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:

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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:

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

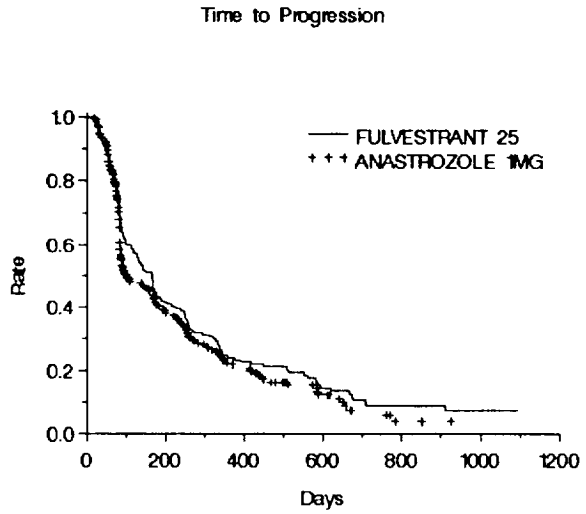
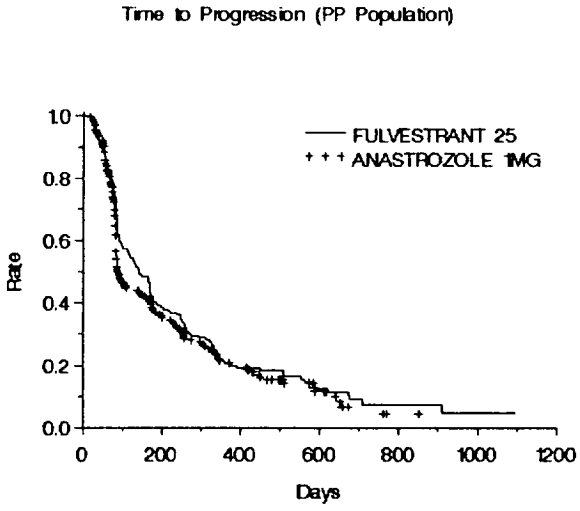


Figure 6: Kaplan-Meier Plot of Time to Progression (PP Population)



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(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:

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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:

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