenandrosta-1,4-diene-3,17-dione) in the treatment of postmenopausal patients with metastatic breast cancer failing tamoxifen**

Principal Investigator: Not stated

Protocol Milestones:

**Reviewer Table 20:  
Protocol #120002-999 Milestones**

Milestone	Dates	Comments
Amendment #1	August 3, 1993	-
First patient entered	September 24, 1993	-
Last patient entered	November 30, 1995	-
Data cutoff	February 28, 1998	-

**8.2.1 Protocol Review**

This phase 2 protocol is virtually identical to protocol #93 OEXE 010, including objectives, eligibility criteria, statistical section and case report form (with the exception that laboratory data was not captured on #120002-999). A pharmacodynamic portion was included in this study.

**8.2.2 Results**

**Conduct of the Study:**

- 32 patients were incorrectly stratified at registration
- 5 patients did not fit any of the 3 strata (#0032052, 0122142, 0132182, 0152193, and 3002013)
- 37 patients (28.9%) did not meet all entry criteria
- 108 patients (84.4%) had protocol violations during the study
- Objective responses were not reviewed by an independent panel, but "reported data on tumor burden were internally reviewed by Pharmacia & Upjohn medically qualified officials (study director or clinical program leader) to confirm the previous response and the date of progression."

**Enrollment:** A total of 129 patients were enrolled from 24 sites in the U.S. and 4 sites in Mexico. One screened patient (#0091903) was found to be ineligible due to lack of measurable or lytic disease and was not given study treatment.

**Disposition:** Reasons for withdrawal from study are presented in Sponsor's Display F.

**Sponsor's Display F: Reasons for Discontinuation of Study Therapy\***

Reasons	No. Patients
Progressive disease	104
Patient refusal	5
Adverse event	4
Death	3
Other	2
Protocol violation	1
Still on treatment	9
<b>Total</b>	<b>128</b>

Volume 3.58, p. 57

**Reviewer Comment:**

(a) Patient refusal—Patient #028207 stopped study medication 13 days before the diagnosis of PD by virtue of a new pulmonary lesion. Last visit noted TESS including headache, cough and chest pain.

Patient #0151642 was not satisfied with a response of SD. Information on the other 3 patients are lacking to assess whether medication refusal may be related to study drug.

(b) Adverse event—Review counts number of patients in this category as 5 (see Discontinuations due to TESS below).

(c) Other—Patient #0141623's site was discontinued; patient #0321982 was considered to have PD in error. Further details are unavailable.

(d) Protocol violation—Patient #001903 did not have measurable or evaluable disease.

**Primary Endpoint: Response Rate**

Response rate according to investigator assessments was 27.3% (1 CR and 34 PRs in 128 patients). CRFs (not radiographs) were reviewed by physicians at Pharmacia and Upjohn. The internal review by the sponsor changed 7 assessments (3 PRs were downgraded to 2 SD and 1 PD; 4 SD were upgraded to 4 PRs) for a final response rate of 28.1% (1 CR and 35 PRs).

*Reviewer Comment: FDA review of the CRFs of the 4 upgrades agrees with the sponsor and therefore further analyses will be based on their, rather than the investigator's, assessment of response.*

**Tumor Response by Stratum and Other Baseline Characteristics**

Sponsor's Display X (Abridged):  
Tumor Response According to Stratum and Other Baseline Characteristics\*

(Baseline Characteristic)	No. Treated (N = 128)	CR + PR (%)
<b>Stratum</b>		
TAM nonresponders	14	3 (21.4)
TAM responders	62	18 (29.0)
Adjuvant TAM	47	11 (23.4)
Stratum not applicable	5	4 (80.0)
<b>Receptor Status</b>		
ER and/or PR +	105	27 (25.7)
ER and PR unknown	22	9 (40.9)
ER and PR negative	1	0 (0.0)
<b>Washout from TAM (weeks)</b>		
< 4	5	0 (0.0)
4 - 8	93	25 (26.9)
> 8 - 52	26	9 (34.6)
> 52	4	2 (50.0)
<b>Predominant Site of Disease</b>		
Soft tissue only	16	7 (43.8)
Bone +/- soft tissue	45	7 (15.6)
Visceral +/- others	67	22 (32.8)
<b>Type of lesion</b>		
≥ 1 measurable lesion	88	39 (34.1)
only evaluable or nonevaluable lesions	40	6 (15.0)
<b>Number of Sites</b>		
1	61	17 (27.9)
2	48	12 (25.0)
3	19	7 (36.8)

\* Sponsor's Display X did not include the category of "other." However, Table 18.1.4 lists the 5 missing patients that did not fit any strata (see Conduct of the Study).

**Safety Results:**

**Extent of Exposure**

The median duration of treatment was 24.4 weeks (range 1.1 to 181.6 weeks); mean duration was 42.3 weeks.

• **Deaths on Study or Within 30 Days of Treatment:**

Three patients died on treatment and 6 patients died within 30 days of study treatment. Of the 3 adverse events, only one, a cardiac event in a 70 year old woman with baseline hypertension, was coded by the investigator as possibly related to treatment.

**Reviewer Table 21:**  
Deaths on Study or within 30 days of Treatment Cessation\*  
(N = 9)

Cause of Death	Number of Patients	Patient ID
Patients Treated	128	
Deaths During Treatment	3	
Progressive Disease	2	#0011012, #0041301,
Due to Adverse Event	1	#0131252 <sup>b</sup>
Deaths Within 30 Days	6	
Progressive Disease	4	#0011223, #0111312, 0251452,
Due to Adverse Event	2	#0252261, #0252022 <sup>a</sup> , #0171833

\*Reviewer Table derived from CRFs and Sponsor's Displays F, I and J in vol. 3.58

<sup>a</sup>Death due to complications of surgery for hip/femur surgery.

**Reviewer Comment:** Reviewer Table is based on information from the CRFs. Cause of death differs from the sponsor's categorization in the following two patients; however, the overall assessment that the primary cause of death is progressive disease in the majority of patients is unchanged.

- (a) Sponsor counts patient #0252022 as death due to PD. The CRF contains no assessment of tumor response after baseline. The patient went off treatment for an adverse event of femoral fracture and died during surgery the following day. Cause of death is listed as PD, however, this is not substantiated by autopsy or surgical pathology data (nor investigator comment) in the CRF.
- (b) Sponsor counts patient #0131252 as death within 30 days of study treatment because study drug was stopped while patient underwent surgery for hip fracture. The patient died 3 days postoperatively. However, the patient was not taken off study and did not have documentation of PD. The intent may have been to resume treatment and therefore this review counts death as due to an AE on study.

• **Premature Withdrawals due to TESS**

Five patients had treatment discontinued due to an adverse event. Only one, a femoral fracture, had an unknown causality. The remaining four were not considered to be drug-related.

**Reviewer Table 22**  
Discontinuations Due to Treatment-Emergent Signs and Symptoms\*

Patient ID	Weeks on Treatment	Event	Causality
#0111312	1.1	Cardiorespiratory Arrest	Tumor
#0171833	10.1	Pulmonary Edema	Intercurrent Illness
#0181482	3.1	Dyspnea	Intercurrent Illness
#0251391	4.1	Bone Pain	Tumor
#0252022	8.2	Fracture of Femur	?

\*Derived from CRFs and Sponsor's Display H, Vol. 3.58

• **Drug-Related or Indeterminate TESS**

Sponsor Display FF:  
**Drug-Related or Indeterminate Signs and Symptoms  
 Reported in > 5% of 128 Patients Treated with Exemestane**

Body System/Event	Treated N = 128		CTC Grade			
	No.	%	1 No.	2 No.	3 No.	4 No.
Gastrointestinal Nausea	13	10.2	10	3	0	0
Body as a whole						
Hot flushes	32	25.0	24	7	1	0
Fatigue	14	10.9	10	4	0	0
Pain	11	8.6	8	3	0	0
Nervous System						
Headache	9	7.0	8	1	0	0
Dizziness	8	6.3	5	2	1	0
Autonomic system						
Incr. Sweating	13	10.2	8	4	1	0

The only other grade 3 - 4 drug-related/indeterminate TESS was one episode of syncope.

• **\_\_\_\_\_ Serious Adverse Events \_\_\_\_\_**

Thirty three patients had serious adverse events that did not result in death or premature withdrawal (Sponsor's Display JJ, vol.3.58, p. 105); however, none were considered drug-related. Only one event, confusion, was considered to have an unknown cause.

**APPEARS THIS WAY  
 ON ORIGINAL**

## 9.0 Integrated Summary of Efficacy (ISE)

Because of trial design considerations, no attempt will be made to integrate the efficacy results across the 3 trials submitted in support of the indication for women failing tamoxifen. Time-to-event endpoints as well as subjective endpoints such as pain and QOL from the uncontrolled trials are well described to be less robust if derived from uncontrolled trials. As expected, response rates are higher in the two uncontrolled trials than in the phase 3 trial, despite similar patient populations and the fact that accrual was multicenter. A tamoxifen withdrawal effect can not be ruled out. However, it is noted that results from the US trial, #120002-999, are similar to results from the non-US trial, #010.

## 10. Integrated Summary of Safety (ISS)

The sponsor's ISS is based on 1058 of the 1062 breast cancer patients who received at least one dose of exemestane 25 mg (either the hard gelatin capsule or sugar-coated tablet) and who had at least one safety assessment (see Reviewer Table 23).

Reviewer Table 23:  
Safety Database for Exemestane 25 mg Daily

Type of Study	No. of Studies	No. of treated patients/subjects
Phase 1	#004, #007	17
Phase 2	#010, #017, #022, #12002, #12003	684
Phase 3	#018	361
<b>TOTAL</b>		<b>1062</b>

Modified from sponsor's Table 8.G-1, vol.3.11, p. 26

### Duration of Exposure

The mean duration was 30.5 and the median duration 17.1 weeks of treatment (See Sponsor's Table 8.G-76). The extent of exposure of the ISS, by these measures, is identical to the exposure in the pivotal trial, #018.

Sponsor's Table 8.G-76:  
Duration of Exposure: Phase 1, 2, 3 Exemestane 25 mg

Study treatment period	No. of exposed patients (%)
< week 1	1062 (100)
week > 1-4	1054 (99.2)
week > 4-8	1015 (95.6)
week > 8-16	867 (81.6)
week > 16-24	598 (56.3)
week > 24-32	436 (41.1)
week > 32-52	342 (32.2)
week > 52-76	189 (17.8)
week > 76-105	103 (9.7)
week > 105	42 (4.0)

Source: Section 22, Table 81

### Demographics

The patient population in the pivotal and 2 supportive phase 2 trials have already been discussed (see Sections 7 and 8). The population in the remaining 3 non-supportive phase 2 trials is similar in terms of age (median 65), race (91.8%), median duration of menopause (16 years), and ECOG PS (90% PS 0-2). However, the population had received more treatment prior to entry onto the studies with 41% having received chemotherapy in the metastatic setting vs. 16% in #018.

• **TESS considered Drug-related or of Indeterminate Cause**

**Sponsor's Table 8.G-81: Distribution of Drug-related or of Indeterminate Cause Treatment-emergent Adverse Events (Any CTC Grade) in  $\geq$  2% of Patients: Phase I, II, III, Exemestane 25 mg Daily (004, 007, 010, 018, 022, 120002, 120003)**

Body system / Adverse event	NCI-CTC Grade 1-4 No. of Patients	%
No. evaluable	1058	
Any adverse event	503	47.5
Autonomic nervous	59	5.6
Increased sweating	59	5.6
Body as a whole	253	23.9
Hot flushes	148	14.0
Fatigue	81	7.7
Pain	36	3.4
Cardiovascular*	38	3.6
Central and peripheral nervous	116	11.0
Dizziness	59	5.6
Headache	49	4.6
Gastrointestinal	223	21.1
Nausea	126	11.9
Abdominal pain	29	2.7
Vomiting	28	2.6
Anorexia	27	2.6
Musculoskeletal*	28	2.6
Psychiatric	75	7.1
Insomnia	37	3.5
Depression	25	2.4
Reproductive, female?*	21	2.0
Respiratory*	33	3.1
Skin and appendages	85	8.0
Rash	30	2.8
Alopecia	21	2.0

Source: section 22, Table 87

No single adverse event occurred in  $\geq$  2% of patients  
Including disorders of the breast and vagina

**APPEARS THIS WAY  
ON ORIGINAL**

Sponsor's Table 8.G-82: Distribution of Grade 3 and 4 Drug-related or of Indeterminate Cause  
 Treatment-emergent Adverse Events: Phase I, II, III Exemestane 25 mg  
 Daily (004, 007, 010, 017, 018, 022, 120002, 120003)

Body system / Adverse event	NCI-CTC Grade 3 No. of Patients (%)	NCI-CTC Grade 4 No. of patients (%)
No. evaluable	1058	
Any adverse event	41 (3.9)	2 (0.2)
Autonomic nervous	5 (0.5)	-
Increased sweating	5 (0.5)	-
Body as a whole	8 (0.8)	1 (0.1)
Hot flushes	3 (0.3)	-
Fatigue	2 (0.2)	-
Pain, tumor site	1 (0.1)	-
Carpal tunnel syndrome	1 (0.1)	-
Syncope	1 (0.1)	1 (0.1)
Cardiovascular	4 (0.4)	-
Cardiac failure	1 (0.1)	-
Hypertension	3 (0.3)	-
Central and peripheral nervous	6 (0.6)	-
Dizziness	2 (0.2)	-
Headache	4 (0.4)	-
Gastrointestinal	9 (0.9)	1 (0.1)
Nausea	8 (0.8)	1 (0.1)
Esophagitis	1 (0.1)	-
Vomiting	3 (0.3)	1 (0.1)
Heart rate and rhythm	2 (0.2)	-
Fibrillation atrial	2 (0.2)	-
Liver and biliary system	1 (0.1)	-
Cholecystitis	1 (0.1)	-
Metabolic and nutritional	2 (0.2)	-
Hypercalcemia	1 (0.1)	-
Hypoglycemia	1 (0.1)	-
Psychiatric	2 (0.2)	-
Anxiety	1 (0.1)	-
Depression	1 (0.1)	-
Insomnia	1 (0.1)	-
Respiratory	2 (0.2)	-
Dyspnea	2 (0.2)	-
Skin and appendages	3 (0.3)	-
Pruritus	2 (0.2)	-
Erythema multiforme	1 (0.1)	-
Rash erythematous	1 (0.1)	-
Urinary	1 (0.1)	-
Urinary retention	1 (0.1)	-
Vascular (extracardiac)	1 (0.1)	-
Cerebrovascular disorder	1 (0.1)	-

Source: section 22, Table 87

• **Discontinuations Due to Adverse Events**

The following Sponsor's Table 8.G-84 displays premature discontinuations due to adverse events. In addition to these thirty patients, seven from #018 (identified by bold type in Reviewer Table 12) should be included, bringing the percentage of withdrawals due to adverse events to 3.5%.

**Sponsor's Table 8.G-84: Discontinuations Due to Adverse Events: Phase I, II, III Exemestane 25mg Daily (004, 007, 010, 017, 018, 022, 120002, 120003)**

Study no.	Patient no.	Adverse event associated with discontinuation (grade)	Relationship to exemestane
010	00101002	Rash erythematous (3)	Probable
	01301501	Dysphagia (3), dyspnea (3)	Unrelated
	02203702	Ascites (3)	Unrelated
	02800300	DIC (4), cardiac failure (3)	Unrelated
017	0200200	Infection (4)	Unrelated
	09400500	Traumatic fracture (n.a.)	Unrelated
	09500100	Nausea (2)	Definite
	13700100	Vomiting (4)	Unrelated
018	02100100	Vomiting (2), nausea (3)	Probable
	02700299	Fatigue (1)	n.a.
		Abdominal pain (3), nausea (1), pain (3)	Probable
		Varicose vein bleeding (1)	Possible
	06600300	Vomiting (3)	Possible
	41400200	Erythema multiforme (3)	Definite
		Conjunctival burning (1)	Possible
	42800700	Malaise (1)	Probable
		Malaise (1)	Probable
	45500100	Bowel perforation (4)	Unrelated
022	00400100	Dizziness (2)	Unrelated
	01100900	Diarrhea (2)	Definite
	02100500	Renal calculus (1,3)	Unrelated
	04900100	Gangrene left foot (4)	Unrelated
	04900300	Nausea (1)	Unrelated
12002	0111312	Cardiac arrest (3)	Unrelated
	0171833	Pulmonary edema (4)	Unrelated
	0181482	Dyspnea (3)	Unrelated
	0251391	Pain at tumor site (2,3)	Unrelated
120003	00611501	Pain on left hip (3)	Unrelated
	00613802	Pain at hips, both sides of pelvis and right shoulder (3)	Unrelated
	01612202	Nausea (2)	Possible
	02317201	Dysphagia (2)	Unrelated
	03118901	DVT right arm (2,3)	Unrelated
	03215702	Asthenia (2)	Possible
	03316602	Nausea (1,2)	Unrelated
Nausea (2,3)		Possible	

Source: Section 22, Table 88 and PNU study reports 9750148, 9850234, 0650095, 9850236, 9850244, 9850170, 9850171, 9850172, 9850169, 9850243

• **Deaths on Treatment or within Thirty Days**

Deaths on study were coded by the investigator as unrelated to treatment with the exception of patient #05900200 from study #018, who died with fever and dehydration (r/o hyperthyroidism) which was considered of "doubtful" relationship to study drug. Forty-one of the 50 deaths within 30 days were secondary to PD. The five adverse events were aspiration pneumonia, chest infection, bowel perforation secondary to peg tube, complications of hip fracture and an MI. Worsening of baseline condition consisted of CHF and/or heart disease; "other" consisted of a cardiac arrhythmia and complications from diabetes. See Sponsor's Table 8.G-85 for details.

**Sponsor's Table 8.G-85:  
Frequency of Deaths by Study Period**

Most likely cause	Total		On Treatment		Within 30 Days of Treatment	
	No.	%	No.	%	No.	%
Any	58	5.5	8	0.8	50	4.7
PD	44	4.2	3	0.3	41	3.9
Adverse Event	9	0.9	4	0.4	5	0.5
Worsening baseline condition	2	0.2	-	-	2	0.2
Other	3	0.3	1	0.1	2	0.2

• **Selected Adverse Events**

**Androgenic side effects.** The sponsor identified 4.3% of patients with androgenic effects: alopecia - 28 patients (2.6%); dysphonia - 8 patients (0.8%); and hypertrichosis - 10 patients (0.9%).

**Secondary malignancies.** The following malignancies were diagnosed while patients were receiving exemestane: basal cell carcinoma - 3 (0.3%); skin cancer NOS - 1 (0.1%); malignant melanoma - 1 (0.1%); uterine cancer - 1 (0.1%) and meningioma - 1 (0.1%). None were considered secondary to study drug; however, extent of exposure is limited in the metastatic setting and conclusions must wait for a potentially curable population.

**Thrombotic or thromboembolic events.** The sponsor identified 4 patients with acute MI, 3 with phlebitis, 2 with thrombophlebitis, 2 with deep vein thrombosis and 1 with thrombosis NOS for a total of 1.3% of patients treated at the dose of 25 mg daily. The investigator coded none as drug-related/indeterminate and no temporal pattern was apparent.

• **Age**

The safety database for the recommended dose, 25 mg daily, was analyzed by age < 65 (518 patients) and ≥ 65 years (540 patients). Sponsor's Table 8.6.-91 (vol. 3.11) presents frequency of events considered drug-related or of indeterminate cause occurring in ≥ 2% of the patients. Hot flushes and nausea were the most common events in either age group, occurring in ≥ 10% of patients. Hot flushes were more common in patients < 65 years of age (15.4% vs. 12.6%), but incidence of events in the other domains was either equivalent between the groups or more frequent in patients aged ≥ 65. The incidence of drug related/indeterminate grade 3-4 toxicities was 3.5% in patients < 65 and 4.6% in patients ≥ 65 years of age. No event was ≥ 2% and nausea was the most frequent in either age group (0.8% and 0.9% for < 65 and ≥ 65, respectively).

Sponsor's Table 8.G-91: Distribution by Age of Drug-related or of Indeterminate Cause Treatment-emergent Adverse Events (Any CTC Grade) in  $\geq 2\%$  of Patients: Phase I, II, III Exemestane 25 mg Daily (004, 007, 010, 017, 018, 022, 120002, 120003)

Body system / Adverse event	Age < 65 yrs		Age $\geq$ 65 yrs	
	No. evaluable	%	No. evaluable	%
	518		540	
Any adverse event	243	46.9	260	48.1
Autonomic nervous	32	6.2	27	5.0
Increased sweating	32	6.2	27	5.0
Body as a whole	124	23.9	129	23.9
Hot flushes	80	15.4	68	12.6
Fatigue	40	7.7	41	7.6
Pain	17	3.3	19	3.5
Cardiovascular*	14	2.7	24	4.4
Central and peripheral nervous	58	11.2	58	10.7
Headache	26	5.0	23	4.3
Dizziness	25	4.8	34	6.3
Gastrointestinal	99	19.1	124	23.0
Nausea	62	12.0	64	11.9
Vomiting	14	2.7	14	2.6
Abdominal pain	11	2.1	18	3.3
Diarrhea	4	0.8	13	2.4
Anorexia	6	1.2	21	3.9
Musculoskeletal*	15	2.9	13	2.4
Psychiatric	38	7.3	37	6.9
Insomnia	19	3.7	18	3.3
Depression	12	2.3	13	2.4
Reproductive, female?*	10	1.9	11	2.0
Respiratory*	11	2.1	22	4.1
Skin and appendages	33	6.4	52	9.6
Rash §	12	2.3	22	4.1
Pruritus	5	1.0	11	2.0
Alopecia	7	1.4	14	2.6

Source: Section 22 - Table 103

\* No single adverse event occurred in  $\geq 2\%$  of patients

♀ Including disorders of the breast and vagina

§ Including rash n.o.s., erythematous, follicular, and maculo-papular rash

**Medical Comment:** Differences between the age groups are minimal; however, other ways of analyzing the data, e.g., by decade, might be more revealing of a pattern with regard to a specific event.

- **Race**

Four racial groups were captured by the CRFs: white (971 patients), black (38 patients), Asian (15 patients) and "other" (34 patients - hispanics, mexican mestizos, native americans and philippinos). The sponsor has provided tabulations of TESS sorted by race in Section 22, table 104 for TESS due to any cause and Section 22, Table 105 for drug-related or indeterminate events. Conclusions are limited by the few numbers of non-white patients; however, no apparent difference in safety profile emerges. The commonly reported events of nausea, hot flushes and increased sweating are seen across the races.

- **Exemestane 200 mg Daily**

The phase 2 study #009 treated patients with 200 mg daily, the highest repeated daily dosing. The following summary comments are made vis-a-vis the margin of safety.

Eighty patients were entered and 78 treated. A total of 75 patients (96.2%) reported at least one TESS of any cause. The only serious drug related toxicity > grade 2 was akathisia, which resolved without sequelae when drug was withdrawn. The frequency of the most common adverse events considered drug-related/indeterminate are shown in Reviewer Table 24, along with the frequency seen in the pivotal trial and the ISS for 25 mg daily.

**Reviewer Table 24**  
**Frequency (%) of Common Adverse Events at 200 mg Daily**

Adverse Event	200 mg	25 mg: #018	25 mg: ISS
Nausea	19.2	9.2	11.9
Hot Flashes	20.0	12.6	14.0
Dizziness	11.3	3.4	5.6

Acne occurred in 3.8% of patients, alopecia in 10.3% and hypertrichosis in 5.1% vs 0%, 1.2% and 0.8%, respectively in #018. Trends with regard to laboratory abnormalities were less clear. Eleven of 73 evaluable patients (15.1%) had elevations of SGPT; one patient had a grade 3 elevation (attributed to cancer). Eight of 68 evaluable patients (11.8%) had an elevated bilirubin; one of these patients had grade 3 and another patient had grade 4 hyperbilirubinemia. One was due to cancer and the other indeterminate. The incidence of grade 3-4 lymphopenia of all causes at 200 mg was 24% vs. 17.2% in # 018.

*Reviewer Comment: A trend toward a higher frequency of the common adverse events and androgenic effects is seen; however, an increase in potentially life-threatening events is not apparent. The isolated case of neurologic toxicity is noted.*

**11. Four Month Safety Update**

Twelve additional patients have been added to the safety database, increasing the denominator from 1058 to 1070. Four additional months of follow-up have increased the median exposure from 17.1 to 18.4 weeks. The frequency of events previously reported in the ISS has not been impacted. No new serious adverse events have been captured. Three additional deaths within 30 days of treatment have been reported; narrative summaries are consistent with the sponsor's assessment of progressive disease.

**12. Foreign Marketing**

At the time of submission of the NDA, no approvals for marketing had been granted. Therefore, no post marketing experience was included for review.

**13. Summary**

Exemestane is an irreversible, steroidal inhibitor of aromatase, the principal enzyme involved in the conversion of androgens to estrogens. The ability of exemestane to suppress circulating serum estradiol to undetectable levels in postmenopausal women has been demonstrated in multiple studies, including in phase 2 and 3 clinical trials of postmenopausal women with metastatic breast cancer.

*Postmenopausal Women with Progressive Metastatic Breast Cancer following Tamoxifen.* Efficacy claims rest primarily on data from protocol #018, 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 (RR, CR + PR) between exemestane 25 mg q.d. and the control arm, megestrol 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.

A total of 769 patients were randomized, 366 to exemestane and 403 to megestrol. The imbalance is believed to have resulted from minimization being carried out within each country, with small accruals being more subject to variability (Section 7.2.2). The United States, which had its own randomization center and was the largest accruing country, randomized 75 patients to each arm.

The investigator determined RR was 19.1% for exemestane and 14.6% for megace. As specified in the protocol, objective responses were submitted to an external, blinded review committee composed of oncologists and radiologists (PRC) whose assessment would prevail in cases of disagreement. The RR according to the PRC was 15% for patients receiving exemestane and 12.4% for patients receiving megace. The difference in RR (megace - exemestane) was -2.6% (95% C.I. for the difference: -7.5%, +2.3%). The criterion for equivalence is met. Median duration of response is similar at 76.1 weeks for exemestane and 71.0 weeks for megace.

Subsequent to the regulatory history of this NDA, the International Committee for Harmonization (ICH) issued their statistical guidance (E9) that testing for equivalency in the ITT population biases toward equivalency. However, the ITT population had been accepted by the Division and was 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.

Initial attempts with the sponsor to determine response rate in an evaluable population have not been successful (see Section 7.2.3.1). Although the precise response rate might increase or decrease in another patient population, these responses could be accepted as robust for a number of reasons: data were derived from a randomized trial with an accepted control arm; CRs as well as PRs were seen; responses occurred in visceral as well as soft tissue disease, in patients who had progressed on tamoxifen and in those who relapsed subsequent to treatment with tamoxifen; rates are comparable to other agents in the class which were compared in randomized trials to the same control arm; responses have been reviewed by an external, blinded committee; and, random review of CRFs of the responders by the Division found no significant disagreements. The two phase 2 trials being considered supportive were multicenter, had at least limited peer review and accrued a combined total of 265 patients who met similar eligibility criteria.

The sponsor claims a statistically significant advantage for exemestane (medians of 20.3 vs. 16.6 weeks,  $p=0.037$ ). The robustness of the sponsor's finding can be questioned for a variety of 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.

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) and Kaplan-Meier estimates of median survival could not be estimated. Interpretation of the EORTC QLQ C30 data is limited by a dropout rate of close to 50% of patients in both groups beyond 16 weeks of treatment. In addition, the large number of QOL measures increases the likelihood of spurious positive findings. Thus, statistical claims for improvement in QOL are not warranted.

The *safety profile* of exemestane 25 mg daily appears commensurate with other marketed aromatase inhibitors. The most common drug-related side effects—nausea, vomiting and hot flushes—were more common in patients receiving exemestane than in those receiving megace (95% C.I. for the odds ratio excluded 1). Other side effects more common in one arm than the other were rash in patients taking exemestane and dyspnea in patients treated with megace. Treatment was discontinued more frequently in patients receiving megace (6.7% vs. 3.6%), although there was no single event predictive of premature withdrawal.

One percent of patients in either arm died while receiving study drug; however, 3 of the 4 patients on exemestane died due to a cardiac event. The ISS did not support the hypothesis of an increase in risk for cardiac events nor was there an increase in cardiac events leading to premature withdrawal. No difference was seen in incidence of hypertension between the two arms; effect on cholesterol was not formally studied. The sponsor analyzed adverse events by age, either < or  $\geq$  65 years of age and found a slight increase in risk for a cardiac event in patients  $\geq$  65 years of age (2.7% vs. 4.4%); however, this was not statistically significant. At this point in exemestane's drug development, the most plausible hypothesis is comorbid conditions in a postmenopausal population.

Laboratory abnormalities were uncommon. NCI Common Toxicity grade 3 - 4 abnormalities that reached an incidence of 5% were lymphopenia and an elevated gamma GT. The clinical relevance of either was not apparent in this patient population; however, it should be noted that the median duration of treatment was 17 weeks.

*Other potential safety issues.* (1) There was no evidence of an increase in pathologic fractures in patients receiving exemestane. The incidence in the randomized trial was 2.7% on exemestane and 2.5% on megestrol. (2) Steroidal inhibitors may be more specific with regard to aromatase inhibition, but may also have other hormonal agonist or antagonist effects via steroidal receptor activation. The metabolite 17-dihydroexemestane does have a 100X greater affinity for the androgen receptor than the parent compound. Clinical experience indicates that higher doses ( $\geq$  100 mg daily) may be associated with androgenic effects. No effect was seen on cortisol or aldosterone secretion at baseline or in response to ACTH.

*Treatment of postmenopausal women with advanced breast cancer whose disease has progressed following multiple hormonal therapies.* Previous discussions with the sponsor throughout the regulatory history of this application and in conjunction with two ODAC representatives, that for uncontrolled trials to provide the sole basis of approval of an indication, response rates must be dramatic, which in this population would be at least 20%. The response rates from three trials averaged 10% (6.6%, 9.4%, 13.2%). The Agency noted that the usual outcome of review at FDA is that response rates 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.

If approved, Exemestane will be the third in the class of aromatase inhibitors (AI) to be marketed in the United States. Anastrozole was approved in 1995 and letrozole in 1997. These earlier aromatase inhibitors are nonsteroidal in structure and their inhibition competitive and reversible. Although the irreversible inhibition of exemestane requires new enzyme production for escape, phase 1 studies on the weekly schedule were unsuccessful in maintaining maximal estrogen suppression and the recommended dosing for all three AIs is daily. The clinical relevance of the mechanistic differences remain to be determined.

#### 14. Recommended Regulatory Action

Approval for the indication: treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.



## **APPENDIX I: Summary of Clinical Trials with Aromasin®**

**Reviewer Table: Phase I or PK/PD Studies Conducted with  
Aromasin®**

STUDY	SITE	DESCRIPTION	# PT TREATED	DOSE Mad
<b>PHASE I STUDIES</b>				
002	UK/Australia	Daily and Weekly	34 PM ♀/BC	5 - 400
003	Norway	Daily	13 PM ♀/BC	5 - 200
004	Belgium	Daily	27 PM ♀/BC	5 - 600
005	Germany	Weekly	29 PM ♀/BC	25 - 1600
007	Italy	Phase I/Endocrinologic Evaluation; daily	80 PM ♀/BC	2.5 - 25
<b>PK/PD STUDIES</b>				
001	UK	Single dose	15 PM <sup>1</sup> ♀/HV <sup>2</sup>	25 - 800
008	UK	Crossover study of bioavailability of gelatin vs. sugar-coated tablets; single oral dose	12 PM ♀/HV	50
011	UK	Drug Disposition; single oral dose	4 PM ♀/HV	100
012	France	Crossover study of bioavailability of tablet vs. suspension; food effect study; single oral dose	12 PM ♀/HV	25
013	France	PK; evaluate CYP3A4; single and repeat oral dose	8 PM ♀/HV	25
014	France	PK; single dose	9 PM ♀/HV	25 - 200
015	France	PK with hepatic impairment; single oral dose	11 PM ♀ (9 HV)	25
016	France	PK with renal impairment; single oral dose	7 PM ♀ (9 HV)	25
019	France	PK/PD at low, repeat doses	32 PM ♀/HV	1 - 10
022	US	PK; single and repeat doses	15 PM ♀/BC	25
023	Japan	Single dose (includes food effect study)		25 - 50
024	Japan	Repeat oral dose	32 PM ♀	0.5 - 50
028	Sweden	Evaluation of CYP3A4 inhibition of PK; single dose with and without ketoconazole	5 PM ♀/HV	10 (+ketoconazole 200)
035	US	Bioequivalent study of three batches; single oral dose	36 ♀/HV	25

PM<sup>1</sup> = postmenopausal  
HV<sup>2</sup> = healthy volunteers

## Reviewer Table: Phase 2 and 3 Studies Conducted with Aromasin®

STUDY DESIGN	TITLE	SITE	NO. OF PTS ENROLLED
Phase 3 study: second-line hormonal treatment	94 OEXE 018: Exemestane versus megestrol acetate in postmenopausal patients with metastatic breast cancer failing tamoxifen: A phase 3, double-blind, randomized, parallel-group, comparative study	Multi-national	769
Phase 2 studies: second-line hormonal treatment	120002-999: Efficacy trial of Exemestane in the treatment of postmenopausal women with metastatic breast cancer failing tamoxifen	US & Mexico	129
	93 OEXE 010: Antitumor efficacy of exemestane in postmenopausal patients with metastatic breast cancer, failing to tamoxifen	Europe & So. Africa	140
Phase 2 studies: third-line hormonal treatment	120003-999: Antitumor efficacy of FCE 24304 as third-line hormonal therapy in the treatment of postmenopausal women with metastatic breast cancer refractory to tamoxifen and Megace	US	92
	92-OEXE-009: Antitumor efficacy of exemestane in postmenopausal patients with metastatic breast cancer, failing to aminoglutethimide	Europe & Australia	80
	95-OEXE-022: Antitumor efficacy of exemestane in postmenopausal women with metastatic breast cancer failing tamoxifen and Megace	US	87
	94-OEXE-017: Antitumor efficacy of exemestane in postmenopausal patients with metastatic breast cancer, failing nonsteroidal aromatase inhibitors	Multi-National	242

## Reviewer Table: Clinical Studies Not Reported in the NDA

STUDY DESIGN	TITLE or IDENTIFICATION	SITE	NO. OF PTS ENROLLED
Controlled studies	94-OEXE-021: Open label, randomized controlled trial of exemestane vs. tamoxifen in postmenopausal breast cancer	Europe	39
	95-OEXE-025: Open label, comparative study of 10 vs. 25 mg in postmenopausal breast cancer	Japan	73 (Closed)
	021: Phase 2 trial of exemestane vs. tamoxifen in previously untreated postmenopausal patients with breast cancer	Europe	31
	031: Phase 3, double-blind study in postmenopausal women with early breast cancer randomized to exemestane vs. tamoxifen for 2 years after 2-3 years of tamoxifen	Europe, Latin America, Australia, So. Africa	392
Other	96-OEXE-033: Compassionate use in postmenopausal women with breast cancer	Europe	100
	036: Phase 3: Neoadjuvant therapy of stage IIIB	Europe	
	037: Neoadjuvant therapy of stage IIIB	?	?
	027: Bone, lipid, coagulation assessments in resected postmenopausal breast cancer	Norwegian Breast Cancer Group	(planned)

## **APPENDIX II: Protocol #018**

### **Excerpts from the Protocol**

**Sponsor's Table: Derivation of Overall Pain Score (According to Purohit)**

Parameter	Description	Score
Pain	None	0
	Mild	1
	Moderate	2
	Severe	3
	Very severe	4
	Intolerable	5
Analgesic use	None	0
	Non-opioid analgesic or adjuvant <sup>a</sup>	1
	Non-opioid analgesic and adjuvant <sup>a</sup>	2
	Codeine and codeine-like preparations	3
	Oral morphine < 40 mg/day <sup>b</sup>	4
	Oral morphine 40-100 mg/day <sup>b</sup>	5
Performance status (ECOG scale)	Normal	0
	Light work possible	1
	Up and about > 50% of the day	2
	Confined to bed > 50% of the day	3
	Completely bed bound	4
Symptom score expressed as a percentage of maximum total		15 (100%)

<sup>a</sup>NSAIDs, bisphosphonates, tricyclic antidepressants, anticonvulsants

<sup>b</sup>or another strong opioid in an equianalgesic dose; to convert doses of analgesics into the equianalgesic dose of oral morphine the tables provided below may be used.

A drug or a dose will be considered for analgesic requirement grading if it is taken regularly, i.e., at a stable daily dose even if the dose is not equally distributed over 24 hours, e.g., the patient has night pain only and, therefore, takes her analgesics every day at bedtime.

At baseline visit, the analgesic regime used during the previous week period will be considered.

In case a drug or a dose is changed in the course of the last week prior to visit, the drug or dose which has been taken for a longer period will be used for grading. (If 2 drugs or doses are administered for equal periods of time, the most potent one will be considered.)

**Sponsor's Table: Approximate Oral Opioid Potency Ratios**

Meperidine/pethidine	1/8	Methadone	3-4
Dipipanone	1/4	Levorphanol	5
Papaveretum	2/3	Phenazocine	5
Morphine	1	Hydromorphone	6
Oxycodone	1	Buprenorphine	60*
Dextromoramide	2	Tramadol	1/4

\*Refers to sublingual route

**Sponsor's Table: Approximate Oral/Parenteral Equianalgesic Dose Ratios**

	Oral/Parenteral		Oral/Parenteral
Morphine	2:1	Levorphanol	2:1
Hydromorphone	5:1	Methadone	2:1
Meperidine	4:1	Buprenorphine	2:1

EORTC QLQ-C30 (Version 2.0) QUESTIONNAIRE

WE ARE INTERESTED IN SOME THINGS ABOUT YOU AND YOUR HEALTH. PLEASE ANSWER ALL OF THE FOLLOWING QUESTIONS YOURSELF BY CIRCLING THE NUMBER THAT BEST APPLIES TO YOU. THERE ARE NO "RIGHT" OR "WRONG" ANSWERS. THE INFORMATION THAT YOU PROVIDE WILL REMAIN STRICTLY CONFIDENTIAL.

Today's date:

		NO	YES					
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2					
2.	Do you have any trouble taking a long walk?	1	2					
3.	Do you have any trouble taking a short walk outside of the house?	1	2					
4.	Do you have to stay in a bed or a chair for most of the day?	1	2					
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2					
6.	Were you limited in doing either your work or other daily activities?	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH			
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4			
8.	Were you short of breath?	1	2	3	4			
9.	Have you had pain?	1	2	3	4			
10.	Did you need to rest?	1	2	3	4			
11.	Have you had trouble sleeping?	1	2	3	4			
12.	Have you felt weak?	1	2	3	4			
13.	Have you lacked appetite?	1	2	3	4			
14.	Have you felt nauseated?	1	2	3	4			
15.	Have you vomited?	1	2	3	4			
16.	Have you been constipated?	1	2	3	4			
17.	Have you had diarrhea?	1	2	3	4			
18.	Were you tired?	1	2	3	4			
19.	Did pain interfere with your daily activities?	1	2	3	4			
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4			
21.	Did you feel tense?	1	2	3	4			
22.	Did you worry?	1	2	3	4			
23.	Did you feel irritable?	1	2	3	4			
24.	Did you feel depressed?	1	2	3	4			
25.	Have you had difficulty remembering things?	1	2	3	4			
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4			
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4			
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4			
29.	How would you rate your overall health during the past week?	1	2	3	4	5	6	7
		Very Poor				Excellent		
30.	How would you rate your overall quality of life during the past week?	1	2	3	4	5	6	7
		Very Poor				Excellent		

## **APPENDIX III: Protocol #018**

### **Additional Tabulations and Analyses**

Sponsor's Display 1:

Summary of medical history: number (%) of patients with concomitant and prior diseases

Type of disease	Exemestane (N=366)				Megestrol acetate (N=403)			
	Present at study entry	No longer present at study entry	Unknown	Total	Present at study entry	No longer present at study entry	Unknown	Total
Any type of disease	279 (76.2)	176 (48.1)	14 (3.8)	304 (83.1)	311 (77.2)	193 (47.9)	7 (1.7)	349 (86.6)
Cardiovascular	154 (42.1)	40 (10.9)	2 (0.5)	175 (47.8)	182 (45.2)	29 (7.2)	2 (0.5)	195 (48.4)
Infectious parasitic		7 (1.9)		7 (1.9)	2 (0.5)	7 (1.7)		9 (2.2)
Pulmonary	29 (7.9)	18 (4.9)	1 (0.3)	45 (12.3)	39 (9.7)	21 (5.2)		54 (13.4)
Neoplasms	2 (0.5)	12 (3.3)		14 (3.8)	2 (0.5)	11 (2.7)		12 (3.0)
Liver	18 (4.9)	6 (1.6)	2 (0.5)	25 (6.8)	22 (5.5)	13 (3.2)		33 (8.2)
Other G.I.	39 (10.7)	58 (15.8)	2 (0.5)	87 (23.8)	52 (12.9)	75 (18.6)		110 (27.3)
Blood, blood forming organs	7 (1.9)	3 (0.8)		10 (2.7)	6 (1.5)	5 (1.2)		11 (2.7)
Genito-urinary	37 (10.1)	79 (21.6)	4 (1.1)	104 (28.4)	40 (9.9)	83 (20.6)	2 (0.5)	114 (28.3)
Endocrine metabolic	89 (24.3)	16 (4.4)	2 (0.5)	104 (28.4)	115 (28.5)	22 (5.5)		125 (31.0)
Mental	48 (13.1)	4 (1.1)		51 (13.9)	50 (12.4)	16 (4.0)		64 (15.9)
Neurologic	38 (10.4)	22 (6.0)	1 (0.3)	55 (15.0)	51 (12.7)	33 (8.2)	1 (0.2)	73 (18.1)
Musculo-skeletal	96 (26.2)	23 (6.3)	3 (0.8)	114 (31.1)	96 (23.8)	31 (7.7)	1 (0.2)	114 (28.3)
Allergies	50 (13.7)	6 (1.6)		56 (15.3)	52 (12.9)	5 (1.2)	1 (0.2)	58 (14.4)

Type of disease	Exemestane (N=366)		Megestrol acetate (N=403)			
Skin and subcutaneous	11 (3.0)	5 (1.4)	15 (4.1)	10 (2.5)	11 (2.7)	21 (5.2)
Congenital anomalies	1 (0.3)		1 (0.3)	1 (0.2)		1 (0.2)
Ill-defined conditions	8 (2.2)	2 (0.5)	10 (2.7)	14 (3.5)	7 (1.7)	19 (4.7)
Injuries poisoning		1 (0.3)	1 (0.3)	1 (0.2)	2 (0.5)	3 (0.7)
Other (includes other malignancies)	2 (0.5)		2 (0.5)	1 (0.2)		1 (0.2)

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Exemestane (PNU 155971) – Protocol 94OEXE018 (EXEMESTANE-018)  
 Sponsor's Table 20.2 – Prognostic factor 1 : response to prior TAM

	Treatment															
	Exemestane								Megestrol Acetate							
	At randomization								At randomization							
	(Neo) Adjuvant		CR/PR/NC=>6 mos		NC<6mos/P D/NE		Total		(Neo) Adjuvant		CR/PR/NC=>6 mos		NC<6 Mos/PD/NE		Total	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
At baseline																
(Neo) Adjuvant	129	90.2	15	7.77	1	3.33	145	39.8	140	93.9	11	4.89	1	3.45	152	37.7
CR/PR/NC=>6 mos	5	3.50	171	88.8	3	10.0	179	48.9	5	3.36	202	89.7	3	10.3	210	52.1
NC<6 mos/PD/NE	9	6.29	7	3.63	26	86.6	42	11.4	4	2.68	12	5.33	25	86.2	41	10.1
Total	143	100.0	193	100.0	30	100.0	366	100.0	149	100.0	225	100.0	29	100.0	403	100.0

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Exemestane (PNU 155971) – Protocol 94OEXE018 (EXEMESTANE-018)  
 Sponsor's Table 20.2 – Prognostic factor 2 : prior chemotherapy

	Treatment															
	Exemestane								Megestrol Acetate							
	At randomization								At randomization							
	No Chemotherapy		Adjuvant chemotherapy Only		Advanced Chemotherapy		Total		No Chemotherapy		Adjuvant Chemotherapy Only		Advanced Chemotherapy		Total	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
At baseline																
Missing data	1	0.47					1	0.27	1	0.43	1	0.98			2	0.50
No chemotherapy	202	94.84	1	1.06			203	55.46	224	95.32	1	0.98	1	1.52	228	56.08
Adjuvant chemotherapy only	10	4.69	87	92.55	7	11.86	104	28.42	9	3.83	95	93.14	4	6.06	108	26.80
Advanced chemotherapy			6	6.38	52	88.14	58	15.85	1	0.43	5	4.90	61	92.42	67	16.83
Total	213	100.0	94	100.0	59	100.0	366	100.0	235	100.0	102	100.0	66	100.0	403	100.0

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Exemestane (PNU 155971) – Protocol 94OEXE018 (EXEMESTANE-018)  
 Sponsor's Table 20.2 – Prognostic factor 3 : site of metastasis

	Treatment																			
	Exemestane										Megestrol Acetate									
	At randomization										At randomization									
	Visceral +/- others		Bone only		Bone + Soft Tissue		Soft tissue only		Total		Visceral +/- others		Bone only		Bone + Soft tissue		Soft tissue only		Total	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
At baseline																				
Missing data	1	0.47							1	0.27	2	0.82							2	0.50
Visceral +/- others	197	92.49	6	8.70	1	2.78	3	6.25	207	56.56	22	94.24	3	3.90	3	7.89	4	8.89	239	59.31
Bone only	6	2.82	52	75.36	3	8.33			61	16.67	6	2.47	68	85.71	1	2.63			73	18.17
Bone + Soft tissue	2	0.94	10	14.49	28	77.78	3	6.25	43	11.75			7	9.09	30	78.95	1	2.22	38	9.43
Soft tissue only	7	3.29	1	1.45	4	11.11	42	87.50	54	14.75	6	2.47	1	1.30	4	10.53	40	88.89	51	12.68
Total	213	100.0	69	100.0	36	100.0	48	100.0	366	100.0	24	100.0	77	100.0	38	100.0	45	100.0	403	100.0

**Sponsor's Display 2:**

**Serum estrogens levels over time in patients treated daily with 25 mg exemestane**

(excerpted from vol. 3.79, p. 75)

Type of Hormone / Parameter	Visit				
	Baseline	Week 8	Week 24	Week 48	PD
<b>Serum estradiol<sup>c</sup></b>					
Number of patients	59	59	27	14	4
Hormone level (pg/mL) <sup>a,b</sup>	10.3	1.2	1.1	1.0	0.9
95% CI	8.2-13.0	1.0-1.5	0.9-1.4	0.8-1.2	0.5-1.4
% vs baseline <sup>b</sup>	100	11.7	11.6	7.9	6.0
No. patients w/ values <DL	0	22	12	7	2
<b>Serum estrone</b>					
Number of patients	60	60	27	14	4
Hormone level (pg/mL) <sup>a,b</sup>	40.8	8.0	6.2	5.5	8.4
95% CI	33.3-49.9	6.5-9.9	5.3-7.1	4.1-7.5	2.6-27.8
% vs baseline <sup>b</sup>	100	19.9	14.6	11.1	12.8
No. patients w/ values <DL	0	1	0	0	0
<b>Serum estrone sulfate</b>					
Number of patients	61	61	28	14	4
Hormone level (pg/mL) <sup>a,b</sup>	349.8	31.2	29.9	28.1	30.0
95% CI	278-439	26.1-37.4	23.0-38.8	19.1-41.4	10.7-84.2
% vs baseline <sup>b</sup>	100	9.2	8.2	8.1	6.9
No. patients w/ values <DL	0	0	0	1	0

Source: Table 23, Listing 23

<sup>a</sup> Hormone levels falling below the limits of detection of the assay (0.7 pg/mL for estradiol, 1.8 pg/mL for estrone and 6 pg/mL for estrone sulfate) were recorded as the value of the detection limit

<sup>b</sup> Geometric mean

<sup>c</sup> Patient 096027 was excluded from the analysis for estradiol since the baseline value was below the sensitivity limit of the methodology

**Sponsor's Display 3:**

**Serum estrogens levels over time in patients treated daily with 160 mg megestrol acetate**

(excerpted from vol. 3.79, p. 75)

Type of Hormone / Parameter	Visit				
	Baseline	Week 8	Week 24	Week 48	PD
<b>Serum estradiol<sup>c</sup></b>					
Number of patients	61	59	23	12	3
Hormone level (pg/mL) <sup>a,b</sup>	9.5	2.7	2.3	4.0	1.6
95% CI	7.7-11.6	2.1-3.4	1.7-3.3	2.0-8.0	
% vs baseline <sup>b</sup>	100	28.5	24.2	32.6	23.3
No. patients w/ values <DL	0	5	1	0	0
<b>Serum estrone</b>					
Number of patients	64	62	25	12	3
Hormone level (pg/mL) <sup>a,b</sup>	35.6	10.7	8.2	24.4	5.4
95% CI	29.5-43.0	8.5-13.4	6.0-11.3	12.2-49.0	
% vs baseline <sup>b</sup>	100	29.7	22.2	50.5	17.5
No. patients w/ values <DL	0	0	0	0	0
<b>Serum estrone sulfate</b>					
Number of patients	65	65	28	12	4
Hormone level (pg/mL) <sup>a,b</sup>	315.7	81.4	50.6	110.7	31.2
95% CI	256-389	64.4-103.0	35.8-71.7	54.8-223.8	8.2-118.4
% vs baseline <sup>b</sup>	100	26.5	17.3	30.6	23.8
No. patients w/ values <DL	0	0	0	0	0

Source: Table 23, Listing 23

<sup>a</sup> Hormone levels falling below the limits of detection of the assay (0.7 pg/mL for estradiol, 1.8 pg/mL for estrone and 6 pg/mL for estrone sulfate) were recorded as the value of the detection limit.

<sup>b</sup> Geometric mean

<sup>c</sup> Patients 096022, 096023, and 096034 were excluded from the analysis for estradiol since the baseline values were below the sensitivity limit of the methodology

Abbreviations: CI = confidence interval; DL = detection limit; PD = progressive disease.

**Sponsor's Display 4: Number (%) of patients reporting treatment emergent adverse events of all CTC Grades and causes, and occurring in  $\geq 2\%$  of treated patients**

Event	Exemestane (N=358)	Megestrol acetate (N=400)	Odds Ratio (E/M)	95% OR CI
Any adverse event	284 (79.3)	320 (80.0)	0.96	0.67 - 1.37
Any autonomic nervous system event	23 (6.4)	37 (9.3)	0.67	0.39 - 1.16
*Increased sweating	22 (6.1)	36 (9.0)	0.66	0.38 - 1.15
Any body as a whole event	162 (45.3)	186 (46.5)	0.95	0.71 - 1.27
*Fatigue	78 (21.8)	117 (29.3)	0.67	0.48 - 0.94†
*Hot flushes	48 (13.4)	22 (5.5)	2.66	1.57 - 4.50†
Asthenia	4 (1.1)	9 (2.3)	0.49	0.15 - 1.61
Fever	14 (3.9)	13 (3.3)	1.21	0.56 - 2.61
Influenza-like symptoms	21 (5.9)	21 (5.3)	1.12	0.60 - 2.10
Edema	10 (2.8)	8 (2.0)	1.41	0.55 - 3.61
Edema legs	12 (3.4)	15 (3.8)	0.89	0.41 - 1.93
Pain	47 (13.1)	50 (12.5)	1.06	0.69 - 1.62
Weakness generalized	8 (2.2)	13 (3.3)	0.68	0.28 - 1.66
Any cardiovascular event, general	27 (7.5)	46 (11.5)	0.63	0.38 - 1.03
Dyspnea on exertion	8 (2.2)	12 (3.0)	0.74	0.30 - 1.83
Hypertension	17 (4.7)	23 (5.8)	0.82	0.43 - 1.56
Any central & peripheral nervous system event	71 (19.8)	82 (20.5)	0.96	0.67 - 1.37
*Dizziness	29 (8.1)	23 (5.8)	1.44	0.82 - 2.55
Headache	29 (8.1)	26 (6.5)	1.27	0.73 - 2.20
Parasthesia	12 (3.4)	8 (2.0)	1.70	0.69 - 4.21
Any gastrointestinal system event	133 (37.2)	154 (38.5)	0.94	0.70 - 1.27
*Abdominal pain	22 (6.1)	42 (10.5)	0.56	0.33 - 0.95†
*Nausea	66 (18.4)	46 (11.5)	1.74	1.16 - 2.61†
Anorexia	22 (6.1)	19 (4.8)	1.31	0.70 - 2.47
Appetite increased	10 (2.8)	23 (5.8)	0.47	0.22 - 1.00
Constipation	17 (4.7)	32 (8.0)	0.57	0.31 - 1.05
Diarrhea	13 (3.6)	20 (5.0)	0.72	0.35 - 1.46
Heartburn	4 (1.1)	8 (2.0)	0.55	0.17 - 1.85
Vomiting	26 (7.3)	15 (3.8)	2.01	1.05 - 3.86†
Any heart rate and rhythm event	7 (2.0)	10 (2.5)	0.78	0.29 - 2.07
Any metabolic and nutritional event	12 (3.4)	21 (5.3)	0.63	0.30 - 1.29
Any musculo-skeletal system event	26 (7.3)	31 (7.8)	0.93	0.54 - 1.60
Fracture pathological	8 (2.2)	12 (3.0)	0.74	0.30 - 1.83

Event	Exemestane (N=358)	Megestrol acetate (N=400)	Odds Ratio (E/M)	95% OR CI
<b>Any psychiatric event</b>	<b>96 (26.8)</b>	<b>91 (22.8)</b>	<b>1.24</b>	<b>0.89 - 1.73</b>
*Anxiety	36 (10.1)	43 (10.8)	0.93	0.58 - 1.48
*Depression	46 (12.8)	35 (8.8)	1.54	0.97 - 2.45
*Insomnia	39 (10.9)	36 (9.0)	1.24	0.77 - 1.99
<b>Any reproductive event, female</b>	<b>15 (4.2)</b>	<b>22 (5.5)</b>	<b>0.75</b>	<b>0.38 - 1.47</b>
Vaginal hemorrhage	2 (0.6)	14 (3.5)	0.15	0.03 - 0.69†
<b>Any resistance mechanism event</b>	<b>25 (7.0)</b>	<b>15 (3.8)</b>	<b>1.93</b>	<b>1.00 - 3.72</b>
Infection	12 (3.4)	4 (1.0)	3.43	1.10 - 10.74†
<b>Any respiratory system event</b>	<b>89 (24.9)</b>	<b>116 (29.0)</b>	<b>0.81</b>	<b>0.59 - 1.12</b>
Breath shortness	8 (2.2)	19 (4.8)	0.46	0.20 - 1.06
Bronchitis	13 (3.6)	9 (2.3)	1.64	0.69 - 3.88
Coughing	21 (5.9)	28 (7.0)	0.83	0.46 - 1.49
Dyspnea	35 (9.8)	60 (15.0)	0.61	0.39 - 0.96†
Sinusitis	10 (2.8)	6 (1.5)	1.89	0.68 - 5.25
<b>Any skin and appendages event</b>	<b>40 (11.2)</b>	<b>30 (7.5)</b>	<b>1.55</b>	<b>0.94 - 2.55</b>
Itching	7 (2.0)	2 (0.5)	3.97	0.82 - 19.23
Rash	8 (2.2)	2 (0.5)	4.55	0.96 - 21.56
<b>Any urinary system event</b>	<b>18 (5.0)</b>	<b>31 (7.8)</b>	<b>0.63</b>	<b>0.35 - 1.15</b>
Urinary tract infection	9 (2.5)	12 (3.0)	0.63	0.35 - 2.00
<b>Any vascular (extracardiac) event</b>	<b>10 (2.8)</b>	<b>16 (4.0)</b>	<b>0.69</b>	<b>0.31 - 1.54</b>
<b>Any vision event</b>	<b>15 (4.2)</b>	<b>8 (2.0)</b>	<b>2.14</b>	<b>0.90 - 5.12</b>
<b>Any white cell and res (sic) event</b>	<b>11 (3.1)</b>	<b>12 (3.0)</b>	<b>1.02</b>	<b>0.45 - 2.35</b>
Lymphedema	10 (2.8)	10 (2.5)	1.12	0.46 - 2.72

Source: Table 26.1

\* elicited adverse events (patients specifically asked about these adverse events)

† interval does not include 1

## **APPENDIX IV: Labeling-Review**