Table 43: Reviewer's Results of Sensitivity Analysis of Difference [a] in Response Rates

Population	Estimated % Difference in Response Rates (fulvestrant – anastrozole)	95.4% CI
ITT	-0.02	(-8.02, 7.98)
PP	0.29	(-8.58, 9.17)

[a] A difference in response rates greater than 0 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg.

Reviewer comment: FDA concurred with the Applicant's conclusions that with a non-inferiority margin of 10% fulvestrant 250 mg was non-inferior to anastrozole with respect to best objective response rate.

(d) Subgroup Analyses (exploratory)

Response rates for subpopulations based on age and race are summarized in the following table:

Table 44: Best Objective Response Rate by Age and Race (Trial # 21)

Population	Subgroup		Number (%) of responders	
			Fulvestrant 250 mg	Anastrozole 1 mg
ITT	Age			
		< 65	24 /108 (= 22.2%)	20 /114 (= 17.5%)
		≥ 65	11 /98 (= 11.2%)	13 /80 (= 16.3%)
	Race			
		White	431 /177 (= 17.5%)	27 /157 (= 17.2%)
		Non-white	3 / 20 (= 15.0%)	6 /24 (= 25.0%)
PP	Age			
		< 65	18 /89 (= 20.2%)	16 /89 (= 18.0%)
		≥ 65	11 /82 (= 13.4%)	10 /67 (= 14.9%)
	Race			
		White	25 /146 (= 17.1%)	21 /128 (= 16.4%)
		Non-white	4 / 25 (= 16.0%)	5 / 28 (= 17.9%)

Response rates for subpopulations based on hormonal receptor status are summarized in the following table:

Table 45: Best Objective Response Rate by Hormonal Receptor Status (Trial # 21)

Population	(ER, PR) status	Number (%) of responders		
		Fulvestrant 250 mg N = 206	Anastrozole 1 mg N = 194	Combined N = 400
ITT				
	(+, +)	27/128 (= 21.0%)	20/106 (= 18.9%)	47/234 (= 20.1%)
	(+, -)	2/37 (= 5.4%)	6/40 (= 15.0%)	8/77 (= 10.4%)
	(+, ?)	1/5 (= 20.0%)	1/10 (= 10.0%)	2/15 (= 13.3%)
	(-, +)	1/9 (= 11.1%)	3/12 (= 25.0%)	4/21 (= 19.0%)
	(-, -)	1/14 (= 7.1%)	2/9 (= 22.2%)	3/23 (= 13.0%)
	(-, ?)	0/0	0/1	0/1
	(?, +)	0/0	0/1	0/1
	(?, ?)	3/13 (= 23.1%)	1/15 (= 6.7%)	4/28 (=14.3%)

Reviewer comment: Although definitive conclusions can not be reached from non pre specified post hoc analyses, response rates may be decreased in the elderly population. A few patients in this trial who are negative for estrogen and/or progesterone receptors appeared to respond to hormonal therapy.

(3) Time to Progression

(a) Descriptive Results

Time to progression was defined as the time from randomization to the time of objective disease progression. Most of the patients had disease progression by the data cutoff date. The Applicant's description of time to disease progression data is summarized in the table below, followed by the Kaplan-Meier plots.

Table 46: Applicant's Descriptive Summary of Time to Disease Progression

Population	Fulvestrant 250 mg		Anastrozole 1 mg	
	Median (in days)	# of patients censored (%)	Median (in days)	# of patients censored (%)
ITT	165	34 (16.5%)	103	27 (13.9%)
PP	141	23 (13.5%)	90	19 (12.1%)

In the intent to treat population, median time to progression was 165 days for fulvestrant and 103 days for anastrozole. Per protocol data similarly show a longer median time to progression in the fulvestrant arm, suggesting a longer time to progression for Fulvestrant over anastrozole. The Kaplan-Meier plots for the different arms, however, are similar and the point differences observed at the medians are not sustained:

Figure 5: Kaplan-Meier Plot of Time to Progression (ITT Population)

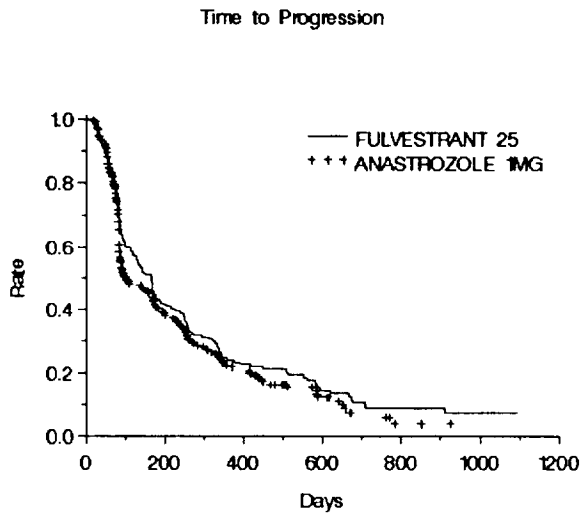
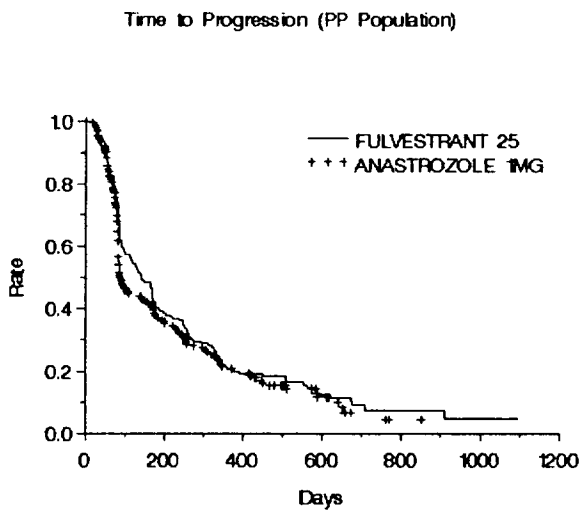


Figure 6: Kaplan-Meier Plot of Time to Progression (PP Population)



(b) Statistical Analysis of TTP

The analyses of time to disease progression are summarized in table 42 below:

Table 47: Results of Analysis of Time to Disease Progression

Population	Analysis	Applicant's Estimated hazard ratio [a] (95.14% CI)	FDA Estimated hazard ratio (95.4% CI)
ITT	Adjusted [b]	0.92 (0.74, 1.14) p = .4295	0.92 (0.74, 1.14) p = .4295
	Unadjusted [c]	0.88 (0.71, 1.10) p = .2594	0.88 (0.71, 1.10) p = .2594
PP	Adjusted	0.95 (0.74, 1.21) p = .6662	0.95 (0.74, 1.21) p = .6662
	Unadjusted	N/A	0.91 (0.72, 1.15) p = .4134

[a] A hazard ratio of less than 1 indicates that fulvestrant 250 mg is associated with a longer time to disease progression compared with anastrozole 1mg.
[b] Primary analysis. Cox proportional-hazards model with baseline covariates: age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease.
c Cox proportional-hazards model without baseline covariates.

Whether analyses were performed on the ITT or PP population, adjusted or unadjusted analysis, the p-values were relatively large, indicating that there was no statistically significant difference in TTP between the two treatment arms. Superiority in time to progression was therefore not demonstrated. The FDA statistical reviewer defined the per protocol (PP) population slightly differently from the applicant and constructed a 95.4% (instead of 95.14%) confidence interval, adjusting for the interim analysis. None of the confidence intervals of the hazard ratios exceeded 1.25, thus ruling out a 25% shorter time to progression for fulvestrant compared with anastrozole.

(c) Covariate analysis

Patients who had measurable disease only and patients with a performance status of 1 or 2 seemed to be associated with a higher instantaneous risk of disease progression compared with all other patients. Patients whose receptor status was unknown seemed to be associated with a lower risk compared with all other patients although only a very small proportion of patients was in this stratum and the finding was only seen in the ITT population. Results of covariates used in the adjusted analysis are summarized in the following table:

Table 48: Results of Covariates Analysis of Time to Disease Progression

Variable	ITT population		PP population	
	Hazard ratio (95.4% CI)	P-value	Hazard ratio (95.14% CI)	P-value
Measurable disease only	1.62 (1.23, 2.14)	0.0005	1.59 (1.18, 2.14)	0.0019
Who PS 1	1.30 (1.02, 1.65)	0.0317	1.21 (0.93, 1.58)	0.1559
Who PS 2	1.59 (1.06, 2.39)	0.0233	1.77 (1.13, 2.78)	0.0118
Previous response to hormones	1.02 (0.68, 1.54)	0.9288	0.79 (0.47, 1.33)	0.3714
Receptor neg	1.06 (0.67, 1.70)	0.7937	1.16 (0.72, 1.85)	0.5350
Receptor status Unknown	0.48 (0.29, 0.81)	0.0053	0.61 (0.36, 1.04)	0.0658

Hazard Ratio > 1 = higher risk of progression.

(d) Conclusions regarding TTP

Superiority in time to progression was not demonstrated. Although the FDA statistical reviewer used a slightly different confidence level and the PP population was slightly different from the Applicant's, the FDA was able to concur with the Applicant's finding that, with a non-inferiority margin of 25%, fulvestrant 250-mg was non-inferior to anastrozole with respect to time to progression. As in trial #20, patients with worse performance status appeared to have a higher risk for progression, and patients whose hormone receptor status was unknown appeared to have a lower risk of progression. Bisphosphonate therapy, age over 65, and previous chemotherapy were not risk factors for progression. Unlike trial #20, receptor negativity and a previous response to hormones were not associated with increased or decreased risk of progression, respectively. The increased risk for progression in patients with measurable disease only was not seen in trial #20. The numbers are small, and the differences between studies may be due to artifact of small numbers.

(4) Survival analysis

The survival data in the original NDA submission was cut off on June 30, 2000. Since the original survival data were not mature (65.5% of the 400 patients were censored), the Division requested the applicant for an updated survival data. The updated survival data were received on August 28, 2001; the data were cut off on April 30, 2001. The FDA statistical reviewer's survival data analysis results are summarized in the following tables:

Table 49: Descriptive Survival Results (ITT population)

Data cut-off date	Fulvestrant (N = 206)		Anastrozole (N = 194)	
	Median	# of deaths	Median	# of deaths
June 30, 2000	848	73 (35.4%)	878	65 (33.5%)
April 30, 2001	837	109 (52.9%)	901	92 (47.4%)

Figure 7: Reviewer's Kaplan-Meier Probability of Updated Survival Time (ITT Population) Study #21

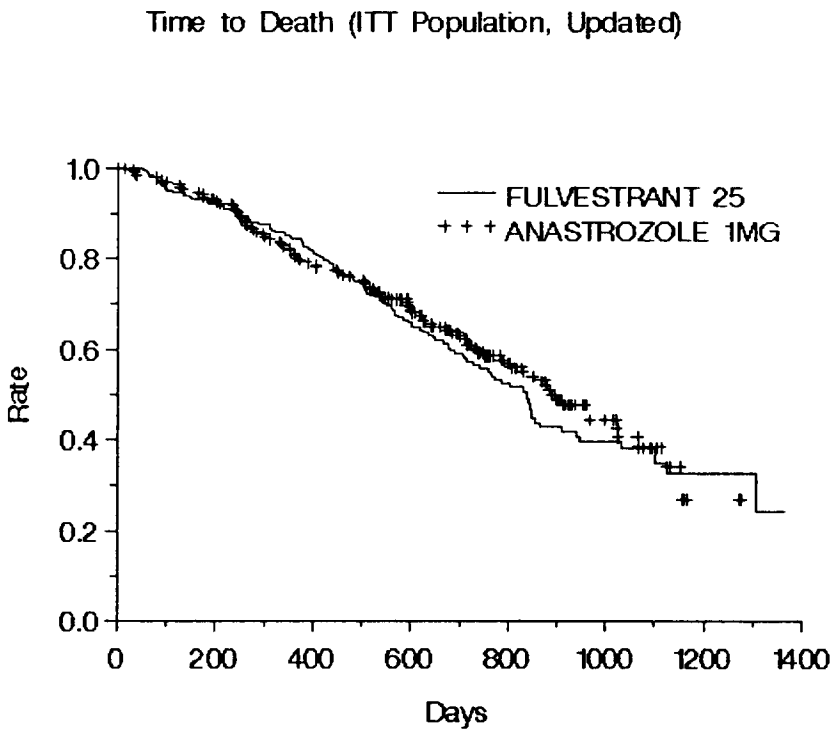


Table 50: FDA Statistical Reviewer's Analysis of Survival

Population	Data cut-off date	Comparison	Hazard ratio [a]	95% two-sided CI	P-value
		fulvestrant: anastrozole			
ITT	April 30, 2001	Adjusted analysis [b]	1.12	(0.85, 1.49)	0.422
		Unadjusted analysis [c]	1.10	(0.83, 1.45)	0.509
PP	April 30, 2001	Adjusted analysis	1.16	(0.84, 1.59)	0.366
		Unadjusted analysis	1.14	(0.84, 1.56)	0.405

[a] A hazard ratio of less than 1 indicates that fulvestrant 250 mg is associated with a longer time to death compared with anastrozole 1 mg.
b Cox proportional-hazards model with baseline covariates: age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease.
c Cox proportional-hazards model without baseline covariates.

Reviewer comment: As in study #20, all hazard ratios were approximately 1, and the Kaplan Meier curves are similar, suggesting no difference in survival between the two treatment groups. However, the study was not designed to show non-inferiority or superiority with respect to survival; therefore, there was limited power to detect treatment difference in survival.

(5) Time to Treatment Failure

The Applicant's analysis results of time to treatment failure are summarized as below.

Table 51: Applicant's Results of Descriptive Summary of Time to Treatment Failure

Population	Fulvestrant 250 mg (N = 206)		Anastrozole 1 mg (N = 194)	
	Median (in days)	# of patients censored (%)	Median (in days)	# of patients censored (%)
ITT	141	28 (13.6%)	101.5	24 (12.4%)

The Applicant's results did not suggest any treatment difference with respect to time to treatment failure. FDA does generally not regard this endpoint as clinically relevant.

(6) Duration of Objective Response

Duration of objective response was assessed in responders only (patients who has an objective response of CR or PR) in two ways:

1. from the date of randomization to the date of first determined progression or death from any cause, and
2. from the date of first documentation of response to the date of first determined progression or death from any cause.

Per Applicant's report, 36/206 (=17.5%) patients randomized to the fulvestrant 250-mg group and 34/194 (=17.5%) patients randomized to the anastrozole group had an objective response. The Applicant's results are summarized as below.

Table 52: Results of Duration [a] of Best Objective Response (ITT Population)

	Treatment	
	Fulvestrant 250 mg	Anastrozole 1 mg
# of Responders	36	34
Median response duration (days) from Date of Randomization	587.5	319.6
Median response duration (days) from Date of Response	335	171
FDA 95% CI for median	(192, 623)	(132, 271)

[a] from date of response started.

Reviewer comment: The duration of response defined from the date of randomization may not be clinically meaningful since duration of response for patients who started response late tends to be overestimated. The duration of response between the two groups should not be compared because the two respective responder subgroups were treatment-outcome dependent. The duration of response should be reported only for the specific treatment under consideration along with the response rate.

(7) Duration of Clinical Benefit

Clinical benefit was defined by the applicant as patients who had CR, PR, or SD≥24 weeks. Duration of clinical benefit was defined by the applicant as the time from the date of randomization to date of clinical benefit. Per Applicant's report, 87/206 (=42.2%) patients randomized to the fulvestrant 250-mg group and 70/194 (=36.1%) patients randomized to the anastrozole group had a clinical benefit. When performed on the ITT population the median duration of clinical benefit was 391 days for patients with clinical benefit who were randomized to the fulvestrant 250-mg group and 329 days for patients with clinical benefit who were randomized to the anastrozole group.

(8) Quality of Life analysis

In trial #21, most patients participated in QOL assessments. A total of 317 (83.6%) of 379 patients completed all questionnaires for data collected in the periods up to the date of the patient's last visit within the previous 12 months or the visit at which the patient was determined to have disease progression. The majority [42 (67.7%) of 62] of patients who did not complete the required number of questionnaires missed only 1 visit. The pattern of TOI for patients who completed the last questionnaire was similar to that of patients who did not complete the last questionnaire.

(a) Treatment Outcome Index (TOI)

There was no significant difference in TOI between the 2 groups (p = .8) . Additionally, there was no evidence at the 5% level of a treatment-by-time interaction. This suggested that there was no evidence of change in TOI over time for either treatment group.

(b) Time to Deterioration in Quality of Life

Most patients in the North American trial (#21) participated in the QOL surveys. Patients excluded from the QOL analysis were those either did not have a baseline TOL value or whose baseline questionnaire was completed more than 7 days after treatment. Approximately 95% of all patients were included in the analysis of time to deterioration. Insufficient quality-of-life data were collected after disease progression to allow the data after progression to be used in the statistical analysis. Only 113 (35.1%) of 322 patients with disease progression completed all the questionnaires up to the data cutoff date. The FDA statistical reviewer obtained the distribution of patients included in the analysis of time to deterioration, and obtained the 95% confidence interval for the median time to deterioration, included in Table 48:

Table 53: Descriptive Summary of Time to Deterioration (ITT population)

	Fulvestrant 250 mg		Anastrozole 1 mg	
	Median, days (FDA 95% C.I.)	# of patients censored (%)	Median, days (FDA 95% C.I.)	# of patients censored (%)
	260 (165,276)	106 (54.4%)	209 (165, 276)	85 (46.2%)
# of pts. (%) included in the TTD analysis	195 /206 (94.7%)		184 /194 (94.8%)	
# patients (%) with deterioration in QOL	89/195 (45.6%)		99/184 (53.8 %)	

Differences between treatment groups in median time to deterioration were 51 days in favor of fulvestrant; this was not statistically significant (p=0.1971). Time to deterioration in QOL was comparable between treatment groups.

(c) Symptomatic Response

(i) Analgesic use

The proportions of patients in the fulvestrant group who used no analgesics from month 1 onward were similar to or slightly greater than that for patients in the anastrozole group.

(ii) Global Pain Score

Global pain scores (patients' assessments) were generally similar between treatment groups for Visits 1 to 12 (compared with baseline scores). Slightly more patients in the fulvestrant group reported global pain scores of no pain compared with patients in the anastrozole group. Differences were not statistically significant.

Reviewer comment: QOL responses were comparable between treatment arms. Despite a higher initial rate of collection of QOL data in trial #21 compared with trial #20, meaningful conclusions on time to deterioration could not be made on account of censoring due to the low rate of collection of data following progression.

x. Preliminary Results of trial #0025 in first line indication

(1) Introduction

Trial 0025 was a double-blind, randomized, parallel-group, multicenter, comparative trial conducted in postmenopausal women with advanced breast cancer designed to compare the efficacy and safety of fulvestrant with tamoxifen in the initial treatment of advanced breast cancer. Patients had received no prior therapy or had completed adjuvant tamoxifen at least 12 months prior to entry. Preliminary results of this trial were supplied by the applicant but the data was not reviewed in detail. This trial was intended to support registration of fulvestrant in the hormonal treatment of advanced metastatic breast cancer in the first-line indication.

The population of breast cancer patients studied in this trial was distinct and different from that included in trials 0020 and 0021 which were reviewed in the previous sections. These trials included patients who had progressed or relapsed after prior endocrine therapy as adjuvant therapy or treatment of advanced disease. In trial 0025, patients who had received previous endocrine treatment for breast cancer were excluded, although patients who had received tamoxifen as adjuvant treatment were eligible provided treatment had been stopped at least 12 months before randomization. Patients who had received surgical oophorectomy or ovarian radiation were also eligible. The primary statistical analyses of the objective efficacy end points in the trial (ie, time to progression, objective response rate, and time to treatment failure) were conducted using an randomized patients on an intention-to-treat basis. Secondary (supportive) statistical analyses of these end points were conducted using a per-protocol population.

(2) Reported Results

A total of 587 patients from 170 centers, including 60 patients from 17 Japanese centers, were randomized to trial treatment with either fulvestrant 250 mg (313 patients) or tamoxifen 20 mg (274 patients). Patients were followed for a median of 441 days. 234/313 (75%) of patients treated with fulvestrant were strogen receptor positive, 202/274 (74%) of patients treated with tamoxifen were estrogen receptor positive.

Table 54: Study 0025 Median Time to Progression

Population	Fulvestrant	Tamoxifen 20	Hazard Ratio (F:T)	95% C.I.	P value
(All pts)	206 days	252 days	1.18	.98, 1.44	.0876
Hormone receptor positive	250 days	252 days	1.1	.89, 1.36	.3882
receptor negative or unknown	107 days	211 days	1.43	.95, 2.14	.0823

TTP was not statistically significantly different at the 5% level between fulvestrant and o tamoxifen (p=0.0876). The hazard ratio indicates that the average risk of progression, over a given period of time, for patients randomized to fulvestrant 250mg was approximately 18% higher than for those randomized to tamoxifen 20 mg. The 95% confidence interval indicates that the risk for patients randomized to fulvestrant could be between 2% lower and 44% higher than for those randomized to tamoxifen. The upper limit of the 95% confidence interval (1.44) does not satisfy the predefined criterion 1.25 for concluding noninferiority of fulvestrant compared with tamoxifen.

Table 55: Response rates in study #25

Efficacy Parameter	Fulvestrant 250 mg N = 313	Tamoxifen 20 mg (N = 274)	Odds Ratio	95% C.I.	P value
Complete Response	30 (9.6%)	19 (6.9%)			
Partial Response	69 (22 %)	74 (27%)			
Any Response	99 (31.6%)	93 (33.9%)	.87	.61, 1.24	.45
Clinical Benefit	54.3%	62 %	.68	.48, .95	.026

The proportion of patients who were classed as responders (CR plus PR) was similar in the 2 treatment groups, although the proportion of patients considered to have clinical benefit was lower in the fulvestrant group compared with the tamoxifen group. Randomization to fulvestrant 250 mg was not statistically significantly different at the 5% level from randomization to tamoxifen 20 mg in terms of objective response rate (p=0.4508). The odds ratio indicates that the odds of having a response for patients randomized to fulvestrant 250 mg was 13% lower than for those randomized to tamoxifen 20 mg, given that both groups had the same baseline covariates. The 95% confidence interval indicates that the odds of a response for patients randomized to fulvestrant could be between 39% lower and 24% higher than for those randomized to tamoxifen.

(3) Conclusions

Trial 0025 demonstrated evidence of the antitumor activity of fulvestrant in postmenopausal women with advanced breast cancer, as shown by a 32% objective response rate. The trial did not, however, achieve its primary objectives, demonstrating neither superiority nor noninferiority of fulvestrant relative to tamoxifen for the primary end point of time to

progression. Survival data are not yet mature and have not yet been analyzed. The study population in registration trials 0020 and 0021 showed resistance to prior endocrine therapy, whereas patients in Trial 0025 were endocrine therapy naive or showed no evidence of resistance to prior endocrine therapy. Because of the difference in patient populations, FDA agrees with the applicant that the review of data from Trials 0020 and 0021 can be viewed independently of the efficacy results of Trial 0025.

Reviewer Comment: Although the results of this trial have not been reviewed, the reported results suggest that fulvestrant may not be equally efficacious as tamoxifen in the first line setting.

xi. Overall Efficacy Conclusions

(1) Trial Population

The trial population for Trials 0020 and 0021 consisted of postmenopausal women with advanced breast cancer who had either recurrence or progression of disease and required hormonal treatment because of relapse after adjuvant endocrine therapy or progression after first-line treatment for advanced disease. Evidence of hormone sensitivity was an additional trial requirement and was defined as (a) at least 12 months of adjuvant hormonal therapy before relapse, (b) tumor remission or stabilization after at least 3 months of hormonal therapy before progression, or (c) a tumor status of estrogen-receptor positive (ER+) or progesterone-receptor positive (PgR+). Patients with a tumor status of ER negative or ER unknown were permitted to enter the trials as long as they fulfilled either criteria.

The baseline disease characteristics appeared similar between treatment groups, despite lack of stratification for prognostic factors. Over 97% of patients had metastatic disease at entry, and over 75% of patients in each treatment group had ER+ tumors. The population studied appears fairly well to reflect the proposed indication except that it is not clear how many patients had artificially-induced menopause, and over 95% of patients were previously treated with tamoxifen. Previous second line approvals in advanced breast cancer have specified 'disease progression after tamoxifen.' Treatment arms were well balanced for prognostic characteristics, except that in trial 0020 slightly more patients in the fulvestrant arm had an unknown receptor status, and fewer patients were known estrogen receptor positive. This might have biased the trial results against fulvestrant.

(2) Efficacy endpoints

(a) Time to Progression

The original primary objective was demonstration of superiority of time to progression. Response rate was a secondary endpoint. After data analysis revealed that the original objective was not met, TTP was considered as a secondary endpoint for review. Although the FDA statistical reviewer used a slightly different confidence level and the PP population was slightly different from the Applicant's, the FDA concured with the Applicant's finding that, using a non-inferiority margin of 25%, fulvestrant 250-mg was non-inferior to anastrozole with respect to

time to progression. Results of the FDA statistical reviewer's analysis of time to progression are summarized in the table below:

Table 56: Time to Progression

End point	Trial 0020 Europe - open label		Trial 0021 US -double blind	
	Fulvestrant 250 mg (n=206)	Anastrozole I mg (n= 194)	Fulvestrant 250 mg (n=222)	Anastrozole Img (n=229)
Median Time to Progression (ITT)				
Median TTP (days)	166	156	165	103
Hazard ratio[a]	0.98 (p=0.84)		0.92 (p=0.43)	
2-sided 95.4% CI	(0.79 to 1.21)		(0.74 to 1. 14)	
Median Time to Progression (Per Protocol)				
Median TTP (days)	162	124	141	90
Hazard ratio[a]	0.97 (p=0.77)		0.95 (p=0.67)	
2-sided 95.4% CI	(0.77 to 0 1. 21)		(0.74 to 1.21)	

[a] Cox proportional-hazards model with baseline covariates: age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease.

Although median time to progression was slightly longer for patients treated with fulvestrant in trial # 21, examination of the Kaplan-Meier curves did not suggest any lasting difference in time to progression between treatment arms. Analysis of covariates suggested that patients with measurable disease only, or worse performance status, appeared to have a somewhat higher risk for progression. Patients whose hormone receptor status was unknown appeared to have a lower risk of progression.

(b) Response rate

In the pivotal efficacy trials, treatment with fulvestrant produced objective response rates comparable to or greater than those achieved with anastrozole, however, superiority of fulvestrant over anastrozole was not shown. Whether analyses were performed on the ITT or PP population, adjusted or unadjusted analysis, the estimated hazard ratio was not significantly different from 1 in either trial. When the applicant requested approval based on non-inferiority because of failure to demonstrate superiority, the Division's response was to focus on non-inferiority of response rate, since the control effect on time to progression is unknown. Regulatory precedent has allowed registration on the basis of non inferiority in response rates in previous NDA's for the hormonal treatment of breast cancer. Results of the FDA statistical reviewer's analysis of response data is summarized in the table below:

Table 57: Response data from phase 3 trials

End point	Trial 0020 Europe - open label		Trial 0021 US -double blind	
	Fulvestrant 250 mg	Anastrozole I mg	Fulvestrant 250 mg	Anastrozole Img
ITT Population				
	(n=222)	(n=229)	(n=206)	(n= 194)
Number (%) CR	10 (4.5)	4 (1.7)	10 (14.9)	7 (3.6)
PR	36 (16.2)	32 (14.0)	26 (12.6)	27 (13.9)
CR + PR	46 (20.7)	36 (15.7)	36 (17.5)	34 (17.5)
FDA CR + PR	45 (20.3%)	34 (14.9%)	35 (17.0%)	33 (17.0%)
Analysis	Adjusted[a]	Unadjusted[b]	Adjusted	Unadjusted
OR: (FAS/ANA)	1.44	1.46	1.03	1.0
2-sided 95.4%	(0.86, 2.43)	(0.89, 2.41)	(.59, 1.77)	(.59, 1.70)
p-value	p = .16	p = .13	p = .93	p = .996
Estimated % difference in Response Rates [c]				
	5.42		-0.02	
95.4% CI	(-1.44,14.77)		(-6.28, 8.87)	
Per Protocol Population				
N =	187	199	171	156
PP responders	41 (21.9%)	29 (15.%)	29 (17%)	26 (16.7%)
OR: (FAS/ANA)[c]	1.60 (p =.09)		1.03 (p =.92)	
2-sided 95.4%	(0.92, 2.80)		(.56, 1.91)	
Estimated % difference in Response Rates [c]				
	7.35		0.29	
95.4% CI	(-0.39, 17.98)		(-6.51, 10.36)	

[a] logistic-regression model with baseline covariates.

[b] logistic-regression model without baseline covariates.

[c] unadjusted analysis. A difference in response rates greater than 0 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg. See appendix for discussion of statistical sensitivity analysis.

Reviewer comment: The FDA statistical reviewer concurred with the applicant's finding that, using the non-inferiority margin of 10% for response rate, fulvestrant 250-mg was non-inferior to anastrozole 1-mg with respect to objective response rate in both the ITT and PP populations for each trial.

(c) Other efficacy endpoints

There was no apparent difference in the Kaplan Meier survival curves in trial 20. There was a slight trend in Kaplan-Meier curves in favor of anastrozole in survival analysis in Trial 0021. However, since the data were not mature and the trial was not powered for survival analysis, no conclusion regarding survival should be drawn. No statistical significant differences between arms were found in other efficacy and QOL endpoints.

(d) Overall Efficacy Conclusions

Each of the two pivotal trials for the NDA supported noninferiority of fulvestrant versus the comparator, anastrozole, in both response rate and time to progression, in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant exhibited a slightly higher response rate compared with anastrozole in trial #20 and a slightly longer time to progression in trial #21. No statistical significant differences between arms were found in other efficacy and QOL endpoints.

d. Integrated Review of Safety

i. Brief Statement of Conclusions

Overall, fulvestrant 250 mg was well tolerated in postmenopausal women with locally advanced or metastatic breast cancer. The number and types of adverse events were similar between fulvestrant- and anastrozole-treated patients in the 2 pivotal controlled efficacy trials. Adverse reactions commonly reported in the clinical trial program are summarized as follows:

Commonly reported adverse reactions

- whole body: asthenia, usually mild or moderate in nature
- injection- site reactions, including mild transient pain and inflammation in 27% of patients (5% of treatment courses) when given as 2 x 2.5- ml injections;
- injection- site reactions including mild transient pain and inflammation in 8% of patients (1% of injections) when given as a single 5- ml injection;
- hot flashes (predominately mild and usually occur within the first 2 months of therapy);
- headache, mostly mild;
- gastrointestinal disturbance, including nausea, vomiting, diarrhea, and anorexia that are usually mild in nature;
- urinary tract infections, usually mild in nature.

ii. Description of Patient Exposure

A total of 1178 patients were exposed to various doses and schedules of fulvestrant. The largest group included the 588 patients who were included in the pivotal efficacy trials, and these patients also received the longest exposures to fulvestrant. The safety follow-up period was similar for all trials (8 weeks following the last injection). Patients receiving either the LA formulation, SA formulation, oral formulation or iv formulation were followed for 8 weeks after the last dose. Patient exposure to anastrozole and fulvestrant in the clinical trials submitted to NDA 21-344 are summarized in the table below:

Table 58: Fulvestrant and Anastrozole patient exposure in NDA 21-344

Trial category	Number of trials	Number of subjects exposed		
		Fulvestrant[a] (all doses and formulations)	Anastrozole 1 mg	Total
Efficacy Trials				
Pivotal controlled efficacy trials (Trials 0021, 0020)	2	588	423	1011
Phase II efficacy trial (0004)	1	23	0	23
Clinical pharmacology trials				
In postmenopausal women with breast cancer (Trials 0002, 0018, 0039)	3	196	0	196
All doses and formulations of fulvestrant (Trials 0001, 0003, 0007, 0008, 0012, 0017, 0023, 0024, 0026, 0029, 0031, 0034, 0036, 0038, O-15-11)	15	184	0	184
Other trials (Trial 0019)	1	187	0	187
Total	**22**	**1178**	**423**	**1601**

[a] Includes patients given fulvestrant 125 mg (all trials, including Trials 0021 and 0020).

The exposure of patients to single doses of fulvestrant is summarized below:

Table 59: Single dose patient exposure to fulvestrant

Formulation	Predominant Population	Dose	Number of patients exposed
Oral	Healthy Males	25 mg	8
		50 mg	8
		100 mg	10
		200 mg	6
Intravenous	Healthy volunteers	0.5 mg	4
		2 mg	4
		5 mg	4
		10 mg[c]	44
SA – intramuscualr	Healthy Volunteers	2 mg	4
		6 mg	4
		18 mg[c]	11
		36 mg	18
LA – intramuscular	Postmenopausal women with breast cancer	25 mg	5
		50 mg	45
		125 mg	53
		250 mg	97

Patients in the pivotal trials had the greatest cumulative exposure. While some of the 423 subjects in the 2 pivotal trials (LA formulation) were exposed to fulvestrant 250 mg for long periods (up to approximately 3 years), the median exposure was about 6 months. More than half of the 19 patients in the Phase II efficacy trial were exposed to the LA formulation of fulvestrant 250 mg for at least 7 months. The 165 subjects given fulvestrant 125 mg in the 2 pivotal trials

were exposed for a median of less than 4 months, although at least1 subject was treated for nearly 2 years. The exposure to fulvestrant outside of the 2 pivotal trials was greatest in postmenopausal women with breast cancer in Trial 0004, in which the median duration of treatment was 196 days. Peak exposure (C_{max} achieved) was greatest in the pharmacokinetic trial of the iv formulation. Overall, patients in the pivotal trials had the greatest cumulative exposure (Table 54).

Table 60: Patient exposure to fulvestrant (LA formulation) in efficacy trials

Dose	Number of subjects given dose	Duration of treatment[b] (days)		Total exposure (number of courses of injections given)	
Pivotal controlled efficacy trials (# 20, 21)					
		Median	Range	Median	Range
125 mg	165	109	[redacted]	3	[redacted]
250 mg	423	169	[redacted]	6	[redacted]
Phase II efficacy trial (Trial 0004)					
50 mg	4	28	[redacted]	1 (single dose)	[redacted]
100 and/or 250 mg[c]	19	196	[redacted]	7	[redacted]

The four month safety update included additional exposure to fulvestrant 250 mg since the data cutoff dates for the ISS. This included data from 79 patients who continued to be treated and followed for survival status and safety in the phase 3 trials. For the 38 postmenopausal women with advanced breast cancer who participated in Trial 0039 (33 of whom continued treatment beyond the first dose), the median exposure to the LA im formulation of fulvestrant 250 mg was slightly over 3.5 months, with maximum exposure of approximately 1 year and 4 months.

iii. Methods and Specific Findings of Safety Review

For Trials 0021 and 0020, the follow-up period was defined as 8 weeks after the last injection or 30 days after ingestion of the last tablet of trial treatment, as appropriate in Trial 0020 and whichever was longer in Trial 0021. Adverse events experienced by patients in the phase 3 efficacy trials are summarized in the table below:

Table 61: Overview of adverse events in the phase 3 efficacy trials

	Trial 0020		Trial 0021	
	Fulvestrant 250 mg N=219	Anastrozole 1 mg N=230	Fulvestrant 250 mg N=204	Anastrozole 1 mg N=193
Adverse events (AE's)	n (%)	n (%)	n (%)	n (%)
Patients with any AE	183 (83.6)	196 (85.2)	198 (97.1)	181 (93.8)
Patients with drug-related AE	87 (39.7)	77 (33.5)	108 (52.9)	94 (48.7)
Deaths	n (%)	n (%)	n (%)	n (%)
Due to adverse event	4 (1.8)	3 (1.3)	4 (2.0)	3 (1.6)
Due to drug-related AE	0	1 (0.4)	0	0
Not due to an adverse event	77 (35.2)	81 [b] (35.2)	68 (33.3)	62 (32.1)
Withdrawals	n (%)	n (%)	n (%)	n (%)
Due to adverse events	7 (3.2)	3 (1.3)	5 (2.5)	5 (2.6)
Due to drug-related AE	3 (1.4)	3 (1.3)	1 (0.5)	2 (1.0)
Due to disease progression	161 (73.5)	168 (73.0)	155 (76.0)	150 (77.7)
Due to other reasons	9 (4.1)	11 (4.8)	10 (4.9)	5 (2.6)
Serious Adverse Events (SAE's)	n (%)	n (%)	n (%)	n (%)
Patients with SAE's	37 (16.9)	30 (13.0)	38 (18.6)	25 (13.0)
SAE led to withdrawal	5 (2.3)	0	2 (1.0)	3 (1.6)
Drug-related SAE	4 (1.8)	3 (1.3)	3 (1.5)	2 (1.0)
DRSAE led to withdrawal	1 (0.5)	0	0	0

In the combined population of the 2 pivotal trials, approximately 90% of patients in both treatment groups had an adverse event, and about half of all patients had adverse events that were considered drug related. Few deaths due to an adverse event occurred in either treatment group. Approximately 15% of all patients experienced serious adverse events, but few in either treatment group were considered drug related. About 75% of patients were withdrawn because of disease progression (75%). Less than 3% of patients were withdrawn because of an adverse event. Differences between treatment groups in any category were minor. Serious adverse events (SAE's) were experienced in a numerically higher proportion of patients in the fulvestrant group as compared to the anastrozole group. A slight excess of SAE's in the fulvestrant treatment group were seen in the digestive, nervous and metabolic systems, including slightly higher reported numbers of patients with nausea, vomiting, anorexia, diarrhea and gastroenteritis dehydration and edema. There was no excess of SAE's in either treatment arm that were considered by the investigators to be drug related, or drug-related events that led to withdrawal in any body system or adverse event category.

Reviewer comment: Although there was an excess of serious adverse events in the fulvestrant group in both trials, most of these events were ascribed to disease progression, and there was no excess of events in either arm which were considered to be drug-related. Disease progression is measured more directly in the efficacy results, and no conclusion is possible regarding the relative efficacy of the two drugs from this observation.

Adverse events experienced by patients in the phase 3 efficacy trials are summarized in the table below:

Table 62: Adverse Events that occurred with a frequency of > 5% in the phase 3 trials

Body system and adverse event[a]	Fulvestrant 250 mg N=423		Anastrozole 1 mg N=423	
	All intensities n (%)	Severe n (%)	All intensities n (%)	Severe n (%)
Body as a whole	289 (68.3)	41 (9.7)	286 (67.6)	53 (12.5)
Asthenia	96 (22.7)	4 (0.9)	114 (27.0)	9 (2.1)
Pain	80 (18.9)	9 (2.1)	86 (20.3)	10 (2.4)
Headache	65 (15.4)	8 (1.9)	71 (16.8)	5 (1.2)
Back pain	61 (14.4)	5 (1.2)	56 (13.2)	4 (0.9)
Abdominal pain	50 (11.8)	3 (0.7)	49 (11.6)	6 (1.4)
Injection-site pain	46 (10.9)	1 (0.2)	28 (6.6)	0
Pelvic Pain	42 (9.9)	5 (1.2)	38 (9.0)	4 (0.9)
Chest pain	30 (7.1)	0	21 (5.0)	4 (0.9)
Flu syndrome	30 (7.1)	2 (0.5)	27 (6.4)	0
Fever	27 (6.4)	3 (0.7)	27 (6.4)	1 (0.2)
Accidental injury	19 (4.5)	0	24 (5.7)	4 (0.9)
Metabolic and nutr disorders	77 (18.2)	11 (2.6)	75 (17.7)	3 (0.7)
Peripheral edema	38 (9.0)	3 (0.7)	43 (10.2)	0
Musculoskeletal system	108 (25.5)	12 (2.8)	118 (27.9)	12 (2.8)
Bone pain	67 (15.8)	7 (1.7)	58 (13.7)	5 (1.2)
Arthritis	12 (2.8)	2 (0.5)	26 (6.1)	3 (0.7)
Nervous system	145 (34.3)	10 (2.4)	143 (33.8)	9 (2.1)
Dizziness	29 (6.9)	3 (0.7)	28 (6.6)	0
Insomnia	29 (6.9)	0	36 (8.5)	0
Paresthesia	27 (6.4)	1 (0.2)	32 (7.6)	1 (0.2)
Depression	24 (5.7)	0	29 (6.9)	0
Anxiety	21 (5.0)	0	16 (3.8)	1 (0.2)
Respiratory system	163 (38.5)	15 (3.5)	142 (33.6)	12 (2.8)
Pharyngitis	68 (16.1)	0	49 (11.6)	0
Dyspnea	63 (14.9)	5 (1.2)	52 (12.3)	8 (1.9)
Cough increased	44 (10.4)	2 (0.5)	44 (10.4)	1 (0.2)
Skin and appendages	94 (22.2)	4 (0.9)	99 (23.4)	2 (0.5)
Rash	31 (7.3)	2 (0.5)	34 (8.0)	0
Sweating	21 (5.0)	1 (0.2)	22 (5.2)	0
Urogenital system	77 (18.2)	1 (0.2)	63 (14.9)	2 (0.5)
Urinary tract infection	26 (6.1)	0	15 (3.5)	0
Cardiovascular system	128 (30.3)	23 (5.4)	118 (27.9)	13 (3.1)
Vasodilatation	75 (17.7)	4 (0.9)	73 (17.3)	0
Digestive system	218 (51.5)	18 (4.3)	203 (48.0)	15 (3.5)
Nausea	110 (26.0)	9 (2.1)	107 (25.3)	5 (1.2)
Vomiting	55 (13.0)	6 (1.4)	50 (11.8)	4 (0.9)
Constipation	53 (12.5)	1 (0.2)	45 (10.6)	2 (0.5)
Diarrhea	52 (12.3)	1 (0.2)	54 (12.8)	1 (0.2)
Anorexia	38 (9.0)	0	46 (10.9)	1 (0.2)
Hemic and lymphatic systems	58 (13.7)	10 (2.4)	57 (13.5)	12 (2.8)
Anemia	19 (4.5)	2 (0.5)	21 (5.0)	3 (0.7)

The most common symptoms in both treatment groups were asthenia, nausea, pain, vasodilatation, and headache. and differences between treatments in the incidence of any adverse event were minor. The incidences of adverse events judged to be drug related were about half that of all adverse events in both treatment groups, with vasodilatation, nausea, injection-site pain and asthenia being the most frequent in both groups.

Table 63: Injection Site Reactions

Trial #	Administration	Patients			Courses		
		Total #	Events*	%	Total	Events*	%
0020	5 ml x 1 dose	219	16	7.3	1898	20	1.1
0021	2.5 ml x 2 doses	204	55	27	1879	86	4.6

*Events = Local reactions at the injection site, consisting of pain, injection-site reaction, inflammation, and hemorrhage.

Injection- site events, consisting of pain, local reactions and/ or inflammation, were dependent on the method of injection and occurred in about 1.1% of courses in patients receiving fulvestrant as a single 5- ml injection and 4.6% of courses in patients receiving fulvestrant as a 2x2.5- ml injection. Injection- site reactions were transient (lasting only days when a single injection was administered but somewhat longer when a 2x2.5- ml injection was administered) and usually mild. The single monthly injection of 5 cc appeared to be better tolerated than the 2 2.5 cc doses. Four patients withdrew from treatment because of an injection-site event, which included a single report of severe injection site pain in study #21.

At the interim analysis, the DMC determined that an imbalance existed in adverse events in thromboembolic events and urinary tract infections. As joint disorders were a known adverse event associated with anastrozole, the incidence of joint symptomatology (arthritis, arthralgias, arthrosis) in the pivotal trials was also identified as a predefined category. Additionally, events potentially due to the pharmacologic actions of antiestrogens (hot flashes, vaginal symptoms, gastrointestinal disturbance) would be evaluated.

Table 64: Analysis of Selected Adverse Events

Category of adverse event	Fulvestrant 250 mg N=423 n (%)	Anastrozole 1 mg N=423 n (%)	Treatment odds ratio (lower, upper 95% CL)	p-value
Gastrointestinal disturbance	196 (46.3)	185 (43.7)	1.09 (0.830, 1.440)	0.5267
Hot flashes	89 (21.0)	87 (20.6)	1.02 (0.730, 1.423)	0.9120
Urinary tract infection	31 (7.3)	18 (4.3)	1.75 (0.972, 3.248)	0.0624
Joint disorders	**23 (5.4)**	**45 (10.6)**	0.47 (0.272, 0.783)	0.0036
Thromboembolic disease	15 (3.5)	17 (4.0)	0.86 (0.420, 1.757)	0.6830
Vaginitis	11 (2.6)	8 (1.9)	1.36 (0.545, 3.556)	0.5085
Weight gain	4 (0.9)	7 (1.7)	0.56 (0.146, 1.878)	0.3524

The only significant difference found in the final between the 2 treatment groups was in the incidence of joint disorders; the incidence with anastrozole was twice that with fulvestrant. Other adverse experiences of concern such as gastrointestinal disturbances, thromboembolic disease, hot flashes, vaginitis, and weight gain were not different between the 2 treatments in the

final analysis. There was a trend toward more urinary tract infections with fulvestrant treatment. In general the adverse events associated with fulvestrant treatment were mild and tolerable. The pattern of adverse events appears to change with duration of exposure. Nausea and vasomotor symptoms (chiefly hot flashes) are seen as a first event at the initiation of therapy, occurring more in the less than 45 years of age category, but rarely occurred with continued treatment.

The more commonly reported adverse events attributed to treatment with fulvestrant are listed in the following table:

Table 65: Common Drug-related events attributed to Fulvestrant treatment

Very Common: (incidence rate >10%)	
Whole Body	Injection-site reactions, including transient pain and inflammation (when administered as two 2.5-ml injections) Hot flashes
Common: (incidence rate from 1-10%)	
Whole Body	Injection-site reactions, including transient pain and inflammation (when administered as one 5-ml injection) Asthenia Headache
Gastrointestinal	Gastrointestinal disturbance, including nausea, vomiting, diarrhea and anorexia
Skin and appendages	Rash
Urogenital	Urinary tract infection (UTI)[d]

Data from the Phase II efficacy trial, the 125- mg arm of the pivotal trials, and from other patient and healthy patient populations in the clinical pharmacology trials support the findings in the larger pivotal controlled trials. The incidences and types of most frequent adverse events in all women subjects were similar to those observed in postmenopausal women with breast cancer in the 2 pivotal trials. In healthy men, the overall frequency of adverse events was low. No deaths for reasons other than breast cancer occurred in the other trials, serious adverse events were similar in type and frequency, and few withdrawals for adverse events occurred. Few events have been reported with compassionate- use and named- patient treatment and no new safety concerns are indicated. The 4 month safety update reflected additional exposure among patients already participating in clinical trials at the data cutoff dates for the ISS. No additional patients were reported in this update. Small increases in incidence rates for previously reported adverse events were seen in both treatment groups, as expected. However, none of these changes were of a magnitude that warranted addition to the label, and the additional exposure to fulvestrant has revealed no new adverse events of clinical significance.

iv. Adequacy of Safety Testing

At the time of the cutoff, a total of 1877 subjects participated in the clinical trial program, including 1178 patients given fulvestrant. 423 women with locally advanced or metastatic breast cancer in the 2 pivotal controlled efficacy trials were treated with fulvestrant 250 mg for a

median of 170 days. In addition, 165 patients were treated with fulvestrant 125 mg in the phase 3 trials. The Phase II efficacy trial (004) and clinical pharmacology trials included 219 postmenopausal women with breast cancer. Sixty six healthy postmenopausal women, 81 healthy men, 37 premenopausal women and 187 patients from other trials were also given fulvestrant. This exposure is adequate to evaluate common adverse events in postmenopausal patients with metastatic breast cancer.

v. Summary of Critical Safety Findings and Limitations of Data

Overall, fulvestrant 250 mg was well tolerated in postmenopausal women with locally advanced or metastatic breast cancer. A wide variety of adverse events occurred, but both the number and types of adverse events were similar between fulvestrant- and anastrozole- treated patients in the 2 pivotal controlled efficacy trials. Many patients died as a result of breast cancer, but few patients died from adverse events unrelated to breast cancer whether treated with fulvestrant or anastrozole. No relationship to treatment duration was evident. There appeared to be an excess of serious adverse events in the fulvestrant group, however no specific reasons for this inbalance were identified. Most serious adverse events occurred within the first 24 weeks of fulvestrant treatment, and there were no obvious trends in their occurrence with regard to patient age. Few serious adverse events were considered drug- related in either treatment group.

e. Dosing, Regimen, and Administration Issues

The selection of the 250 mg dose for efficacy studies was due to the several factors: the dose that produced sustained antiestrogenic effects in monkey studies was 4 mg/kg; the maximal achievable concentration of fulvestrant in the LA im formulation was 250 mg/5 ml; and the observation that im injections volumes larger than 5 ml are not typically recommended. Therefore, doses higher than 250 mg were not studied in the efficacy trials. In preclinical models, suppression of estrogenic effects was associated with a dose of 4 mg/kg and drug plasma concentrations ranging from [redacted] ng/ml, a range similar to that achieved with the recommended im dose of 250 mg monthly. In Trial 0004, single 250-mg doses produced trough drug plasma concentrations in the therapeutic dose range across the 28-day dosing interval in all but one patient on day 28. Data from the first 30 patients treated at the 125-mg dose showed insufficient evidence of clinical activity; therefore, treatment at this dose was discontinued.

Comparability of the two methods of intramuscular administration were supported by clinical study results: In Trial 0039, the pharmacokinetic parameters of a 250-mg im dose of fulvestrant administered as a single 5-ml injection were similar to those achieved when the 250-mg dose was administered as two 2.5-ml injections. In both Trials 0021 and 0020, treatment with LA im fulvestrant 250 mg, regardless of how administered (2 x 2.5-ml injections or 1 x 5-ml injection), provided similar efficacy results despite the use of different administration modes. In summary, the proposed dose is supported by preclinical, pharmacokinetic, pharmacodynamic, and clinical efficacy data. Higher doses were precluded because of solubility factors and the necessity to keep the volume of injection below 5cc. Comparability between two 2.5cc injections

and 1 5cc monthly injection were supported by pharmacokinetic and clinical efficacy data. The 250 mg intramuscular dose was well tolerated, except for local injection site reactions, which were reported by 27% of patients who received the 2 injections and 7.3% of patients who received the single 5ml monthly injection.

f. Use in Special Populations

i. Evaluation of Applicant's Gender Effects Analyses and Adequacy of Investigation

The efficacy of this product was studied only in postmenopausal women, therefore gender effect analysis was not performed.

ii. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Across the 4 four treatment groups, most patients (76.2% to 81.5%) fell within the age range of 45 to 74 years inclusive; however, slightly greater proportions of patients in Trial 0020 (fulvestrant group, 33.3%; anastrozole group, 33.6%) were 65 to 74 years, inclusive, than in Trial 0021 (fulvestrant group, 29.6%; anastrozole group, 24.7%). Objective response rates were slightly greater for patients in the fulvestrant group younger than 45 years (30.0%) and ≥45 to <65 years (23.2%), compared with the overall results for all ages, however only 20 patients (4.7%) entered in the trial were younger than 45 years old (See table 18). Approximately 90% of patients in the randomized efficacy trials were white. In the nonwhite population, the applicant's analysis of response rates was 13.8% in Trial 0021, 12.5% in Trial 0020, and 13.5% overall. In conclusion, the response rates were slightly higher in younger patients under 45 years of age, and slightly lower in nonwhite populations compared with the overall combined trial population, however the numbers were too smal for definitive conclusions to be reached regarding these populations.

iii. Evaluation of Pediatric Program

This drug has been studied in postmenopausal women with breast cancer, and therefore a pediatric program has not been initiated.

iv. Comments on Data Available or Needed in Other Populations

Fulvestrant is metabolized primarily in the liver. There was no observed effect of renal insufficiency or mild hepatic impairment on the pharmacokinetics of fulvestrant. It is possible that in subjects with more severe hepatic impairment, clearance may be reduced. However, because the pharmacokinetics of the LA IM formulation are controlled by slow drug release, only small changes in plasma fulvestrant concentrations would be anticipated. A PK study in patients with severe hepatic impairment would be helpful for labeling purposes, but since the drug has a low toxicity profile, such a study was not required for NDA filing. Fulvestrant has not been studied extensively in non-white populations. Although there is no reason to believe efficacy would be affected by ethnicity, a study of efficacy in nonwhite populations would be useful to confirm efficacy in different ethnic populations,. Because this drug blocks the action of estrogen, it is contraindicated in pregnancy.

g. Conclusions and Recommendations

i. Conclusions

The trial population for Trials 0020 and 0021 consisted of postmenopausal women with advanced breast cancer, either relapsing after adjuvant therapy or progressing after first-line treatment with antiestrogen tamoxifen for advanced disease. Evidence of hormone sensitivity was an additional trial requirement and was defined as (a) at least 12 months of adjuvant hormonal therapy before relapse, (b) tumor remission or stabilization after at least 3 months of hormonal therapy before progression, or (c) a tumor status of estrogen-receptor positive (ER+) or progesterone-receptor positive (PgR+). Patients with a tumor status of ER negative or ER unknown were permitted to enter the trials as long as they fulfilled criteria. The baseline disease characteristics appeared similar between treatment groups, despite lack of stratification for prognostic factors. Over 97% of patients had metastatic disease at entry, and over 75% of patients in each treatment group were documented to have ER+ tumors. Treatment arms were well balanced for prognostic characteristics, except that in trial 0020 slightly more patients in the fulvestrant arm had an unknown receptor status, and fewer patients were known estrogen receptor positive.

The original primary objective was demonstration of superiority of time to progression. Response rate was a secondary endpoint. After data analysis revealed that the original superiority objective was not met, FDA and the applicant determined that a non inferiority comparison of response rate should be the primary analysis, and that analysis of TTP should be a secondary analysis. In the pivotal efficacy trials, treatment with fulvestrant produced objective responses in 17.5% of patients in Trial 0021, in 20.7% in Trial 0020, and in 19.2% when the data were combined across trials (see Table 1). Fulvestrant exhibited a slightly higher response rate compared with anastrozole in trial #20, and a slightly longer time to progression in trial #21. The FDA and applicant agreed that each of the 2 pivotal trials for the NDA supported noninferiority

of fulvestrant compared with anastrozole, in both response rate and time to progression. No statistical significant differences between arms were found in other efficacy and QOL endpoints.

Overall, fulvestrant 250 mg was well tolerated in postmenopausal women with locally advanced or metastatic breast cancer. The most common drug-related events (>10%) were injection site reactions and hot flashes. Common events (1-10%) included asthenia, headache, and gastrointestinal disturbances including nausea, vomiting, and diarrhea. Rash and urinary tract infections were also commonly reported. Both the number and types of adverse events were similar between fulvestrant- and anastrozole- treated patients in the pivotal controlled efficacy trials. An excess of serious adverse events in the fulvestrant group was reported, however no specific reasons for this imbalance were identified. A slight increase in joint disorders seen in the anastrozole arm was reported. An increase in thromboembolic phenomina seen at interim analysis was not found in final safety analysis. Most serious adverse events occurred within the first 24 weeks of fulvestrant treatment, and there were no obvious trends in their occurrence with regard to patient age. Relatively few serious adverse events were considered drug- related in either treatment group.

ii. Dosing

The proposed dose of 250 mg monthly by intramuscular injection is supported by preclinical, pharmacokinetic, pharmacodynamic, and clinical efficacy data. Higher doses were precluded because of solubility factors and the necessity to keep the volume of injection below 5cc. Comparability between two 2.5cc injections and the single 5cc monthly injection were supported by pharmacokinetic and clinical efficacy data. The 250 mg intramuscular dose was well tolerated, except for reports of local injection site reactions, which were increased in the group in which two 2.5 ml injections were administered.

iii. Tradename issues

Consultation from CDER's Division of Medication Errors and Technical Support (DMETS) revealed potential concerns about confusion between Faslodex, Casodex, and Zoladex. The risk of this error to patient safety appeared negligible since the drug is well-tolerated with relatively mild side effects. In addition, Faslodex will generally be administered by nurses experienced in the treatment of oncology patients, thereby minimizing the risk of confusion. The tradename Faslodex is therefore allowed, however the applicant must agree to monitor postmarketing safety for medication errors caused by tradename confusion.

iv. Recommendations

The clinical and non clinical studies support the approval of fulvestrant (FASLODEX), 250 mg monthly by the intramuscular route, for the treatment of postmenopausal women with locally advanced or metastatic breast cancer following progression or relapse on antiestrogen therapy. The applicant's proposed indication is

[redacted] " The term ' [redacted] is vague, and it is not clear how many patients had their postmenopausal status [redacted] We recommend the indication be revised as folllows: . [redacted] . For detailed labeling comments see the labeling review.

We recommend the following postmarketing commitments:

To update survival data on the randomized studies #20 and #21 and to submit an updated study report when the data are mature (>75% patient mortality).

To perform a study of the effect of ketoconazole on fulvestrant pharmacokinetics. This study may be conducted using the intravenous formulation of fulvestrant. to allow for fewer patients (the IV route has less inter-individual variability than the IM route) and to increase safety during performance of the study.

The sponsor will submit all error reports, both potential and actual, that occur with the drug Faslodex for a period of two years following the date of drug approval. Potential errors include any reports of potential circumstances or events that have the capacity to cause error and should be reported in a quarterly summary. Actual errors include any preventable event that reached the patient and caused harm or reached the patient and did not cause harm. Additionally, the sponsor will report actual errors that occurred but did not reach the patient, such as if the wrong drug was prepared but system checks prevented the drug from reaching the patient or being administered to the patient. All actual errors should be submitted as a 15-day report regardless of patient outcome. The sponsor will agree to provide yearly reports of potential and actual errors occurring with the drug, Faslodex, to the Agency for two years following the date of drug approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Peter Bross
3/28/02 10:03:13 AM
MEDICAL OFFICER
Here it is!
Faslodex NDA Final

Grant Williams
3/28/02 10:52:52 AM
MEDICAL OFFICER
I fully agree with the findings and recommendations of this combined medical-statistical review.