| 9238IL/ 0018 phase 2 PK, efficacy | |
|---|---|
| A Partially-Blind, Randomized, Multi-center Trial to Compare the Anti-Tumour Effects, Pharmacokinetics and Tolerability of 50 mg, 125 mg and 250 mg Single Doses of FASLODEX™ (Long-Acting ICI 182,780) with Tamoxifen and with Tamoxifen Placebo in Postmenopausal Women Prior to Surgery for Primary Breast Cancer. | |
| Location | UK |
| Start/Stop dates | 6/97-8/99 completed |
| Accrual | 200 postmenopausal women with primary breast cancer |
| design | Partially blind comparing tamoxifen with fulvestrant preop[ |
| Objectives | PK, efficacy. tolerability |
| **Conclusions:** Whereas fulvestrant treatment resulted in a reduction in PgR index, tamoxifen caused an increase in the level of this protein, thus supporting the concept that tamoxifen and fulvestrant have different modes of action. Presumably fulvestrant exerts its effects by down-regulation of ER protein. At a dose of 250 mg, fulvestrant also resulted in a statistically significant greater decrease in ER index than tamoxifen. | |

| 9238IL/ 0039 Phase II PK efficacy | |
|---|---|
| An Open, Randomized, Multi-center, Parallel-group Trial to Compare the Pharmacokinetics and Tolerability of 250 mg Single Doses of FASLODEX™ given as a Single 5 ml or as Two 2.5 ml Injections in Postmenopausal Women with Advanced Breast Cancer (9238IL/0039) | |
| Location | UK multicenter |
| Start/Stop dates | 8/99-1/00 completed |
| Accrual | 38 post menopausal women with advanced breast cancer |
| design | Open randomized parallel group |
| Objectives | PK, tolerability |
| **Conclusions:** There was no observed difference in the pharmacokinetics of a 250 mg dose of LA im fulvestrant following administration as either one 5 ml injection or as two 2.5 ml injections. Fulvestrant, at a dose of 250 mg, was well tolerated when administered by either of the 2 methods, and the combined safety data from both treatment groups also demonstrated a good safety profile. | |

## ii. Phase 3 studies reviewed in detail

| 9238IL/ 0020 Phase III efficacy | |
|---|---|
| An Open, Randomized, Multi-center Trial Comparing the Efficacy and Tolerability of 125 mg and 250 mg of FASLODEX™ (Long-acting ICI 182,780) with 1 mg ARIMIDEX ™ (Anastrozole) in Postmenopausal Women with Advanced Breast Cancer | |
| Location | Europe South Africa, Australia multicenter |
| Start/Stop dates | 6/97-9/99 ongoing for survival |
| Accrual | 451 post menopausal women with advanced breast cancer |
| design | Open randomized parallel group |
| Objectives | PK, tolerability, efficacy, safety |

| 9238IL/ 0021 Phase III efficacy | |
|---|---|
| A Double-blind, Randomized, Multicenter Trial Comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX (Long-acting ICI 182,780) With 1 mg of ARIMIDEX (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer | |
| Location | North America multicenter |
| Start/Stop dates | 5/97-8/00 ongoing for survival |
| Accrual | 473 postmenopausal women with advanced breast cancer progressed following hormonal therapy |
| design | Phase III randomized double blind double dummy |
| Objectives | PK, tolerability Efficacy, safety |

### iii. Ongoing studies in first line indication

Preliminary results discussed with Applicant, trials not reviewed in detail.

| 9238IL/ 0025 Phase III efficacy – first Line | |
|---|---|
| A Double-blind, Randomized, Multicenter Trial Comparing the Efficacy and Tolerability of 250 mg of FASLODEX (Long-acting ICI 182,780) with 20 mg of NOLVADEX (Tamoxifen) in Postmenopausal Women With Advanced Breast Cancer | |
| Location | North America multicenter |
| Start/Stop dates | 5/97-8/00 ongoing for survival |
| Accrual | 473 postmenopausal women with advanced breast cancer progressed following hormonal therapy |
| design | Phase III randomized double blind |
| Objectives | Efficacy, safety |
| **Preliminary Conclusions:** Time to progression in patients treated with Faslodex was inferior to TTP in patients treated with Tamoxifen – 206 days vs 252 days for Tamoxifen. | |

**Reviewer comment:** although the TTP results for the first line indication appear to be inferior for Fulvestrant compared with Tamoxifen, after internal discussion these results were not considered to affect conclusions regarding the results of trials in the second line indication. (see appendix 2 for more complete discussion of trial #25)

## c. Detailed Review of Trials by Indication

The descriptions in this section are based on the Applicant's Trial Protocol submitted to the NDA.

### i. Proposed indication

The Applicant's proposed indications is "

## ii. Overview of the clinical trial program

### (1) Summary

The fulvestrant clinical trial program comprises 22 completed or closed trials and 4 ongoing trials, with 1877 subjects exposed to trial treatment (including fulvestrant, anastrozole, tamoxifen, goserelin acetate, or placebo) as of the last data-cutoff date (30 June 2000). Efficacy end points were evaluated only in trials in which patients received the LA im formulation, specifically, in Trial 0004, the Phase II efficacy trial, and in Trials 0020 and 0021, the Phase III controlled trials designated as pivotal for this submission. Of the 1877 subjects enrolled in the clinical trial program, 1014 (54%) patients from 166 centers in North America, Europe, Australia, and South Africa were randomized to treatment in the pivotal efficacy trials, with data from 851 included in the primary efficacy analyses. All patients were included in the evaluations of safety and tolerability.

### (2) Selection of comparator agent

The applicant cited several reasons for selection of anastrozole as the comparator agent in both phase 3 efficacy trials. Anastrozole produces known objective response rates comparable to or better than that of megestrol acetate, the progestin most commonly used as comparator in previous registration trials in the second line setting. In clinical trials, objective response rates with anastrozole reached 10.4% when given as second-line therapy, compared with 5.5% and 10.4% with megestrol acetate. Additionally, anastrozole is well tolerated and does not induce the typical steroid-like side effects seen with progestins. Wide acceptance and use among physicians as an effective treatment of advanced breast cancer in postmenopausal women with disease progression after tamoxifen therapy was also cited. The FDA agreed that anastrozole was an acceptable comparator for both trials, although we did suggest consideration of the use of megestrol as comparator in one of the trials.

**Reviewer Comment:** Previous second line approvals in advanced breast cancer have been based on randomized non inferiority trials against the progestin agent megesterol acetate 160 mg/d in patients who have progressed after treatment with tamoxifen. Anastrozole was approved after review of 2 phase 3 trials in 764 patients with similar entry criteria as the present NDA. The primary endpoints were response rate and time to progression, as in the current trials under review. These trials initially compared the aromatase inhibitor anastrozole against 2 doses of fulvestrant, a the selective estrogen receptor modulator. The trials are therefore of very similar design compared with the previous registration trials and with each other, except that 0021 was a double blind, double dummy and 0020 was an open label design. The trial plans and efficacy data will therefore be reviewed concurrently, and a few minor differences will be noted. The original design was based on achievement of statistical superiority in time to progression. In

retrospect this may not have been realistic, since no previous registration trial had been able to demonstrate superiority of time to progression in the second line treatment of metastatic breast cancer.

## iii. Phase 3 clinical trials

### (1) Overview

The Phase III clinical trial program comprised 2 controlled trials, Trials 0020 and 0021. Both trials were multicenter, randomized, parallel-group trials with patients receiving IM fulvestrant (125 or 250 mg monthly) or oral anastrozole (1 mg daily). Trial 0020 was conducted in Europe, Australia, and South Africa, and Trial 0021 was conducted in North America. In Trial 0020, treatment was open label, and fulvestrant 250 mg was administered as a single 5-ml im injection. In Trial 0021, treatment was double-blind (double-dummy approach), and fulvestrant 250 mg was administered as two 2.5-ml serial im injections (1 per buttock). Each trial compared the efficacy and safety of fulvestrant with that of anastrozole.

### (2) Trial 9238IL/0020: European Trial

#### (a) Title

**An Open, Randomised, Multicentre Trial Comparing the Efficacy and Tolerability of 125 mg and 250 mg FASLODEX™ (Long-Acting ICI 182,780) With 1 mg of ARIMIDEX™ (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer.**

#### (b) Summary of trial design

Trial 0020 was an open-label, randomized, parallel-group, multicenter trial conducted in 83 centers in Europe, Australia, and South Africa. The design was essentially identical to trial 0021, except that it was an open-label trial and fulvestrant 250 mg administered as a 5-ml injection instead of two 2.5-ml injections as in Trial 0021 in accordance with European guidelines which differ from US guidelines concerning intramuscular-injection volumes. Initially, patients who met the eligibility criteria were allocated to the following randomized treatments on a 1:1:1 basis: either

a) fulvestrant 125 mg (2.5 ml) im monthly or

b) fulvestrant 250 mg (5 ml) im monthly, or

c) anastrozole 1 mg po daily

Patients continued treatment until objective disease progression or other events required withdrawal; at such time, trial treatment was stopped, and standard therapy was initiated; thereafter, patients were followed up until death to determine survival interval. Patients who

withdrew from trial treatment before progression were followed up until objective disease progression and death.

### (3) Trial 9238IL/0021: North American Trial

#### (a) Title

**A Double-blind, Randomized, Multicenter Trial Comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX (Long-acting ICI 182,780) With 1 mg of ARIMIDEX (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer.**

#### (b) Summary of trial design

This was a double-blind, randomized, multicenter, parallel-group trial. This trial compared the efficacy and safety (tolerability) of fulvestrant injections with that of oral anastrozole and assessed the pharmacokinetics of fulvestrant following injection of the LA im formulation. Initially, patients who met the eligibility criteria were allocated to the following randomized treatments on a 1:1:1 basis: either

a) fulvestrant 125 mg (2.5 ml) im monthly plus anastrozole placebo po, daily or

b) fulvestrant 250 mg (2x2.5 ml) im monthly plus anastrozole placebo po od, or

c) anastrozole 1 mg po daily plus placebo 2x2.5 ml im monthly

### (4) Design aspects common to both trials:

#### (a) Treatment plan (initial)

| Group | Trial 20 | Trial 21 | |
|---|---|---|---|
| 1 | Fulvestrant 125 mg (2.5 cc) i.m.monthly | Fulvestrant 125 i.m. monthly | Anastrozole placebo daily |
| 2 | Fulvestrant 250 mg (5 ml) i.m. monthly | Fulvestrant 125 i.m. x 2 monthly | Anastrozole placebo daily |
| 3 | Anastrozole 1 mg p.o. daily | Anastrozole 1 mg p.o. daily | placebo 2.5 ml x 2 i.m. monthly |

#### (b) Major Protocol amendments

There were 2 amendments to the protocol. The first occurred after 30 patients randomized to treatment with fulvestrant 125 mg (across trials) had been treated and monitored for 3 months. The responses were assessed, the protocol was subsequently revised, and the 125-mg treatment group was discontinued from this trial. Initially, a total of 588 patients (196 patients per each of the three treatment groups) were to be recruited over a 24-month period, with a minimum

follow-up period of 6 months. When 490 subjects either showed disease progression or died (end-point events), the 3 treatment groups were to be analyzed and compared for efficacy and tolerability.

Effective 27 April 1998, the primary objective was changed to comparing the effect of LA fulvestrant (250 mg im) with oral anastrozole (1 mg daily) in terms of time to progression in postmenopausal women with advanced breast cancer.. The number of patients required was changed from 588 to 392. Recruitment would continue until 340 events from the remaining 2 groups had occurred. When 340 subjects either showed disease progression or died (endpoint events), the treatment groups were to be analyzed and compared for efficacy and tolerability.

**Reviewer comment:** This three arm design was also used in two other registration trials in this indication: anastrozole and letrozole. This design allowed for the determination of a dose-response and optimization of the dose. The initial analysis was not considered an interim analysis and no statistical adjustment was necessary. The trial essentially restarted when the 125mg group was dropped.

The second amendment, effective 24 September 1999, redefined the statistical methods used to analyze quality-of-life data.

### (c) Inclusion criteria relating to indication:

- histologic or cytologic confirmation of breast cancer
- Objective evidence of recurrence or progression of disease not considered amenable to curative treatment
- postmenopausal woman, defined as *any* of the following:
  - age greater than or equal to 60 years
  - age greater than or equal to 45 years with amenorrhea for longer than 12 months and an intact uterus,
  - follicle-stimulating hormone (FSH) levels within the postmenopausal range (utilizing ranges from the testing laboratory facility),
  - having had a bilateral oophorectomy
- relapse after adjuvant endocrine therapy with an antiestrogen or a progesterone and no more than 1 prior hormonal therapy for breast cancer with second-line hormonal treatment or disease progressed after either an antiestrogen or progesterone as first-line treatment for advanced disease
- Evidence of hormone sensitivity, defined as
  - at least 12 months of adjuvant hormonal treatment before relapse, or
  - tumor remission or stabilization resulting from hormonal therapy for at least 3 months before progression in advanced disease,
  - estrogen-receptor positive (ER+) status or
  - progesterone-receptor positive (PgR+) status
- presence of at least 1 measurable or evaluable lesion.
  - Measurable is defined as
  - ✓ clinically measurable in 2 perpendicular axes

- ✓ at least 1 dimension greater than or equal to 2.5 cm or both dimensions greater than or equal to 1 cm.
- ➢ Evaluable is defined as
- ✓ both dimensions less than 2.5 cm (measured clinically) or 1 dimension less than 1.0 cm
- ✓ measurable in 1 axis only,
- ✓ not measurable but visible by photography,
- ✓ ssessable but not measurable by radiographic imaging (mediastinal lymph nodes or diffuse pulmonary infiltration, or osteolytic bone lesions)

- World Health Organization performance status of 0, 1, or 2

### (d) Exclusion criteria

- presence of life-threatening metastatic visceral disease, extensive hepatic, CNS (past or present) or symptomatic pulmonary lymphangitic spread
- previous treatment for breast cancer with fulvestrant, anastrozole, or any aromatase inhibitor
- treatment with LH-RH analogs within 3 months before randomization
- more than 1 prior endocrine medical treatment for advanced breast cancer
- estrogen replacement therapy within 4 weeks before randomization
- The following are considered to be neither measurable or evaluable:
  - ➢ Lesions in previously irradiated fields
  - ➢ Diffuse lesions such as lymphedema, hilar enlargement, pleural effusion, ascites, metastases in the central nervous system, bone marrow infiltration, osteoblastic bone lesions, and osteolytic bone lesions

**Reviewer comment:** Patients were not stratified. Imbalances in previous treatment, hormone receptor status, or performance status could potentially have influenced results, and these population characteristics will be reviewed. The definition of ER/PR positivity was not provided.

### (e) Screening and clinic visits

Screening: Within 3 weeks before randomization, baseline assessments were to be performed including: Medical history, Concomitant therapy, Demographic data, Concurrent conditions, Physical examination, Electrocardiogram, Hematology testing, Prothrombin time, Biochemistry testing, Chest radiograph, Isotopic bone scan or skeletal survey, Tumor assessment, QOL measurements. Table 15 lists the study plan and events:

**Table 14: timing of events and assessments**

| assessments | Screening[1] | Day 1[2] | Monthly X 3[3a] | Every 3 months X 3[3] |
|---|---|---|---|---|
| Concomitant therapy | X | X | X | X |
| Concurrent conditions | X | | X | X |
| Physical examination | X | | X | X |
| Blood pressure and pulse | | X | X | X |
| Weight | | X | X | X |
| Adverse events | | | X | X |
| Hematology testing[c] | X | X | X | X |
| Biochemistry testing[d] | X | X | X | X |
| PK (trough) samples[e] | | X | X | X |
| Primary efficacy assessments | | | | |
| Tumor assessment | X | | X[4] | X |
| Secondary efficacy assessments | | | | |
| Analgesia use | | X | X | X |
| Global pain score | | X | X | X |
| Performance status | X | X | X | X |
| Quality of Life | | X | X | X |
| Local site tolerance | | | X | X |
| Health economics assessment | | | X | X |

[1](within 3 weeks before randomization) [2](within 3 days after randomization) [3](until progression) [4] Soft tissue masses assessed monthly x 3 months, objective radiological assessments q 3 months until progression)

**Reviewer comment**: Since radiological assessments occur at three month intervals and soft tissue assessments occur monthly, an imbalance of measurable vs. evaluable patients could influence the time to progression. The necessity of fulvestrant patients to come into the clinic for injections might bias the progression endpoint against the fulvestrant arm in the open label trial. Clinic visits and trial plan seem otherwise adequate for safety and efficacy evaluation.

## iv. Efficacy assessments

### (1) Objectives

(a) Primary: time to disease progression
(b) Secondary
  (i) objective response rate
  (ii) time to treatment failure
  (iii) time to death
  (iv) duration of response,
  (v) symptomatic response,
  (vi) quality of life.

### (2) Primary end point : time to disease progression.

- Time to progression was defined as the time from randomization to disease progression.
- The date of progression was defined as follows:

- If for a measurable lesion the date when there was a documented increase in the size (product) of more than 25% compared with the minimum dimensions recorded.
- The date progression was documented by the investigator from an evaluable lesion.
- The date a new lesion was noted or progression was documented from an additional lesion or breast-cancer related condition.
- If the patient died, the date of death from any cause

- Patients whose disease had not progressed at the time of data cutoff were right censored using the date of last assessment.

## (3) Objective tumor response

Tumor response was a secondary endpoint, but became a co primary endpoint following revision of the objectives from demonstration of superiority in TTP to non inferiority in response rate and TTP. Assessment of tumor response was made for both measurable and nonmeasurable disease and involved assigning response categories to previously identified lesions or tumors. For each selected clinically measurable lesion, 2 dimensions (length and width) were recorded.

### (a) UICC response criteria

The categories of objective tumor response assigned at each visit were defined according to standard UICC (Union Internationale Contre le Cancer) criteria:

#### (i) Complete response

- No clinical or radiological evidence of residual lesions on 1 visit, with no evidence of disease recurrence or death within 4 weeks of response assessment.
- For patients with evaluable disease of the bone only, the following were required
  - remineralization of all lytic lesions with radiological evidence of calcification,
  - absence of bone pain (without analgesics),
  - no new pathological fractures within 4 weeks of the assessment,
  - evidence of bone remodeling in previously distorted bone, and
  - normalization of bone as determined from bone scan.

#### (ii) Partial response

A PR was recorded when disease improved (compared with baseline assessment) on 1 visit, and disease progression was not evident, based on the following:

- for measurable disease, a **decrease of at least 50% in the sum of the products** of the 2 largest perpendicular diameters of all the measurable lesions **without**
  - (a) an increase of more than 25% in the size of any lesion or
  - (b) the appearance of any new lesion
- for nonmeasurable (evaluable) disease, objective improvement on the basis of radiological, ultrasonic, or photographic evidence.

- For patients with evaluable disease of the bone only, partial remineralization of lytic lesions without new pathological fractures or new bone lesions.

### (iii) Stable disease

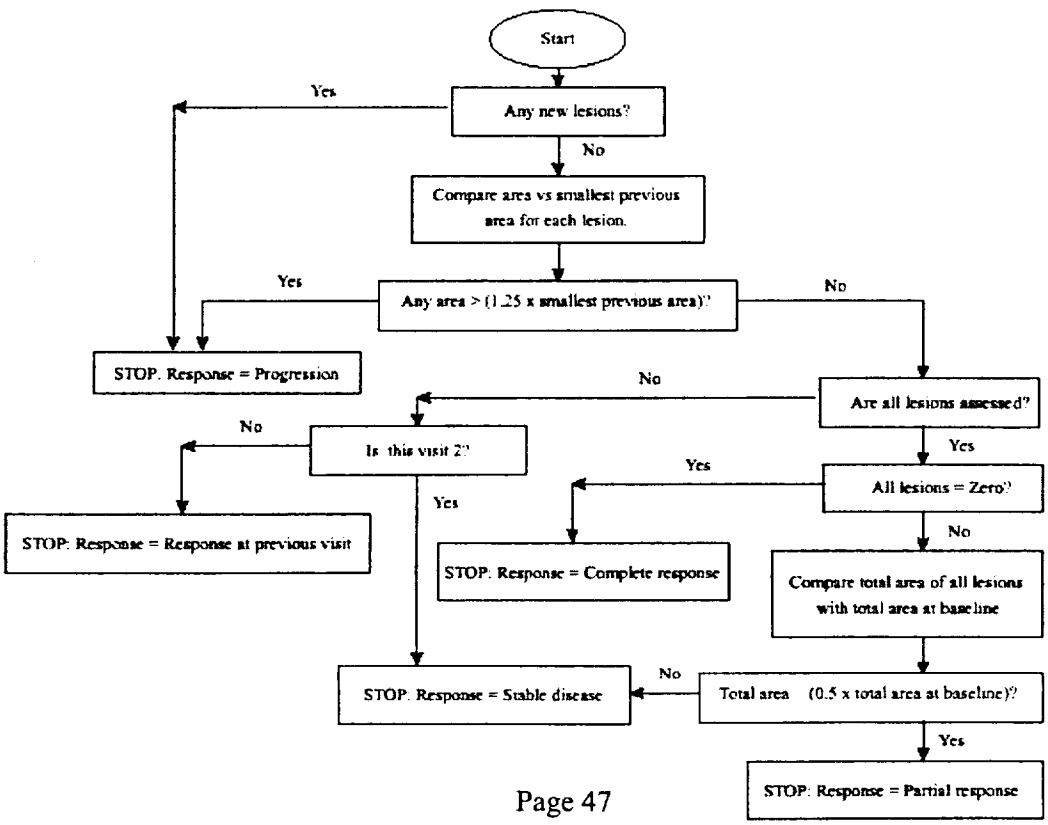
- Lack of objective disease progression and insufficient evidence for designating either complete or partial objective response
- Stable disease was further categorized as either greater or less than 24 weeks (168 days)

### (iv) Disease progression

- any measurable lesion increased in size (product of the 2 largest perpendicular diameters) by more than 25% compared with the minimum dimensions recorded during the trial,
- existing lesions worsened (determined from radiological, ultrasonic, or photographic evidence or clinical assessment) or
- new lesions appeared

## (b) Assignment of response category by computer algorithm in patients with measurable disease only

For patients with measurable disease only, objective response was assigned using a computer algorithm based on UICC response categories. The best response determined by the computer algorithm was used in the primary statistical analysis:



### (c) Assignment of global response by investigator

A best response of CR or PR was assigned when a patient satisfied the respective criteria for response on one visit occasion, with no evidence of disease recurrence or death within 4 weeks of response assessment. The investigator's global overall assessment was also used for a patient with only measurable disease if a bi dimensional lesion became uni dimensional. If progression was assigned as an overall visit objective tumor response, all subsequent visit response assessments were considered progression. For each patient, best objective response over time was determined on the basis of objective response assessment per visit.

**Reviewer comment:** The design of the randomized fulvestrant registration trial was similar to the design of the anastrozole registration trial. UICC response criteria were also used in the previous anastrozole NDA registration trials.[12] These required 2 dimensional measurements, while the newer RECIST criteria allow single measurements to be included as measurable lesions. There are several differences in definition of partial responses and progressive disease, however comparisons between response data assessed by the two techniques have shown comparable response assessments.[13] Therefore, use of the older UICC/WHO efficacy criteria were unlikely to influence the validity of efficacy results. Since final assignment of responses was determined by the investigator in those patients without 'measurable disease only,' investigator bias might potentially have affected the results of the open label European trial (#20).

## (4) Survival

Survival was defined as the number of days from randomization until death.
Survival status of patients was recorded every 3 months after disease progression or after withdrawal for any reason until death. Patients still alive at the time of data cut-off were censored to the last date they were known to be alive.

## (5) Duration of response

Duration of response was calculated only for patients who had best responses of CR or PR. Duration was defined in two ways: (1) as the number of days from randomization until the day

---

[12] Union Internationale Contre la Cancer response criteria were published in 1977 by Hayward et. al. in the *European Journal of Cancer*, 13:89-94, and in the 1979 *WHO Handbook for reporting results of cancer treatment.* Concerns regarding the reproducibility and clinical applicability of the WHO response criteria led to the proposal by James et. al. in *JNCI* 91:523-526 (1999) for the simplification of response evaluation through the use of unidimensional measurements and the sum of the longest diameters instead of the WHO method using two measurements and the sum of the products. See Therasse P, et. al New Guidelines to Evaluate the Response to Treatment in Solid Tumors, *JNCI* 92:205-216, 2000 for a recent discussion.
[13] For a comparison between WHO and RECIST criteria, see Appendix

on which disease progression was first observed and (2) as the number of days from the date that objective response was first documented until the date of disease progression.

#### (6) Time to treatment failure

Time to treatment failure was defined as the number of days from randomization until the earliest occurrence of disease progression, death, or withdrawal from trial treatment for any reason. The date of treatment withdrawal was defined as the date on which a patient or her physician decided to discontinue trial treatment.

#### (7) Symptomatic response

Patients were assessed over time for change in analgesic use, global pain, and WHO performance status or level of daily activity.

#### (8) Quality of Life analyses

##### (a) Treatment outcome index (TOI)

The main QOL variable was the treatment outcome index (TOI). The TOI was created from the FACT-B QOL questionnaire and reflects the sum of scores for the following subscale dimensions: functional well being (questions 27 to 33), physical well being (questions 1 to 7) and breast cancer concerns (questions 35 to 43). In the formal statistical analysis, the difference in TOI over time between fulvestrant 250 mg and anastrozole was compared using a random coefficients model for the intent-to-treat population only. The model was adjusted to account for both within-patient (due to repeated measures) and between-patient information and included terms to account for baseline TOI score and baseline covariates.

##### (b) Time to deterioration in QOL

Time to deterioration in QOL, a secondary variable, was defined as the time between randomization and the earliest occurrence of a 5-point reduction in the TOI from baseline, or death. If a patient had not died or did not have the 5-point reduction in TOI at their last QOL assessment, then this observation was right-censored at the time of the last assessment.

Reviewer comment: QOL analyses are often hampered by incomplete data collection. Labeling claims will have to be subject to scrutiny with attention to data collection.

### v. Statistical plan

#### (1) Population

##### (i) Intention to Treat Primary Analyses

The primary analysis was an intent-to-treat (ITT) analysis and, as such, included data from all randomized patients. Treatment effects were compared on the basis of randomized treatment, regardless of treatment actually received, with data adjusted for baseline effects.

#### (ii) Secondary Analyses

Secondary analyses were conducted for a subset of patients who did not significantly violate or deviate from the protocol, the per-protocol population, by treatment received, and for the ITT population with data unadjusted for baseline effects.

**Reviewer comment:** In a superiority trial the primary analysis is performed in the ITT population because it tends to avoid over-optimistic estimates of efficacy resulting from a per-protocol population, since the non-compliers included in the ITT population will generally diminish the estimated treatment effect. However, in a non-inferiority trial analysis results from the ITT population is generally not conservative; hence, analyses in both populations are equally important for a robust interpretation.

### (2) Sample size

The estimation of sample size was based on the primary end point of time to progression. In previous anastrozole trials the median time to progression was 140 days. To detect a hazard ratio of greater than or equal to 1.43 or less than or equal to 0.70, at a significance level of 5% with 90% power, 490 end point events (disease progression or death before progression) had to occur in each trial. Given that both trials had an estimated accrual time of 24 months, with 6-month follow-up periods, patient requirements were 196 patients per treatment group per trial or at least 588 patients per trial. When the 125-mg treatment group was dropped, 196 patients would still be required in each of the remaining 2 groups for a total of 392 patients per trial. The analysis would be performed when at least 340 events occurred across the remaining 2 groups.

### (3) Interim Analyses

#### (a) Initial Interim Analyses of 125 mg arm

The first review of data occurred after 30 patients randomized to fulvestrant 125 mg (across Trials 0020 and 0021) were treated and monitored for a minimum of 3 months. The objective was to determine whether the 125-mg dose produced adequate evidence of clinical activity. If no response was seen, then treatment at this dose would be discontinued. At the time of the review, 1 (3.3%) patient had withdrawn, 9 (30%) had stable disease, and 20 (66.7%) had disease progression. Since the criteria for continuing treatment at this dose were not met, the 125-mg dose group was dropped from both trials. In conjunction with that decision, the DMC conducted a blinded review of data from the remaining two treatment groups and recommended that the trial continue as provided for in the protocol.

### (b) Planned Interim Analyses

Interim analyses were conducted in both trials after 170 progression events were recorded across the remaining 2 treatment groups (per trial) to confirm the activity of fulvestrant 250 mg compared with that of anastrozole. Both time to progression and objective response rate were evaluated. Statistical analysis was applied to time to progression, with the nominal O'Brien Fleming significance level set at 0.4% for a two sided test (or equivalently, at 0.2% for a one-sided test). Descriptive statistics were used to summarize objective response data. The DMC reviewed the results of the two interim analyses and again recommended that the trials continue.

### (c) Final Analysis

#### (i) TTP Superiority analysis (pre specified)

For both trials, trial design and analysis were geared toward assessing whether fulvestrant was superior to anastrozole. Final analyses were conducted after 340 progression events across the remaining 2 treatment groups (per trial) were recorded. The nominal level of significance was adjusted from 5% to 4.86% because of the interim data summary and analysis. The pre specified response rate analysis was by adjusted logistic-regression 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. The prespecified time to progression analysis was by 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.

#### (ii) Applicant's Non inferiority analysis of Response rate and TTP (retrospective)

When the superiority objectives were not met, the trials were retrospectively assessed for non-inferiority, compared with anastrozole, for the efficacy end points of time to progression, objective response, and time to treatment failure. For the analyses of time to progression and objective response rate, the applicant used a one-sided confidence interval of 97.57% (because of the interim analysis).

#### (iii) FDA non inferiority Analysis

The Division agreed with the applicant that, based on regulatory precedent in the second line hormonal treatment of advanced breast cancer, demonstration of non inferiority could provide the basis for marketing approval. The nominal significance levels pre-specified in the protocol were calculated based on an unadjusted logrank test with a pre-specified correlation between the two statistics (one for the interim and the other for the final analysis). The FDA statistical reviewer did not agree with the protocol-specified nominal significance level used for their final analysis (0.0486 or 95.14% C.I.). Per protocol, in analysis of best objective response rate, a logistic regression model was the primary analysis; in the analysis of time to progression, a Cox

proportional-hazards model with baseline covariates was the primary analysis. Both analyses did not meet the criteria used for calculation of nominal significance levels as specified in the protocol. Therefore, the FDA statistical reviewer instead used the Bonferroni method resulting in a nominal significance level of 0.046 for the final analysis (95.4% C.I.).

**Reviewer Comment:** The existence of a response rate is generally considered evidence in oncology that a drug has *de facto* antitumor activity. In the case of breast cancer, however, tumor response after withdrawal of endocrine therapy for advanced breast cancer with estrogens and androgens is well described. One series reported 5/65 partial responses (8%) after cessation of tamoxifen as first line therapy for advanced disease[14]. It may be difficult to determine if a significant portion of the response rates may be attributable to withdrawal of endocrine therapy. Previous regulatory experience with hormonal treatment for advanced breast cancer, however, have verified that drugs with activity in the second line setting after progression on tamoxifen usually show activity in the initial first line therapy of hormone-sensitive breast cancer. The Division agreed with the applicant that regulatory precedent was sufficient in this indication to justify a retrospective non inferiority analysis for registration purposes. Although non-inferiority analyses were not pre specified, margins of 10% for of response rate and 25% for time to progression were used in previous registration trials and were acceptable to the Division.

#### (d) QOL Analysis

Three statistical analyses were pre specified for quality of life data:

- A general linear mixed model for longitudinal data will be fitted to the TOI, and will contain terms to account for treatment group, baseline TOI score and baseline covariates.
- The analysis of the VAS data will also be undertaking using a general linear mixed model using the same approach as for TOI.
- An analysis of time to deterioration will be carried out in the same way as the analysis of time to progression. A deterioration is defined as a reduction in TOI, from baseline, of 5 points or more.

In addition, dropout pattern in each treatment group will be examined to determine the impact on the results of each analysis. If there are missing items on the FACT-B TOI, subscale scores will be prorated. However, if 50% or more of the questions are not answered then the subscale will be considered as missing.

## vi. Study conduct

### (1) Withdrawals

Table 19 lists the most common reasons for withdrawal from the trials:

[14] Howell A, Dodwell DJ, Anderson H, Redford J. Response after withdrawal of tamoxifen and progestogens in advanced breast cancer. Ann Oncol 1992 Sep;3(8):611-7.

**Table 15: Reasons for withdrawal**

| Reason for withdrawal | Trial 20 n (%) | | Trial 21 n (%) | |
|---|---|---|---|---|
| | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=206 | Anastrozole 1 mg N=194 |
| **Objective progression** | **161 (73.5)** | **168 (73.0)** | **155 (76.0)** | **150 (77.7)** |
| Patient lost to followup | 1 (0.5) | 0 | 0 | 0 |
| **Adverse event** | **7 (3.2)** | **3 (1.3)** | 5 (2.5) | 5 (2.6) |
| Protocol noncompliance | 2 (0.9) | 4 (1.7) | 4 (2.0) | 1 (0.5) |
| Informed consent withdrawn | 2 (0.9) | 2 (0.9) | 2 (1.0) | 1 (0.5) |
| Other (including death) | 4 (1.8) | 5 (2.2) | 4 (2.0) | 3 (1.6) |
| Total | 177 (80.8) | 182 (79.1) | 170 (83.3) | 160 (82.9) |

**Reviewer comment:** Reasons for withdrawal were similar between the 2 treatment arms in both trials, except that slightly more patients withdrew for adverse events in the fulvestrant group in trial #21 (see safety review). The main reason for withdrawal in both of the groups was disease progression. Compliance was good and only one patients was lost to follow up. The study appears mature, with about 75% of patients in both studies having already progressed and off study.

## (2) Protocol violations and deviations

Table 16 lists protocol violations which resulted in exclusion from the per protocol efficacy analysis:

**Table 16: Major Protocol violations**

| Trial # | #20 | | #21 | | Combined | |
|---|---|---|---|---|---|---|
| **Violation** | F | A | F | A | F | A |
| N= | N=222 | N=229 | N=206 | N=194 | N=428 | N=423 |
| No Confirmation of Breast Cancer | 0 | 1 | 0 | 0 | 0 | 1 |
| No Evidence of recurrence or progression | 1 | 0 | 0 | 0 | 1 | 0 |
| No evidence of hormonal sensitivity | 0 | 0 | 1 | 0 | 1 | |
| Treatment with a LH-RH analogs within 3 months of randomization | 0 | 0 | 1 | 0 | 1 | 0 |
| Not postmenopausal | 0 | 1 | 1 | 1 | 1 | 2 |
| Second-line hormonal treatment not required | 1 | | 1 | 4 | 2 | 4 |
| No measurable or nonmeasurable evaluable lesions | 3 | 5 | 1 | 3 | 4 | 8 |
| Presence of life-threatening disease | 1 | 0 | 0 | 2 | 1 | 2 |
| > 1 prior endocrine treatment | 0 | 0 | 1 | 3 | 1 | 3 |
| Active systemic malignancy | 0 | 1 | 1 | 1 | 1 | 2 |
| Lab values met exclusion criteria | 4 | 3 | 2 | 0 | 6 | 3 |

Table 17 lists protocol deviations which resulted in exclusion from the per protocol efficacy analysis:

**Table 17: Major Protocol Deviations**

| Trial # | #20 | | #21 | | Combined | |
|---|---|---|---|---|---|---|
| **Deviation** | F | A | F | A | F | A |
| N= | N=222 | N=229 | N=206 | N=194 | N=428 | N=423 |
| Commencement of treatment affecting hormones | 18 | 18 | 15 | 25 | 33 | 43 |
| Use of systemic treatment affecting breast cancer | 8 | 6 | 8 | 3 | 16 | 9 |
| Total number (%) Violations and deviations resulting in exclusion | 35 (16%) | 32 (14%) | 32 (16%) | 40 (21%) | 68 (16%) | 77(18%) |

**Reviewer comment:** The most common major protocol deviation involved treatment related to disease progression: either the commencement of treatment affecting hormones or the use of systemic treatment affecting breast cancer. There were slightly more patients in the anastrozole arm in study #21 with major violations and deviations, but overall compliance with study protocol was acceptable and arms were generally balanced with respect to protocol deviations and violations. The study is reasonably mature, with approximately ¾ of all patients having progressed. Patients who had not progressed at the time of analysis were censored.

## (3) Per Protocol Populations

The per-protocol population (PP) consisted of the subset of patients who did not significantly violate or deviate from the protocol (see section vi.2 above).

**Table 18: Per protocol populations in the phase 3 trials**

| | #20 | | #21 | |
|---|---|---|---|---|
| Population | F N=219 | A N=230 | F N=204 | A N=193 |
| ITT | 222 | 229 | 206 | 194 |
| Applicant Excluded from protocol Violation or Deviation | 34 | 28 | 34 | 38 |
| Applicant's PP population | 188 | 201 | 172 | 156 |
| Reviewer Excluded from protocol Violation or Deviation | 35 | 30 | 35 | 38 |
| Reviewer's PP population | 187 | 199 | 171 | 156 |

In trial #20, the Applicant included one patient originally randomized to the dropped group – fulvestrant 125 mg. This patient was excluded by the FDA statistical reviewer. One patient, who had neither protocol violation nor deviation, randomized to the fulvestrant 250-mg group actually received anastrozole, and this patient was excluded by the FDA but included by the applicant. One patient randomized to the fulvestrant 125-mg group actually received fulvestrant 250-mg, so this patient was included in the fulvestrant 250-mg group in the PP population by the Applicant but the FDA did not include any patient originally randomized to the dropped treatment group – fulvestrant 125 mg. In trial #21, the FDA statistical reviewer excluded one patient from the PP population who was randomly assigned to the fulvestrant 250-mg group but received anastrozole, resulting in a different PP population size from the Applicant's.

**Reviewer comments:** The slight differences in PP population sizes between the applicant and the FDA are unlikely to have any significant affect on efficacy results. Compliance with the protocol was good, with over 80% of the ITT population included in the PP population.

### (4) Follow-up

Patients continued treatment until objective disease progression or other events required withdrawal; at such time, trial treatment was stopped, and standard therapy was initiated; thereafter, patients were followed up until death to determine survival interval. Patients who withdrew from trial treatment before progression were followed up until objective disease progression and death. To avoid the introduction of bias in the estimation of time to disease progression, the assessment schedule was maintained as closely as possible. Assessments were performed earlier than scheduled only when disease progression was suspected. Patients withdrawn from treatment for reasons other than disease progression continued to have objective tumor assessment every 3 months, even when treatment was subsequently changed.

**Table 19: Median Duration of follow-up**

| | Until last follow up or death | Until progression |
|---|---|---|
| Trial 0021 (N=400) Median Follow up (days) | 510 | 140.5 |
| Trial 0020 (N=451) Median Follow up (days) | 439 | 150 |

## vii. Combined Results of Randomized Trials

### (1) Demographics

A total of 1014 patients from 83 centers in North America and 83 centers in Europe, Australia, and South Africa were randomized to treatment in Trials 0021 and 0020. Of these, 428 patients were randomized to monthly treatment with fulvestrant 250 mg, 423 to daily treatment with anastrozole 1mg, and 163 to monthly treatment with fulvestrant 125 mg. In trial #20, the first patient was randomized on June 11, 1997 and the last patient on September 8, 1999 Data were cut off on December 31, 1999. In trial #21, the first patient was randomized on May 15, 1997 and the last patient on August 13, 1999. Data were cut off on June 30, 2000.

The demographic data are summarized in table 20:

**Table 20: Demographic data for the phase 3 trials**

| Demographic characteristic | Trial 0021 North American | | Trial 0020 European | | Combined trials | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg N=206 | Anastrozole 1 mg N=194 | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=428 | Anastrozole 1 mg N=423 |
| **Age (y)** | | | | | | |
| Mean | 63 | 62 | 63 | 64 | 63 | 63 |
| SD | 11 | 12 | 10 | 11 | 11 | 11 |
| **Age distribution, n (%)** | | | | | | |
| <45 | 12 (5.8) | 12 (6.2) | 8 (3.6) | 8 (3.5) | 20 (4.7) | 20 (4.7) |
| ≥45 to <65 | 96 (46.6) | 102 (52.6) | 107 (48.2) | 103 (45.0) | 203 (47.4) | 205 (48.5) |
| ≥65 to <75 | 61 (29.6) | 48 (24.7) | 74 (33.3) | 77 (33.6) | 135 (31.5) | 125 (29.6) |
| ≥75 | 37 (18.0) | 32 (16.5) | 33 (14.9) | 41 (17.9) | 70 (16.4) | 73 (17.3) |
| **Weight (kg)** | | | | | | |
| Mean | 71.7 | 72.7 | 68.9 | 67.8 | 70.2 | 70.0 |
| SD | 14.7 | 16.3 | 13.0 | 11.8 | 13.9 | 14.3 |
| **Race (%)** | | | | | | |
| White | 177 (85.9) | 157 (80.9) | 214 (96.4) | 218 (95.2) | 391 (91.4) | 375 (88.7) |
| Black | 20 (9.7) | 24 (12.4) | 0 | 0 | 20 (4.7) | 24 (5.7) |
| Hispanic | 8 (3.9) | 10 (5.2) | 0 | 1 (0.4) | 8 (1.9) | 11 (2.6) |
| Asian/Oriental | 0 | 1 (0.5) | 1 (0.5) | 2 (0.9) | 1 (0.2) | 3 (0.7) |
| Other | 1 (0.5) | 2 (1.0) | 7 (3.2) | 8 (3.5) | 8 (1.9) | 10 (2.4) |
| **WHO performance status, n (%)** | | | | | | |
| 0 | 90 (43.7) | 84 (43.3) | 104 (46.8) | 104 (45.4) | 194 (45.3) | 188 (44.4) |
| 1 | 94 (45.6) | 95 (49.0) | 93 (41.9) | 98 (42.8) | 187 (43.7) | 193 (45.6) |
| 2 | 21 (10.2) | 15 (7.7) | 25 (11.3) | 27 (11.8) | 46 (10.7) | 42 (9.9) |

Accrual was limited to postmenopausal females. The mean age was similar across trials and between treatment groups. The youngest patient was 33 years. The mean weight was slightly more in the North American trials. The European trials were almost entirely limited to Caucasians, whereas the North American trials accrued a wider variety of ethnic backgrounds. Performance status appeared to be well balanced across trials and between treatment groups.

**Reviewer comment:** Demographic characteristics appeared to be well balanced across trials and between treatment groups, except that the North American studies accrued slightly heavier patients and the European patients were almost entirely Caucasian. Performance status favored WHO PS 0 or 1 and was balanced across studies and between treatment groups.

## (2) Baseline Disease status at entry

Table 15 lists the baseline disease status of patients in the 2 phase 3 trials at entry:

**Table 21: Baseline Disease Status at entry**

| Disease at entry | Trial 0021 | | Trial 0020 | | Combined trials | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg N=206 | Anastrozole 1 mg N=194 | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=428 | Anastrozole 1 mg N=423 |
| Baseline tumor assessment, n (%) | | | | | | |
| Measurable only | 35 (17.0) | 41 (21.1) | 44 (19.8) | 55 (24.0) | 79 (18.5) | 96 (22.7) |
| Any evaluable | 169 (82.0) | 150 (77.3) | 166 (74.8) | 161 (70.3) | 335 (78.3) | 311 (73.5) |
| Measurable + evaluable | 79 (38.3) | 66 (34.0) | 78 (35.1) | 79 (34.5) | 157 (36.7) | 145 (34.3) |
| No measurable or evaluable[a] | 2 (1.0) | 3 (1.5) | 3 (1.4) | 5 (2.2) | 5 (1.2) | 8 (1.9) |
| Sites of metastatic disease, n (%) | | | | | | |
| Local Disease Only | 1(0.5%) | 2 (1.0%) | 5 (2.3%) | 6 (2.6%) | 6 (1.4%) | 8 (1.9%) |
| Breast | 8 (3.9) | 8 (4.1) | 21 (9.5) | 30 (13.1) | 29 (6.8) | 38 (9.0) |
| Skin and soft tissue | 43 (20.9) | 41 (21.1) | 40 (18.0) | 35 (15.3) | 83 (19.4) | 76 (18.0) |
| Bone | 90 (43.7) | 85 (43.8) | 115 (51.8) | 117 (51.1) | 205 (47.9) | 202 (47.8) |
| Liver involvement | 47 (22.8) | 45 (23.2) | 48 (21.6) | 56 (24.5) | 95 (22.2) | 101 (23.9) |

[a] Protocol violators.

In Trial 0020, in both treatment groups, slightly greater proportions (fulvestrant group, 9.5%; anastrozole group, 13.1%) had local breast disease, compared with patients in Trial 0021 (fulvestrant group, 3.9%; anastrozole group, 4.1%); slightly greater proportions (fulvestrant group, 51.8%; anastrozole group, 51.1%) had bone disease compared with patients in Trial 0021 (fulvestrant group, 43.7%; anastrozole group, 43.8%); and slightly greater proportions (fulvestrant group, 35.1%; anastrozole group, 36.2%) had lymph node involvement compared with patients in Trial 0021 (fulvestrant group, 28.2%; anastrozole group, 28.9%) Comparable or somewhat comparable proportions of patients across treatment groups, in both trials, had lung involvement (25.2% to 30.9%), skin or soft tissue involvement (15.3% to 21.1%), or liver involvement (21.6% to 24.5%).

**Reviewer comment:** The baseline disease characteristics appeared similar between treatment groups, despite lack of stratification for prognostic factors. The primary analysis was based on an adjusted analysis with pre-specified covariates, including whether or not the disease was measurable only. Both adjusted and unadjusted analyses led to consistent results. Over 97% of patients had metastatic disease at entry. Eligibility criteria required the presence of at least 1 measurable or evaluable lesion. 13 patients had neither measurable nor evaluable disease, in violation of the protocol. These patients were unlikely to have any significant effect on response rates, since response data could not be interpreted on these patients. It is not likely that inclusion of these patients would affect the secondary endpoints.

### (3) Previous treatment

Table 20 summarizes the previous treatment received by study participants:

**Table 22: Previous treatment**

| Breast cancer history | Trial 0021 | | Trial 0020 | | Combined trials | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg N=206 | Anastrozole 1 mg N=194 | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=428 | Anastrozole 1 mg N=423 |
| Previous treatment, n (%)[a] | | | | | | |
| Tamoxifen | 196 (95.2) | 187 (96.4) | 215 (97) | 225 (98) | 411 (96) | 412 (97) |
| Surgery | 194 (94.2) | 182 (93.8) | 204 (91.9) | 200 (87.3) | 398 (93.0) | 382 (90.3) |
| Cytotoxic chemotherapy | 129 (62.6) | 122 (62.9) | 94 (42.3) | 98 (42.8) | 223 (52.1) | 220 (52.0) |
| Loco-regional RT | 99 (48.1) | 91 (46.9) | 128 (57.7) | 125 (54.6) | 227 (53.0) | 216 (51.1) |
| Palliative RT | 68 (33.0) | 53 (27.3) | 40 (18.0) | 47 (20.5) | 108 (25.2) | 100 (23.6) |
| Previous hormonal treatment for advanced disease, n (%) | | | | | | |
| Total n | 110 (53.4) | 97 (50.0) | 126 (56.8) | 129 (56.3) | 236 (55.1) | 226 (53.4) |
| Tumor remission <3 mo | 6 (2.9) | 10 (5.2) | 7 (3.2) | 6 (2.6) | 13 (3.0) | 16 (3.8) |
| Tumor remission ≥3 mo | 104 (50.5) | 87 (44.8) | 119 (53.6) | 123 (53.7) | 223 (52.1) | 210 (49.6) |
| Relapse during adjuvant hormonal treatment, n (%) | | | | | | |
| Time on treatment | 122 (59.2) | 116 (59.8) | 121 (54.5) | 119 (52.0) | 243 (56.8) | 235 (55.6) |
| Relapse after <12 mo | 16 (7.8) | 13 (6.7) | 10 (4.5) | 9 (3.9) | 26 (6.1) | 22 (5.2) |
| Relapse after ≥12 mo | 106 (51.5) | 103 (53.1) | 111 (50.0) | 110 (48.0) | 217 (50.7) | 213 (50.4) |

[a] Patients may appear in more than 1 previous-treatment category. RT= Radiotherapy

Comparable proportions of patients across treatment groups, for both trials, had history of surgery for breast cancer (87.3% to 94.2%). Differences between trials, however, were seen for previous treatment with chemotherapy and radiotherapy. Greater proportions of patients per treatment group in the North American trial (0021) had history of chemotherapy for breast cancer (approximately 20% greater) or history of radiotherapy for metastatic disease (approximately 7% to 15% greater), compared with patients in Trial 0020. Conversely, a smaller proportion of patients per treatment group in Trial 0021 had history of loco-regional radiotherapy (approximately 8% to 10% smaller), compared with patients in Trial 0020. It is likely that many of the patients with no prior surgery had locally advanced disease.

Comparable proportions of patients across treatment groups, in both trials (50.0% to 56.8%), had history of previous hormonal treatment for advanced breast cancer . Of those, most had tumor remission for more than 3 months, with proportions smallest (44.8%) for patients in the Trial 021 anastrozole group, compared with patients in the other groups (Trial 0021: fulvestrant group, 50.5%; Trial 0020: fulvestrant group, 53.6%; anastrozole group, 53.7%). In both treatment groups per trial, the most common previously used hormonal therapy was tamoxifen: in 95.2% and 96.4% of patients in the fulvestrant and anastrozole groups, respectively, in Trial 0021 and in 96.9% and 98.3% in the fulvestrant and anastrozole groups, respectively, in Trial 0020.

**Reviewer comment:** Despite differences between the 2 trials, combined data show that, overall, patients had comparable histories of previous treatment for breast cancer per treatment group. Over 95% of all patients had been treated previously with Tamoxifen. Previous hormonal treatment responses appeared to be fairly well balanced among trials and between treatment

groups except that four more patients in the anastrozole arm in trial 21 had remissions of less than 3 months. This small imbalance was unlikely to affect results.

## (4) Hormone Receptor status

Table 21 summarizes hormone receptor status of patients at entry:

**Table 23: Hormone receptor status**

| Hormone Receptor | Trial 0021 | | Trial 0020 | | Combined trials | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg N=206 | Anastrozole 1 mg N=194 | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=428 | Anastrozole 1 mg N=423 |
| Estrogen Receptor Positive, n (%) | | | | | | |
| ER + PgR+ | 128 (62.1) | 106 (54.6) | 86 (38.7) | 95 (41.5) | 214 (50.0) | 201 (47.5) |
| ER + PgR– | 37 (18.0) | 40 (20.6) | 35 (15.8) | 43 (18.8) | 72 (16.8) | 83 (19.6) |
| PgR unknown | 5 (2.4) | 10 (5.2) | 35 (15.8) | 35 (15.3) | 40 (9.3) | 45 (10.6) |
| Total ER+ | 170 (82.5) | 156 (80.4) | 156 (70.3) | 173 (75.5) | 326 (76.2) | 329 (77.8) |
| Estrogen Receptor Negative, n (%) | | | | | | |
| ER– PgR+ | 9 (4.4) | 12 (6.2) | 7 (3.2) | 10 (4.4) | 16 (3.7) | 22 (5.2) |
| ER– PgR– | 14 (6.8) | 9 (4.6) | 6 (2.7) | 7 (3.1) | 20 (4.7) | 16 (3.8) |
| PgR unknown | 0 | 1 (0.5) | 2 (0.9) | 2 (0.9) | 2 (0.5) | 3 (0.7) |
| Estrogen Receptor Unknown, n (%) | | | | | | |
| PgR+ | 0 | 1 (0.5) | 0 | 0 | 0 | 1 (0.2) |
| ER/PgR unknown | 13 (6.3) | 15 (7.7) | 51 (23.0) | 37 (16.2) | 64 (15.0) | 52 (12.3) |

Several small differences between trials were noted in terms of hormone receptor status. Slightly greater proportions of patients in Trial 0021, both treatment groups, were ER+ (fulvestrant group, 82.5%; anastrozole group, 80.4%) compared with that in Trial 0020 (fulvestrant group, 70.3%; anastrozole group, 75.5%). Among those with ER+ status, approximately 16% in both treatment groups in Trial 0020 had unknown PgR status compared with 2.4% and 5.2% in the fulvestrant and anastrozole groups, respectively, in Trial 0021. In Trial 0021, a greater proportion of patients in both treatment groups were both ER+ and PgR+ (fulvestrant and anastrozole groups, 62.1% and 54.6%, respectively), compared with patients in Trial 0020 (fulvestrant and anastrozole groups, 38.7% and 41.5%, respectively). The proportions of patients with ER– but PgR+ status were small but comparable across all treatment groups (3.2% to 6.2%). fulvestrant group, 65.6% (214 patients); anastrozole group, 61.1% (201 patients). Among patients with tumors designated as ER–, a small percentage had tumors that were PgR+ (fulvestrant group, 3.7% [16 patients]; anastrozole group, 5.2% [22 patients]), and a small percentage had tumors that were PgR– (fulvestrant group, 4.7% [20 patients]; anastrozole group, 3.8% [16 patients]). ER and PgR tumor status were unknown in 15.0% (64 patients) in the fulvestrant group and in 12.3% (52 patients) in the anastrozole group.

**Reviewer comment:** Over 75% of patients in each treatment group had ER+ tumors. Among these patients, more than half had tumors that were PgR+ as well. Receptor status was well balanced among treatment arms in trial #21. Although the percentage of patients with positive

estrogen receptors was lower in the European trials, this appeared to be attributable to a higher percentage of patients with ER/PR unknown status. More patients in the fulvestrant arm in trial 20 had unknown receptor status, and fewer patients were known estrogen receptor positive. This would have been most likely to have biased the trial results against fulvestrant.

#### (5) Study Population Overall Conclusions

Despite minor differences between trials, the treatment groups were well balanced in terms of demographic characteristics, and the population studied reflects the proposed usage of this drug. Hormone receptor status was well balanced between arms in the North American trial (#21). The European trial (#20) accrued more estrogen positive patients to the anastrozole arm, and more patients with unknown hormone receptor status to the fulvestrant arm. This imbalance could have biased the trial against fulvestrant.

### viii. Efficacy results by trial: Trial #20 (European open label)

#### (1) Randomization procedures

The eligibility of each patient was established before allocation to treatment. The treatment given to individual patients was determined for each center by a randomization schedule prepared by the Biostatistics Group, AstraZeneca. The randomization schedule and associated code breaks were produced by computer software that incorporates a standard procedure for generating random numbers. A separate randomization schedule was produced for each center, but all the schemes were held and administered by a central randomization center at [redacted] Due to the removal of the fulvestrant 125 mg arm, the randomization schemes were amended such that patients were randomized to receive either 250 mg fulvestrant or 1 mg anastrozole. The consequence of amending the original randomization schemes was that patient numbers were no longer allocated sequentially. Because this was an open-label trial, the trial treatment that each patient was randomized to was known to all parties (AstraZeneca, investigator and patient) following randomization.

#### (2) Response Analysis

##### (a) Applicant's Response analysis

Applicant's results for both intent to treat (ITT) and per protocol (PP) populations are summarized in Table 20 below:

**Table 24:Applicant's best Response for Trial #20**

| | ITT | | PP | |
|---|---|---|---|---|
| | Fulvestrant 250 mg N=222 | Anastrozole 1 mg N=229 | Fulvestrant 250 mg N=188 | Anastrozole 1 mg N=201 |
| **Responders** | | | | |
| CR | 10 (4.5%) | 4 (1.7%) | 9 (4.8%) | 4 (2.0%) |
| PR | 36 (16.2%) | 32 (14.0%) | 33 (17.6%) | 27 (13.4%) |
| CR + PR | 46 (20.7%) | 36 (15.7%) | 42 (22.3%) | 31 (15.4%) |
| **Nonresponders** | | | | |
| SD ≥ 24 weeks | 53 (23.9%) | 67 (29.3%) | 43 (22.9%) | 59 (29.4%) |
| SD < 24 weeks | 3 (1.4%) | 3 (1.3%) | 2 (1.1%) | 2 (1.0%) |
| Not Progressed * | 10 (4.5%) | 6 (2.6%) | 7 (3.7%) | 3 (1.5%) |
| Progression | 110 (49.5%) | 117 (51.1%) | 94 (50.0%) | 106 (52.7%) |
| Total | 176 (79.3%) | 193 (84.3%) | 146 (77.7%) | 170 (84.6%) |

When analyses were performed on the applicant's ITT population, at the time of data cutoff 46 (20.7%) patients in the fulvestrant 250-mg group and 36 (15.7%) in the anastrazole group responded to treatment; i.e., had a best objective response (CR or PR) to treatment. When analysis was conducted on the PP population, 42 (22.3%) patients in the fulvestrant 250-mg group and 31 (15.4%) in the anastrazole group responded to treatment; i.e., had a best objective response (CR or PR) to treatment.

### (b) FDA Reviewer's Response Analysis

Review of clinical data and analysis of clinical response datasets were performed using an FDAcomputer algorithm to confirm a 50% decrease in the sum of the products of tumor diameters to adjudicate responses. The following table lists response reassignments according to the FDA review of response data. Only 3/82 (3.6%) of the applicants' claimed responses were affected by FDA analysis, 2 of these were in the anastrozole arm:

**Table 25: FDA response reassignments for study #20**

| Patient ID | Treatment Received | Applicant response assignment | FDA response assignment | FDA sum of products of tumor diameters[a] % maximum |
|---|---|---|---|---|
| 00280009 | Fulvestrant | PR | SD | 75% |
| 00980008 | Anastrozole | PR | SD | 80% |
| 00990005 | Anastrozole | PR | SD | 53% |

[a]UICC criteria require < 50% for PR

Discussion with the applicant confirmed that the discrepancies were attributable to the investigators' assignment of global response in a few patients with evaluable as well as measurable disease. In order to evaluate the effects of possible investigator bias, the response data were analyzed using the FDA objective responses as well as the applicant's response analysis. The reviewer's response data are summarized below:

**Table 26: Reviewer's best response by population study #20**

| | ITT | | PP | | Measurable only | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg | Anastrozole 1 mg | Fulvestrant 250 mg | Anastrozole 1 mg | Fulvestrant 250 mg | Anastrozole 1 mg |
| | N = 222 | N = 229 | N = 187 | N = 199 | N = 44 | N = 55 |
| **Responders (CR+PR)** | 45 (20.3%) | 34 (14.9%) | 41 (21.9%) | 29 (14.6%) | 11 (25.0%) | 14 (25.5%) |
| **Nonresponders** | 177 (79.7%) | 195 (85.1%) | 146 (78.1%) | 170 (85.4%) | 33 (75.0%) | 41 (74.5%) |

FDA response analysis based on the medical reviewer's re-adjudicated data show similar results to the applicant's analysis: 45 (20.3%) patients in the fulvestrant 250-mg ITT group and 34 (14.9%) in the anastrazole ITT group responded to treatment. Per protocol analysis showed that and 41 (21.9%) patients in the fulvestrant 250-mg group and 29 (14.6%) in the anastrazole group responded to treatment; i.e., had a best objective response (CR or PR) to treatment. In a subgroup analysis of patients with measurable disease only, 25% of patients in each arm responded to treatment.

**Reviewer comment:** Minor differences between the FDA and applicant's response assignments resulted in minimal differences in reported response rates. In this study, a higher response rate was observed in the fulvestrant arm, but this difference was not statistically significant (see below). In patients with measurable disease only, response rates appeared to be similar in both arms.

### (c) Superiority analysis

The applicant's response results are summarized in Table 27. Whether analyses were performed on the ITT or PP population, adjusted or unadjusted analysis, the estimated odds ratio was greater than 1, favoring fulvestrant, although the differences were not significant.

### (d) Applicant's Non inferiority analysis

Based on regulatory precedent, and given the adjustment in alpha due to interim analysis, demonstration of non inferiority of response required ruling out with 95.14% confidence a deficiency in response rate of greater than 10%. The applicant's analysis estimated the difference in response rates (fulvestrant 250 mg minus anastrozole 1 mg) for the 2 treatments was 4.78% in favor of the fulvestrant arm, with the 95.14% confidence interval indicating this difference could be between -2.19% and 14.23%. Therefore, by the applicant's analysis, based on a Logistic-regression model, a deficiency of greater than 10% was ruled out.

**Table 27: Summary of Applicant's and FDA's Odds Ratio [a] and Difference [b] in Best Objective Response Rates for study # 20**

| Population | Analysis | Applicant's Estimated odds ratio (95.14% CI) | FDA Estimated odds ratio (95.4% CI) | Applicant's Estimated % difference in response rates (95.14% CI) | FDA Estimated % difference in response rates (95.4% CI) |
|---|---|---|---|---|---|
| ITT | Adjusted [c] | 1.38 (0.84, 2.29) p = 0.2010 | 1.44 (0.86, 2.43) p = 0.1564 | 4.78 (-2.19, 14.23) | N/A |
| | Unadjusted [d] | 1.40 (0.86, 2.29) p = 0.1684 | 1.46 (0.89, 2.41) p = .1294 | 5.00 (-1.83, 14.17) | 5.42 (-1.44, 14.77) |
| PP | Adjusted | 1.54 (0.91, 2.64) p = 0.1087 | 1.60 (0.92, 2.80) p = .0827 | 6.50 (-1.25, 17.08) | N/A |
| | Unadjusted | N/A | 1.65 (0.97, 2.83) p = 0.0607 | N/A | 7.35 (-0.39, 17.98) |

[a] An odds ratio of greater than 1 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg.
[b] A difference in response rates of greater than 0 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg.
[c] Logistic-regression 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.
[d] Logistic-regression model without baseline covariates.

### (e) FDA Statistical Reviewer's Non inferiority Analysis

The applicant's applicant primary analysis was an adjusted logistic regression model that included seven prognostic factors. The applicant's adjusted analysis was questionable in assessing the difference in response rates because the applicant assumed a constant difference in response rates across all possible combinations of prognostic factors, which needs to be verified. Therefore, the FDA statistical reviewer performed an unadjusted analysis[15] without using a logistic regression model as a sensitivity analysis. The Applicant constructed a 95.14% confidence interval (corresponding to a nominal significance level of 0.0486) for the final analyses, which failed to control the overall type-I error rate at level of 0.05. In order to control the overall all type-I error rate at level of 0.05, the FDA statistical reviewer constructed a 95.4% confidence interval (corresponding to a nominal significance level of 0.046) of the odds ratio and of the difference in response rates for the final analysis. The results for both ITT and PP populations using the pre-specified methods are summarized in the previous table. The results of sensitivity analysis are summarized in the following table:

[15] Joseph L. Fleiss, Statistical Methods for Rates and proportions, 2nd edition, John Wiley & Sons, New York. , 1981.

**Table 28: Reviewer's Results of Sensitivity Analysis of Difference [a] in Best Objective Response Rates**

| Population | Estimated % Difference in Response Rates (fulvestrant – ansatrozole) | 95.4% CI |
|---|---|---|
| ITT | 5.42 | (-2.16, 13.00) |
| PP | 7.35 | (-1.00, 15.70) |

[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:** The lower limit of the two-sided 95.4% confidence interval for the difference in response rates of each FDA analysis was greater than –10%, The FDA therefore 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.

## (f) Subgroup Analysis (exploratory)

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

**Table 29: Best Objective Response Rate by Age and Race (trial # 20)**

| Population | Subgroup | | Number (%) of responders | |
|---|---|---|---|---|
| | | | Fulvestrant 250 mg | Anastrozole 1 mg |
| ITT | Age | | | |
| | | < 65 | 28 /115 (= 24.3%) | 18 /111 (= 16.2%) |
| | | ≥ 65 | 17 /107 (= 15.9%) | 16 /118 (= 13.6%) |
| | Race | | | |
| | | White | 44 /214 (= 20.6%) | 33 /218 (= 15.1%) |
| | | Non-white | 0 / 3 (= 0.0%) | 0 /5 (= 0.0%) |
| | | | (5 missing values) | (6 missing values) |
| PP | Age | | | |
| | | < 65 | 26 /97 (= 26.8%) | 15 /97 (= 15.5%) |
| | | ≥ 65 | 15 /90 (= 16.7%) | 14 /102 (= 13.7%) |
| | Race | | | |
| | | White | 40 /180 (= 22.2%) | 29 /191 (= 15.2%) |
| | | Non-white | 0/3 = (0.0%) | 0 /4 (= 0.0%) |
| | | | 4 missing values | 4 missing values |

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

**Table 30: Reviewer's Summary of Best Objective Response Rate by Hormonal Receptor Status in trial # 20**

| Population | (ER, PR) status | Number (%) of responders | | |
|---|---|---|---|---|
| | | Fulvestrant 250 mg N = 222 | Anastrozole 1 mg N = 229 | Combined N = 451 |
| ITT | | | | |
| | (+, +) | 15/86 (= 17.4%) | 10/95 (= 10.5%) | 25/181 (= 13.8%) |
| | (+, -) | 7/35 (= 20.0%) | 4/43 (= 9.3%) | 11/78 (= 14.1%) |
| | (+, ?) | 5/35 (= 14.3%) | 9/35 (= 25.7%) | 14/70 (= 20.0%) |
| | (-, +) | 1/7 (= 14.3%) | 3/10 (= 30.0%) | 4/17 (= 23.5%) |
| | (-, -) | 2/6 (= 33.3%) | 0/7 (= 0%) | 2/13 (= 15.4%) |
| | (-, ?) | 0/2 (= 0%) | 0/2 (= 0%) | 0/4 (=0%) |
| | (?, ?) | 15/51 (= 29.4%) | 8/37 (= 21.6%) | 23/88 (= 26.1%) |

Reviewer comment: Although the numbers were small and subgroup analyses were not prespecified, it appears that a few patients with negative hormone receptor status achieved a response to faslodex.

## (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 a disease progression by the data cutoff. The Applicant's results of time to disease progression are summarized in the following table:

**Table 31: Applicant's Results of 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 | 166 | 39 (17.6%) | 156 | 38 (16.6%) |
| PP | 162 | 30 (16.0%) | 124 | 31 (15.4%) |

In the intent to treat population, time to progression was similar (166 days for fulvestrant and 156 days for anastrozole), however the per protocol data show a some what shorter time to progression in the anastrozole arm. These differences were not statistically significant.

### (b) Analysis of TTP

Applicant analyses of time to disease progression are summarized in table 30 below:

**Table 32: Applicant's and FDA's Results of Analysis of Time to Disease Progression in Study #20**

| Population | Analysis | Applicant's Estimated hazard ratio [a] (95.14% CI) | FDA Estimated hazard ratio (95.4% CI) |
|---|---|---|---|
| ITT | Adjusted [b] | 0.98(0.80, 1.21)<br>p = 0.8402 | 0.98 (0.79, 1.21)<br>p = 0.8402 |
| | Unadjusted [c] | 0.94(0.76, 1.15)<br>p = 0.5210 | 0.94 (0.76, 1.15)<br>p= 0.5210 |
| PP | Adjusted | 0.97(0.78, 1.21)<br>p = 0.7888 | 0.97 (0.77, 1.21)<br>p = 0.7665 |
| | Unadjusted | N/A | 0.92 (0.74, 1.15)<br>p = 0.4752 |

[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 estimated hazard ratio was less than but close to 1. A hazard ratio of less than 1 indicates that fulvestrant 250 mg is associated with a lower instantaneous risk of disease progression, hence, a longer time to disease progression, compared with anastrozole 1mg. The p-values approached unity, indicating no evidence that the instantaneous risk of disease progression in one treatment group differs from the other. The FDA statistical reviewer performed analyses on the PP population that was defined slightly different from the Applicant and constructed a 95.4% (instead of 95.14%) confidence interval. This reviewer's results were consistent with the Applicant's. 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. The FDA statistical reviewer's Kaplan-Meier plots for the ITT and PP populations are attached in the end of this section.

**Reviewer comment:** Relatively few patients were censored. There was a slight trend towards longer time to progression in the fulvestrant arm, however, analysis revealed that no statistically significant differences in time to progression were observed between the two treatment arms,

## (c) Covariate analysis

Results of covariate analysis based on Cox proportional-hazards model are summarized in the following table:

**Table 33: Reviewer's Results of Covariates in Adjusted Analysis of Time to**

**Disease Progression**

| Variable | ITT population | | PP population | |
|---|---|---|---|---|
| | Hazard ratio (95.4% CI) | P-value | Hazard ratio (95.4% CI) | P-value |
| Who PS 1 | 1.38 (1.09, 1.74) | 0.0057 | 1.33 (1.04, 1.70) | 0.0215 |
| Who PS 2 | 1.67 (1.18, 2.38) | 0.0033 | 2.06 (1.39, 3.07) | 0.0003 |
| Previous response to hormones | 2.04 (1.25, 3.32) | 0.0036 | 1.76 (0.97, 3.18) | 0.0577 |
| Receptor neg | 2.23 (1.31, 3.80) | 0.0026 | 2.32 (1.33, 4.03) | 0.0024 |
| Receptor status Unknown | 0.74 (0.56, 0.98) | 0.0318 | 0.75 (0.56, 1.01) | 0.0557 |

Hazard Ratio > 1 = higher risk of progression

Risk factors associated with a higher risk of progression included performance status of 1 or 2, negative receptor status, and previous response to hormones. Patients whose receptor status was unknown seemed to be associated with a lower risk compared with all other patients, however only a very small proportion of patients were in this stratum and this finding was only seen in the ITT population. Measurable disease only, history of bisphosphonate therapy, age > 65, and previous chemotherapy were not associated with differences in risk of progression.

**Figure 2: Kaplan-Meier Plot of Time to Progression (ITT Population)**

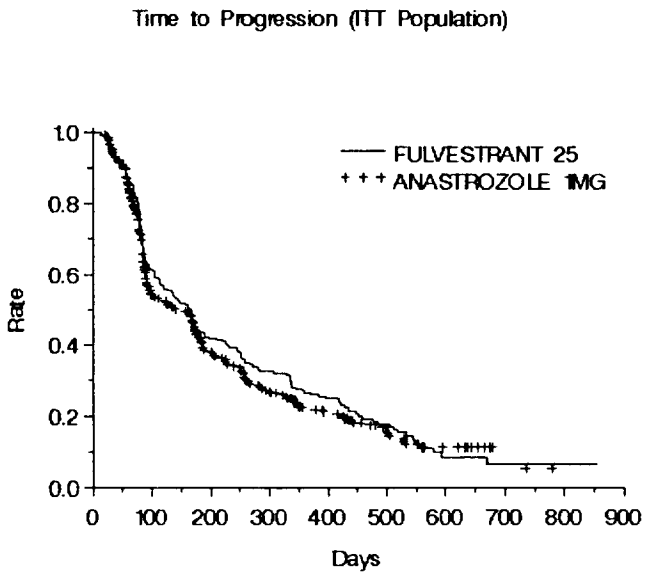
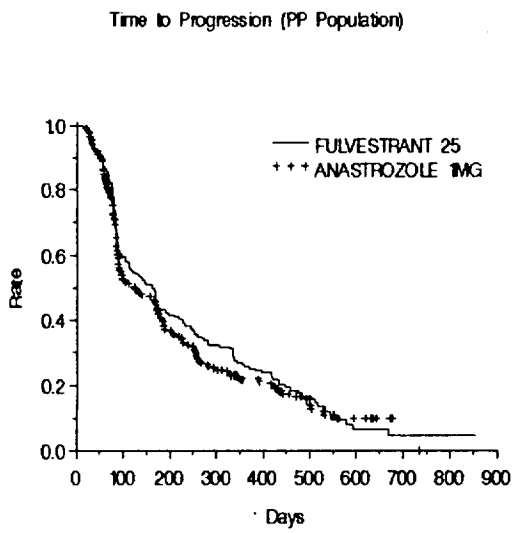



**Figure 3: Kaplan-Meier Plot of Time to Progression (PP Population)**



### (d) Conclusions regarding TTP

Superiority in time to progression was not demonstrated, ( all hazard ratios ≅ 1). Studies were balanced for prognostic factors associated with effects on progression, including performance status, receptor status, and previous response to hormones. Although the FDA statistical reviewer used a slightly different confidence level and a slightly different PP population than the Applicant, the FDA reviewers and the Applicant agree that, using a non-inferiority margin of 25%, fulvestrant 250-mg was non-inferior to anastrozole with respect to TTP. Patients with worse performance status, hormone receptor negative and those with a history of previous response to hormones appeared to be at higher risk for progression. In contrast, patients whose receptor status was unknown seemed to have a lower risk of progression.

## (4) Survival

The survival data in the original NDA submission was cut off on December 31, 1999. Since the original survival data were not mature (63.4% of the 451 patients were censored), the Division requested the applicant for an updated survival data. These data, with acut off date of February 1, 2001, were received on August 28, 2001. The statistical reviewer's survival analysis are summarized as below, followed by the Kaplan-Meier plots:

**Table 34: Reviewer's Survival Results (ITT Population): Study #20**

| Data Cut-off date | Fulvestrant (N = 222) | | Anastrozole (N = 229) | |
|---|---|---|---|---|
| | Median | # of deaths | Median | # of deaths |
| December 31, 1999 | 679 | 82 (36.9%) | 668 | 83 (36.2%) |
| February 1, 2001 | 803 | 125 (56.3%) | 742 | 130 (56.8%) |

**Table 35: Reviewer's Statistical Analysis of Survival (Data Cut-off as of February 1, 2001) Study #20**

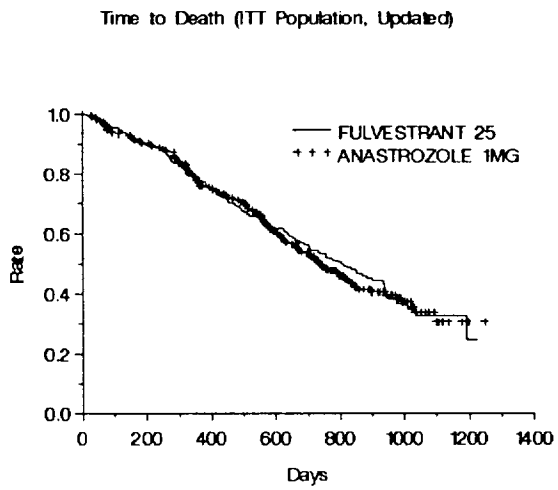
| Population | Data cut-off date | Comparison | Hazard ratio [a] (F:A) | 95% two-sided CI | P-value |
|---|---|---|---|---|---|
| ITT | February 1, 2001 | Adjusted analysis [b] | 1.02 | (0.79, 1.31) | 0.890 |
| | | Unadjusted analysis [c] | 0.97 | (0.76, 1.24) | 0.801 |
| Per Protocol | February 1, 2001 | Adjusted analysis | 0.99 | (0.75, 1.31) | 0.956 |
| | | Unadjusted analysis | 0.93 | (0.71, 1.22) | 0.592 |

[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.

**Figure 4: Reviewer's Kaplan-Meier Probability of Survival Time (ITT Population) – Data Cut-off as of February 1, 2001**




## (a) Conclusions regarding Survival

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.

## (b) Time to Treatment Failure

The Applicant's analysis results of time to treatment failure are summarized as below. The results did not suggest any treatment difference with respect to this endpoint.

**Table 36: Applicant's Results of Descriptive Summary of Time to Treatment Failure**

| Population | Fulvestrant 250 mg (N=222) | | Anastrozole 1 mg (N=229) | |
|---|---|---|---|---|
| | Median (in days) | # of patients censored (%) | Median (in days) | # of patients censored (%) |
| ITT | 139 | 34 (15.3%) | 126 | 33 (14.4%) |

**Reviewer Comment:** The Applicant's results did not suggest any treatment difference with respect to time to treatment failure. Time to treatment failure is a composite endpoint and generally not considered to be useful for registration trials.

## (5) 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. (This was the assessment included in applicant's proposed label)
2. from the date of first documentation of response to the date of first determined progression or death from any cause.

**Table 37: Results of Duration [a] of Best Objective Response (ITT Population)**

| | Treatment | |
|---|---|---|
| | Fulvestrant 250 mg | Anastrozole 1 mg |
| # of Responders | 45 | 34 |
| Median (days) from Date of Randomization | 434 | 425 |
| Median (days) from Date Response Observed | 280 | 274 |
| FDA 95% CI for median | (193, 357) | (194, 448) |

[a] from date of response started.

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

## (6) 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, 99/222 (=44.6%) patients randomized to the fulvestrant 250-mg group and 103/229 (=45.0%) patients randomized to the anastrozole group had a clinical benefit. Per the Applicant's results, when performed on the ITT population the median duration of clinical benefit was 360 days for patients with clinical benefit who were randomized to the fulvestrant 250-mg group and 348 days for patients with clinical benefit who were randomized to the anastrozole group.

**Reviewer comment:** Clinical benefit as defined by the applicant or the duration thereof are not clinically meaningful terms and should not be included in labeling.

### (7) Time to Deterioration in Quality of Life

Included in the Applicant's qualitative of life analysis were 124 (55.5%) out of 222 patients randomized to the fulvestrant 250-mg group and 133 (58.1%) out of 229 patients randomized to the anastrozole group. Some centers did not participate in QOL analysis. 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. The FDA statistical reviewer obtained the 95% confidence intervals for the median time to deterioration:

**Table 38: Descriptive Summary of Time to Deterioration (ITT population)**

| | Fulvestrant 250 mg (N=124) | | Anastrozole 1 mg (N=133) | |
|---|---|---|---|---|
| | Median in days (FDA 95% C.I) | # of patients censored (%) | Median in days (FDA 95% C.I) | # of patients censored (%) |
| | 124 (62, 254) | 51 (41.1%) | 161 (80, 293) | 61 (45.9%) |
| # pts. included in the TTD analysis | 124 /222 (= 55.9%) | | 133 /229 (= 58.1%) | |

**Reviewer comment**: Data collection was insufficient in trial #20 for meaningful conclusions regarding QOL data on time to clinical deterioration. Many patients were not included in the analysis and many of those who were included were censored. Claims regarding time to deterioration in QOL based on results form this trial should not be included in the label.

## ix. Efficacy results by trial: Trial #21 (North American - double blind double dummy)

### (1) Randomization procedures

Treatment given to individual patients was determined for each center by a randomization schedule prepared by the Biostatistics Group, AstraZeneca. The randomization schedule and associated code breaks were produced by computer software that incorporated a standard procedure for generating random numbers. A separate randomization schedule was produced for each center. Patients were allocated to treatment in balanced blocks by [redacted] The randomization schemes were included in the Applicant's report. The original randomization scheme used to allocate patients to treatment before the 125-mg fulvestrant treatment group was discontinued was used until all patient numbers (ie, and associated drug) for 250-mg fulvestrant plus 1-mg anastrozole placebo and 1-mg anastrozole plus 250-mg fulvestrant placebo had been used. When additional drug had to be packaged, a new randomization scheme (with a new set of patient numbers, 100 series) was issued to [redacted] for allocation of new patients to randomized treatment with fulvestrant 250 mg or anastrozole 1 mg.

This was a double-blind trial. Fulvestrant was administered with anastrozole placebo (identical in presentation and administration to anastrozole), and anastrozole was administered

with fulvestrant placebo (identical in presentation and administration to fulvestrant). Only an AstraZeneca statistician not involved in the conduct of the trial who prepared the randomization scheme, [redacted] who allocated approved patients to randomized treatment, and AstraZeneca personnel in the Investigational Products Section who packaged trial drugs knew which drug was given to which patient. Treatment remained blinded to all others involved in the conduct of the trial (ie, patients, investigators, AstraZeneca personnel).

After a decision had been made to withdraw a patient from trial treatment, the investigator was provided with a description of the treatment for the patient (code break) by [redacted] after consultation with AstraZeneca if knowledge of the trial medication was needed for nonemergency clinical management of the patient. Additionally, after a decision was made to withdraw a patient from trial treatment (during an emergency) the investigator was allowed to break the treatment code by peeling off the label from the trial drugs containers stored in the pharmacy or other secure location.

## (2) Response Analysis

### (a) Applicant's Response analysis

Applicant's results for both ITT and PP populations are summarized in Table 24 below:

**Table 39:Applicant's best Response for Trial #21**

| | ITT | | PP | |
|---|---|---|---|---|
| | **Fulvestrant** 250 mg N=206 | **Anastrozole** 1 mg N=194 | **Fulvestrant** 250 mg N=172 | **Anastrozole** 1 mg N=156 |
| **Responders** | | | | |
| **CR** | 10 (4.9%) | 7 (3.6%) | 7 (4.1%) | 5 (3.2%) |
| **PR** | 26 (12.6%) | 27 (13.9%) | 24 (14.0%) | 22 (14.1%) |
| **CR + PR** | 36 (17.5%) | 34 (17.5%) | 31 (18.0%) | 27 (17.2%) |
| **Nonresponders** | | | | |
| **SD ≥ 24 weeks** | 51 (24.8%) | 36 (18.6%) | 39 (22.7%) | 24 (15.4%) |
| **SD < 24 weeks** | 3 (1.5%) | 1 (0.5%) | 0 (0%) | 0 (0%) |
| **Not Progressed** [a] | 11 (5.3%) | 19 (9.8%) | 10 (5.8%) | 16 (10.3%) |
| **Progression** | 105 (51.0%) | 104 (53.6%) | 92 (53.5%) | 89 (57.1%) |
| **Total** | 170 (82.5%) | 160 (82.5%) | 141 (82.0%) | 129 (82.7%) |

In the applicant's ITT population, 36 (17.5%) patients in the fulvestrant 250-mg group and 34 (17.5 %) in the anastrazole group responded to treatment; i.e., had a best objective response (CR or PR) to treatment. In the PP population, thirty-one (18%) patients in the fulvestrant 250-mg group and 27 (17.2%) in the anastrazole group responded to treatment; i.e., had a best objective response (CR or PR) to treatment.

### (b) FDA Reviewer's Response Analysis

FDA confirmed responses using clinical response datasets, JMP software, and a computer algorithm that applied the protocol-specified UICC standard of a 50% decrease in the sum of the products of tumor diameters (See appendix for comparison of UICC-WHO response criteria with RECIST criteria). The following differences in response assignment were observed between the applicant's response assignments and the FDA response analysis in patients with both measurable and evaluable disease:

**Table 40 FDA response reassignments for study #21**

| Patient ID | Treatment Received | Applicant response | FDA response | FDA sum of products of tumor diameters[a] % of maximum |
|---|---|---|---|---|
| 00020101 | Anastrozole | PR | SD | 75% |
| 00070101 | Fulvestrant 250 | PR | SD | 56.8% |
| 0026005 | Fulvestrant 125 | PR | SD | 60% |

[a]UICC criteria require < 50% for PR

Discussion with the applicant confirmed that the differences are attributable to the investigators' assignment of global responses in a few patients with evaluable as well as measurable disease. In order to minimize the effects of possible investigator bias, the response data were analyzed conducted using both the FDA objective responses as well as the applicant's response analysis. Response analysis based on the reviewer's results are summarized below:

**Table 41: Reviewer's best response by population, study #21**

| | ITT | | Per Protocol | | Measurable only | |
|---|---|---|---|---|---|---|
| | Fulvestrant 250 mg | Anastrozole 1 mg | Fulvestrant 250 mg | Anastrozole 1 mg | Fulvestrant 250 mg | Anastrozole 1 mg |
| | N=206 | N=194 | N=171 | N=156 | N = 35 | N = 41 |
| Responders (CR+PR) n (%) | 35 (17.0%) | 33 (17.0%) | 29 (17%) | 26 (16.7%) | 8 (22.9%) | 10 (24.4%) |

FDA response analysis based on the medical reviewer's re-adjudicated data show similar results to the applicant's response analysis: 35 (17.0%) patients in the fulvestrant 250-mg ITT group and 33 (17.0%) in the anastrozole ITT group responded to treatment, and 29 (17%) patients in the fulvestrant 250-mg per protocol group and 26 (16.7%) in the anastrozole per protocol group responded to treatment; i.e., had a best objective response (CR or PR) to treatment. In a subgroup analysis of patients with measurable disease only, 23% of patients in the fulvestrant 250-mg arm and 24% of patients in the anastrozole arm responded to treatment.

**Reviewer comment:** Minor discrepancies between the reviewer's response assignments and the applicants' resulted in negligible differences in calculated response rates. In this study, response rates were similar in the two treatment arms by both the applicant's and FDA's response analyses in 3 subgroups: ITT per protocol, and measurable disease only.

The Applicant's and FDA statistical reviewer's analyses of odds ratios and differences in response rates are summarized in the following table:

**Table 42: Summary of Applicant's and FDA's Odds Ratios [a] and Differences [b] in Best Objective Response Rates**

| Population | Analysis | Applicant's Estimated odds ratio (95.14% CI) | FDA Estimated odds ratio (95.4% CI) | Applicant estimated % difference in response rates (95.14% CI) | FDA Estimated % difference in response rates (95.4% CI) |
|---|---|---|---|---|---|
| ITT | Adjusted [c] | 1.01 (0.59, 1.73) p = .9647 | 1.03 (0.59, 1.77) p = .9273 | 0.17 (-6.31, 9.30) | NA |
| | Unadjusted [d] | 1.0 (0.59, 1.68) p = .9895 | 1.0 (0.59, 1.70) p = .9957 | -0.05 (-6.34, 8.77) | -0.02 (-6.28, 8.87) |
| PP | Adjusted | 1.05 (0.58, 1.91) p = .8622 | 1.03 (0.56, 1.91) p = .9197 | 0.76 (-6.43, 11.26) | NA |
| | Unadjusted | NA | 0.98 (0.55, 1.77) p = 0.9543 | NA | 0.29 (-6.51, 10.36) |

[a] An odds ratio of greater than 1 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg.
[b] A difference in response rates of greater than 0 indicates that fulvestrant 250 mg is associated with higher response rate compared with anastrozole 1mg.
[c] Logistic-regression 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.
[d] Primary Analysis. Logistic-regression model without baseline covariates.

### (c) Non inferiority analysis

There was no statistical difference in response rates between treatment arms. Based on regulatory precedent, demonstration of non inferiority of response required ruling out a deficiency in response rate of greater than 10%. The applicant's primary analysis was an adjusted logistic regression model that included seven prognostic factors. Thisapplicant adjusted analysis is questionable because the applicant assumed a constant difference in response rates across all possible combinations of prognostic factors, an assumption which needs to be verified. The FDA statistical reviewer performed an unadjusted analysis without using a logistic regression model as a sensitivity analysis. Whether analysis was performed on the ITT or PP population, adjusted or unadjusted analysis, logistic regression model or other sensitivity analysis, the estimated difference in response rates did not exceed –10%, thereby ruling out a 10% loss of response and demonstrating non inferiority according to the specified criteria.