CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-344

Medical/Statistical Review(s)

CLINICAL REVIEW

NDA 21-344:

New Drug Application

Fulvestrant (FASLODEX™)

FDA Center for Drug Evaluation and Research

Division of Oncology Drug Products

Combined Medical/Statistical NDA Review

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Clinical Review for NDA 21-344

1. Executive Summary

a. Recommendations

i. Recommendation on Approvability

We recommend the approval of fulvestrant (FASLODEX), 250 mg monthly by the intramuscular route, for the treatment of Proposed Labeling. This recommendation is based on a review of clinical and non clinical studies submitted in support of the NDA application as well as a review of the literature.

ii. Recommendation on Phase 4 Studies and/or Risk Management Steps

We recommend the following phase 4 commitments:

- To update survival data on the randomized studies #20 and #21 and to submit a study report when the data are mature.
- To perform a study of the effect of ketoconazole on fulvestrant pharmacokinetics. This study may be conducted using the intravenous formulation of fulvestrant. to allow for fewer patients (the IV route has less inter-individual variability than the IM route) and to increase safety during performance of the study.
- The sponsor will submit all error reports, both potential and actual, that occur with the drug Faslodex for a period of two years following the date of drug approval. Potential errors include any reports of potential circumstances or events that have the capacity to cause error and should be reported in a quarterly summary. Actual errors include any preventable event that reached the patient and caused harm or reached the patient and did not cause harm. Additionally, the sponsor will report actual errors that occurred but did not reach the patient, such as if the wrong drug was prepared but system checks prevented the drug from reaching the patient or being administered to the patient. All actual errors should be submitted as a 15-day report regardless of patient outcome. The sponsor will agree to provide yearly reports of potential and actual errors occurring with the drug, Faslodex, to the Agency for two years following the date of drug approval.

b. Summary of Clinical Findings

This NDA includes information on two randomized (phase 3) trials and 24 supportive clinical trials. The phase 3 randomized trials were designed to compare the effectiveness and safety of Faslodex (fulvestrant) with that of Arimidex (anastrozole) in the treatment of advanced breast cancer in postmenopausal women. The supportive trials were designed to provide supplementary information such as data on the pharmacokinetics and effects of fulvestrant in different populations and the mechanism of action of fulvestrant on breast tumors. Fulvestrant and anastrozole are manufactured by Astra Zeneca Pharmaceuticals, the NDA applicant. Fulvestrant is a monthly injection and anastrozole is a tablet given daily by mouth. The applicant claims that the data submitted demonstrate that fulvestrant is safe and effective in the treatment of advanced breast cancer in postmenopausal women, and that fulvestrant works by a different mechanism than tamoxifen and represents a new class of drugs for the hormonal treatment of breast cancer.

i. Brief Overview of Clinical Program

The Faslodex clinical trial program consisted of 26 trials in which 854 subjects received various formulations and schedules of fulvestrant. One thousand fourteen patients were randomized to treatment in the pivotal efficacy trials, and data from 851 postmenopausal women with advanced breast cancer was included in the primary efficacy intent to treat (ITT) analyses. Four hundred twenty three patients received monthly injections of 250 mg of fulvestrant for a median of six months and an equal number received anastrozole tablets. 163 patients were randomized to receive fulvestrant 125mg, however this dose was shown in a planned interim analysis to be less effective than 250 mg and these patients were not included in the ITT population efficacy analysis. A total of 1277 subjects received treatment in the clinical trials and were included in the evaluations of safety and tolerability.

The trial population for randomized efficacy trials #0020 and #0021 consisted of postmenopausal women with advanced breast cancer who had recurrence or progression of disease and required treatment because of either relapse after adjuvant tamoxifen therapy or progression after first-line treatment with tamoxifen for advanced disease. Entry characteristics were similar between treatment arms in both trials. Approximately 75% of the patients were reported to be estrogen receptor positive, with slightly higher percentages in the North American trial #0021and in the anastrozole arm of the European trial #0020. The remainder of the patients showed clinical evidence of hormone sensitivity. The median age was 63, the population was predominantly Caucasian, and 90% had a relatively good activity tolerance with a WHO performance status of 0 or 1. Over 96% had been previously treated with Tamoxifen, either in the adjuvant setting or as treatment for metastatic disease. Sixty-two percent of patients on the North American trial #0021 and 42% of patients on the European trial #0020 had been previously treated with conventional cytotoxic chemotherapy.

ii. Efficacy

Table 1: Summary of Efficacy results

	Trial 0020 Europe - open label		Trial 0021 US -double blind	
End point	Fulvestrant 250 mg (n=222)	Anastrozole I mg (n=229)	Fulvestrant 250 mg (n=206)	Anastrozole Img (n= 194)
Overall Response Rates (ITT Population)				
FDA CR + PR	45 (20.3%)	34 (14.9%)	35 (17.0%)	33 (17.0%)
Estimated % difference in Response Rates[a]				
	7.35		0.29	
95.4% CI	(-0.39, 17.98)		(-6.51, 10.36)	
Median Time to Progression (ITT)				
Median TTP (days)	166	156	165	103
Hazard ratio[b]	0.98 (p=0.84)		0.92 (p=0.43)	
2-sided 95.4% CI	(0.79 to 1.21)		(0.74 to 1. 14)	

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

[b] A hazard ratio of less than 1 indicates that fulvestrant 250 mg is associated with a longer time to disease progression, as compared with anastrozole 1mg.

Efficacy end points were evaluated in the randomized trials 0020 and 0021, the Phase III controlled trials submitted for registration. Patients received either the long acting intramuscular injection (I.M.). formulation of fulvestrant or daily anastrazole tablets. The primary objective of the studies was to demonstrate that patients treated with fulvestrant had a decreased time to disease progression (superiority in time to progression) compared with anastrozole. After initial data analysis revealed that the study data failed to show a significantly longer TTP in the fulvestrant treatment group, the applicant proposed a non-inferiority analysis of TTP and response rate, to demonstrate that fulvestrant was no worse than anastrozole in terms of TTP and response rate. When evaluating hormonal drugs for the treatment of breast cancer, demonstration of non-inferiority based on the endpoint of TTP can not provide sufficient basis for marketing approval, because the effect of the active control drugs on TTP is not known with any degree of certainty. Therefore, demonstration of non-inferiority in response rates has provided the basis for previous NDA approvals for the hormonal treatment for advanced breast cancer. The FDA agreed to the applicant's proposed analysis, provided that TTP was considered to be a supportive endpoint and not the primary objective.

Results

Superiority in any endpoint was not shown for fulvestrant over anastrozole. The FDA medical reviewer analyzed the submitted NDA response data using the primary electronic datasets and the results were similar to those reported by the applicant. FDA-adjudicated response rates in the European trial #0020 were 20.3 % in the fulvestrant arm and 14.9% in the anastrozole arm. In the North American trial #0021, the FDA response rates were 17% in both arms. A few patients with

tumors that tested negative for estrogen or progesterone receptors or receptor status unknown also appeared to respond to therapy with fulvestrant or anastrozole. Although median time to progression (TTP) was somewhat longer in the fulvestrant arm in trial #0021, analysis of Kaplan – Meier survival curves were similar between arms in both trials and did not suggest any clinically meaningful differences between treatment arms. Analysis of the difference in response rates by both the applicant and FDA demonstrated that in each of the 2 pivotal trials for the NDA a deficiency in response of greater than 10% with respect to anastrozole was ruled out with two-sided 95.4% confidence intervals (CI's) thereby achieving the accepted criterion for non inferiority. Some patients with unknown hormone receptor status and a few patients who were estrogen and progesterone receptor negative responded to fulvestrant in these trials. Faslodex may be effective in an occasional patient who is hormone receptor negative.

The FDA and applicant agreed that the upper 1-sided 97.5% confidence limit for the hazard ratio for TTP did not exceed 1.25 and a potential deficiency in time to progression of more than 25% for the experimental treatment was also ruled out. The applicant claimed that this showed that fulvestrant was "non-inferior" to anastrozole for TTP. However there is no accepted standard for non-inferiority of time to progression in this setting and therefore this analysis was considered supportive of, but not definitive proof of, fulvestrant efficacy. No statistically significant differences were found between treatment arms in any of the secondary endpoints including survival, duration of response, clinical benefit, and deterioration of quality of life.

Preliminary results of trial #25 comparing fulvestrant with tamoxifen in the initial treatment of metastatic breast cancer showed a trend toward longer time to progression in the tamoxifen treatment group. Therefore, fulvestrant should not be used for the initial treatment of hormone-sensitive breast cancer.

iii. Safety

Overall, fulvestrant 250 mg was well tolerated in postmenopausal women with locally advanced or metastatic breast cancer. Relatively few serious adverse events were considered drug-related in either treatment group. The most common drug-related events (>10%) were injection site reactions and hot flashes. Common events (1-10%) included asthenia, headache, and gastrointestinal disturbances including nausea, vomiting, and diarrhea. Rash and urinary tract infections were also reported. An increase in joint disorders reported in patients treated with anastrozole was the only specific finding.. The most common side effects noted were weakness or asthenia, headache, flushing or vasodilatation, back pain and gastrointestinal disturbances including nausea, vomiting, and diarrhea.

Both the number and types of adverse events were similar between fulvestrant- and anastrozole- treated patients in the pivotal controlled efficacy trials. Local injection reactions with mild transient pain and inflammation were more common in patients given the 2 x 2.5 mL injections compared with patients given the single 5 mL injection (27% vs. 8%). An increase in thromboembolic phenomena (blood clots) reported at interim analysis in the fulvestrant

treatment group was not found in the final safety analysis. Most serious adverse events (SAE's) occurred within the first 24 weeks of fulvestrant treatment, and there was no obvious relationship between the occurrence of SAE's and patient age.

iv. Dosing

The proposed dose of 250 mg monthly by intramuscular injection is supported by preclinical, pharmacokinetic, pharmacodynamic, and clinical efficacy data. Higher doses were not tested because of solubility factors and the necessity to keep the volume of injection below 5cc. The 125mg dose was not efficacious. Comparability between two 2.5cc injections and the single 5cc monthly injection were supported by pharmacokinetic and clinical efficacy data. The 250 mg intramuscular dose was well tolerated, except for reports of local injection site reactions, which were increased in the group in which two 2.5 ml injections were administered.

v. Special Populations

Fulvestrant was studied in a population consisting primarily of elderly postmenopausal women. Because this drug blocks the action of estrogen, it is contraindicated in pregnancy. Short-term pharmacokinetic and endocrine studies were completed in a small number of normal male volunteers and healthy premenopausal women. Fulvestrant has not been studied in the pediatric population. Because fulvestrant is metabolized primarily in the liver, a study of pharmacokinetics in patients with severe liver impairment would be helpful to determine the safety of fulvestrant in these populations. The predominant population was Caucasian. A study of efficacy in other populations might provide data to confirm efficacy in different ethnic populations.

2. Clinical Review

a. Introduction and Background

i. Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

FASLODEX® (fulvestrant) (ICI 182,780) injection for intramuscular administration is a steroidal antiestrogen. The proposed indication is for

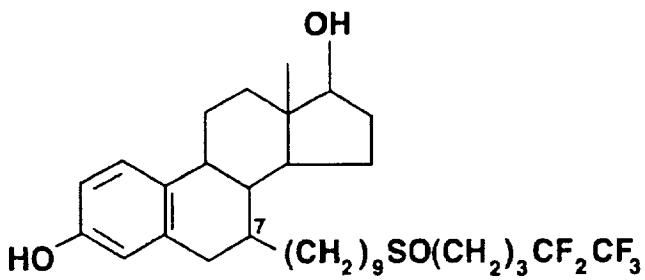
DRAFT

The recommended dose is 250 mg to be

administered intramuscularly into the buttock at intervals of one month as either a single 5 mL injection or two concurrent 2.5 mL injection.

ii. Drug Chemical Structure

Figure 1: FASLODEX® (fulvestrant) (ICI 182,780)



iii. State of Armamentarium for Indication(s)

Existing hormonal treatments for advanced breast cancer

The goals of treating patients with metastatic breast cancer are to prolong survival, slow or halt disease progression, and enhance the patient's quality of life. In patients with estrogen receptor (ER)-positive cancers that are not progressing rapidly, hormonal therapy is generally the first treatment option. If a patient initially responds to an endocrine agent and then progresses, or if a patient has been previously treated in a adjuvant setting and then recurs, another endocrine agent may still provide benefit[1]. There are 3 main classes of hormonal treatments for breast cancer: antiestrogens such as tamoxifen and toremifene; progestins such as megesterol; and aromatase inhibitors such as anastrozole, letrozole, and exemestane. The applicant has suggested that fulvestrant represents a new class of hormonal treatments for breast cancer: estrogen receptor downregulators.

Tamoxifen.

The most clinical experience in the hormonal treatment for breast cancer is with the nonsteroidal antiestrogen tamoxifen (NOLVADEX™), which has been used not only as first-line treatment in advanced disease but as an adjuvant treatment following surgery. Tamoxifen has been used as first-line therapy for metastatic breast cancer for many years. Until recently, no other endocrine agent has shown superiority to tamoxifen in this setting. At usual daily doses of 20 to 40 mg, tamoxifen is effective in patients of different ages and different stages of disease, in

[1] Buzdar A., Semin Oncol. 2001 Jun;28(3):291-304.

both pre- and postmenopausal women, in patients with tumors designated as ER positive and unknown.[2] Although tamoxifen competes with endogenous estrogen for binding to ERs, its precise mechanism of action is elusive. The biological activity of tamoxifen ranges from full estrogen agonist to partial agonist to full antagonist which may account for undesirable effects, such as increased endometrial proliferation and a slightly increased risk of endometrial cancer.[3,4] Several researchers postulate that tamoxifen's ability to stimulate the estrogen receptor is partly responsible for the tamoxifen resistance that develops in some patients (as demonstrated in preclinical models).[5]

Treatment following progression on tamoxifen

In postmenopausal patients with disease progression following treatment with tamoxifen (or related nonsteroidal antiestrogens), the choice of next-step treatment includes progestins (eg, megestrol acetate and medroxyprogesterone) or aromatase inhibitors (eg, aminogluthetimide and anastrozole).

(a) Progestins

The beneficial effects of progestins in the treatment of advanced breast cancer are attributed to their ability to counteract or oppose the stimulatory effects of estradiol on tumor. However, drug-related adverse effects, notably weight gain, edema, and thromboembolic complications, pose additional health concerns and raise compliance issues.

(b) Aromatase inhibitors

Aromatase inhibitors offer an effective means of reducing estrogen production by inhibiting the enzyme aromatase (estrogen synthetase), which serves as the catalyst in the conversion of androgens to estrogens. In post-menopausal women, the principal source of circulating estrogen, estradiol, is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue, with further conversion of estrone to estradiol.The presence of aromatase in human breast tumors and surrounding stromal tissue may provide a local source as well.

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[2] Buzdar, AU. Tamoxifen's clinical applications: old and new. Arch Fam Med. 9:906-12, 2000.

[3] Jordan VC, Murphy CS. Endocrine pharmacology of antiestrogens as antitumor agents. Endocrinology Review 11:578-610, 1990.

[4] Graham JD, Bain DL, Richer JK, Jackson TA, Tung L, Horwitz KB. J Steroid Biochem Mol Biol74:255-9, 2000.

[5] Howell A, DeFriend D, Anderson E. Mechanisms of response and resistance to endocrine therapy for breast cancer and the development of new treatments. Rev Endocrine-Related Cancer 43:5-21, 1993.

(i) Aminoglutethimide

The nonspecific aromatase inhibitor aminoglutethimide has well-established efficacy, but even at conventional doses, it causes moderate toxicity and inhibits production of corticosteroids, making it necessary for patients to take supplemental corticosteroids. In addition, approximately one third of patients require mineralocorticoid replacement because of inhibited aldosterone production, and 5% require thyroxyine replacement because of reduced synthesis.[6] In the United States, aminoglutethimide is not approved for use in the treatment of breast cancer.

(ii) Anastrozole:

The nonsteroidal aromatase inhibitor anastrozole was the first to receive marketing approval from the FDA, "for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy." Two randomized double blinded phase 3 trials comparing 2 doses of anastrozole with megace were submitted for registration. A total of 764 postmenopausal women who had disease progression after treatment with tamoxifen for metastatic disease or as adjuvant therapy were enrolled. Some patients had also received prior chemotherapy as adjuvant or for metastatic disease. Most patients were ER +, a smaller fraction were ER unknown or negative. 262 patients were treated with anastrozole 1 mg; 248 patients with anastrozole 10 mg; and 253 patients with Megace 160 mg.

The primary endpoints of the two trials were objective response rate and TTP. Only patients with measurable disease could be considered partial responders. Objective response rates were calculated based on the Union Internationale Contre le Cancer (UICC) criteria.[7] Both trials included over 375 patients; demographics and other baseline characteristics were similar for the three treatment groups in each trial. [8] The efficacy results from the 2 trials showed no statistical differences between treatment arms in TTP, objective response rate, TTF or survival (see Table 2). Anastrozole subsequently received marketing approval for the first-line indication after it was shown to have at least non-inferior efficacy compared with tamoxifen.

Statistical Issues:

- Sample size calculations were based on the assumption of anastrozole superiority over megestrol acetate in both endpoints; however, superiority was not shown.

(iii) Letrozole:

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[6] Manni A. Clinical use of aromatase inhibitors in the treatment of breast cancer. Journal of Cellular Biology 1993;17G:242-6.

[7] UICC response criteria were incorporated into WHO (bidimensional) response criteria – see World Health Organization (WHO) Handbook for Reporting Results of Cancer Treatment. Geneva, WHO. 1979;48:7.

[8] Buzdar AU, Jonat W, Howell A, Jones SE, Blomqvist CP, Vogel CL, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study group. Cancer 1998;83:1142-52.

Letrozole (Femara® - Novartis) is a nonsteroidal aromatase inhibitor which was granted marketing approval in 1997 in the second line indication "for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy." Registration trials consisted of two randomized phase 3 multinational trials comparing 2 doses of letrozole (0.5, 2.5) with megestrol acetate in one study, and aminoglutethimide 250 mg b.i.d. (with corticosteroid supplementation) in the other study. A total of 552 postmenopausal women with disease progression after treatment with antiestrogens for metastatic disease or as adjuvant therapy were enrolled in the megestrol acetate trial and 557 patients in the aminoglutethimide study. Fifty-seven percent of patients were ER +, 43% were ER unknown or negative. The primary endpoints of the two trials were objective response rate and TTP. Response rate was significantly higher in the letrozole 2.5 mg arm compared with letrozole 0.5mg, with a trend for superiority ($p = 0.08$) compared with megestrol acetate. The comparison of letrozole 2.5 mg with aminoglutethimide did not show any significant difference in tumor response. The risk of progression was significantly lower for letrozole in both trials with a hazard ratio (letrozole to megesterol) of 0.77 ($p = 0.03$) in the megestrol acetate trial and a hazard ratio (letrozole to aminoglutethimide) of 0.74 ($p= 0.02$) in the aminoglutethimide trial. Letrozole therefore received marketing approval "for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy."

(iv) Exemestane:

Exemestane (AROMASIN® - Pharmacia \& Upjohn) is an orally bioavailable irreversible steroidal aromatase inactivator. Examestane received marketing approval in 1999 "for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy." One pivotal multicenter, randomized, double-blind trial and 2 supportive phase 2 studies supported approval. The pivotal trial compared exemestane 25 mg administered once daily to megestrol acetate 40 mg four times daily. A total of 769 postmenopausal women who had disease progression after treatment with tamoxifen for metastatic disease or as adjuvant therapy were enrolled in the pivotal trial. Some patients had also received prior chemotherapy as adjuvant (28%) or for metastatic disease (16%). Sixty-seven percent of the women were ER positive and 32% were receptor unknown.

The primary endpoint of the trials was objective response rates, which were found to be 15% in the examestane arm and 12% in the megace arm. Response rates from the single-arm trials were a little higher: 23.4% and 28%. These efficacy results failed to show that the exemestane response rate was significantly greater than that of megace. The pivotal trial was powered to show non-inferiority, defined in the protocol in terms of the difference between the tumor objective response in the two groups: registration was to be allowed on the basis of demonstration that the upper limit of the two-sided 90% C.I. for the difference in response rates (Megace minus Exemestane) was < 25% of megace response rate. The difference in response rate, megace minus exemestane, was 2.6%, and the upper limit of the corresponding confidence interval did not exceed the pre-specified margin. Therefore, the criterion for non-inferiority was met.

Secondary endpoints included multiple time to event measures (TTP, TTF, Time to response), duration of response and survival. The protocol stated that for TTP, a hazard ratio (examestane to megace) of <1.25 was evidence of non-inferiority. There was a trend towards a longer TTP (medians of 20.3 versus 16.6 weeks, p=0.037). P-values were considered uninterpretable and were excluded from the label as the applicant did not adjust for multiplicity of endpoints. There was a trend towards a longer median survival with exemestane by logrank test (p=0.039), but this analysis bears the same issues of multiplicity as the TTP analysis. There were insufficient events at the time of NDA submission to make a conclusion regarding survival, with 73% censored observations on exemestane and 68% on megestrol acetate. The robustness of the TTP findings were questioned because (1) the applicant did not adjust for multiplicity of secondary endpoints, (2)the treatment code breaking was continuous and (3) in the US (the second largest accruing country) the direction of TTP was favoring Megace.

(v) Conclusions

To date, three selective aromatase inhibitors have been granted marketing approval by the FDA for the treatment of metastatic breast cancer following treatment with tamoxifen (Table 2). Exemestane is an irreversible steroidal inhibitor of aromatase; anastrozole and letrozole are non steroidal selective inhibitors. The populations for these trials consisted of postmenopausal women with metastatic breast cancer who had been previously treated with tamoxifen. Most tumors in the patients accrued to these registration trials were positive for hormonal receptors, although a significant minority were receptor unknown. Comparators have been either the progestin megesterol, or the nonspecific aromatase inhibitor aminoglutethimide. The distinct mechanism of action of hormonal therapy as compared with cytotoxic chemotherapy has provided a biologic rationale for the incorporation of different endpoints in clinical trials with hormonal treatments for metastatic breast cancer as compared with cytotoxic chemotherapy. Superiority in time to progression is accepted as a primary endpoint for registration. Stable disease for >24 weeks was included as a secondary endpoint in the exemestane and arimidex labels based on data derived from randomized trials, and duration of response was included in the exemestane and letrozole labels.

Superiority of TTP was the primary protocol objective in two of the NDA submissions, however this was demonstrated in only one submission (Letrozole). Since the control treatments for these studies have no known proven consistent effect on TTP, non-inferiority in time-to-progression is not an acceptable basis for marketing approval. Approval was granted for anastrozole, toremifene, and examestene on the basis of non-inferiority of response rates. Non-inferiority of response rates was defined in the anastrozole second line trial against megace and in the toremifene first-line trial against tamoxifen, by ruling out a deficiency in response rate of greater than 10%, with one-sided 97.5% confidence limits. For examestene, non-inferiority was defined when the upper limit of the two-sided 90% C.I. for the difference in response rates (Megace minus Exemestane) was < 25% of megace response rate.

Table 2 Hormonal Drugs Approved for the Second Line Treatment of Metastatic Breast Cancer

Hormone	Anastrozole Arimidex®				Exemestane Aromasin®		Letrozole Femara®	
Number of trials	2				1 Pivotal, 2 Phase-2		1 Pivotal, 1 confirmatory	
Design	Randomized controlled				Randomized double blind		Randomized controlled	
Objective	Superiority (TTP)				Non-inferiority (RR)		Superiority (TTP)	
Sample Size	764				769		552	
	Trial 0004		Trial 0005		Exem	Mega	F	M
	A	M	A	M				
Dose (mg)	1	160	1	160	25	160	2.5	160
ER + status	85%	79%	62%	58%	67%	68%	57%	57%
Response Rate %	10%	5.5%	10%	10%	15%	12%	24%	16%
TTP median days	170	151	132	120	142	116	170	168

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b. Important Milestones in Product Development

(1) Summary of developmental history

Fulvestrant was developed as a result of the search for a specific or "pure" antiestrogen with high affinity for ER without any agonist effects.[9] The physicochemical properties of fulvestrant, and particularly its low aqueous solubility, necessitated the development of unusual formulations to allow administration to animals and humans. Oral delivery was explored in animals and man using a range of formulation types, but it was not possible to achieve adequate bioavailability by this route. A "short-acting " SA" formulation—intended for daily im administration—was developed and used in early trials that examined fulvestrant's pharmacokinetics and pharmacodynamics, as well as safety. This formulation produced rapid release of fulvestrant from the injection site. A depot long-acting "LA" formulation for intramuscular administration, the proposed commercial formulation, was also developed and evaluated in subsequent safety and efficacy trials. This formulation produced sustained release of fulvestrant from the injection site over a period time compatible with the proposed 1-month dosing interval.

(2) Regulatory history:

(a) IND filed 12/9/96

(b) End-of-Phase II meeting 24 January 1997.

- The FDA and applicant agreed upon the Phase III clinical trial design with 2 pivotal trials: 9238IL/0021 and 9238IL/0020 (double-blind double-dummy and open-label, respectively). Anastrozole was accepted as the comparison agent. The FDA recommended but did not require that one trial include megace as comparator. Time to progression was accepted as the primary end point only if superiority was demonstrated. Time to response should also be evaluated.
- Regarding the quality-of-life (QOL) assessment, the FDA recommended a formal longitudinal analysis. The reviewer asked for clarification on which patients would participate in QOL assessments. (Clarification was provided by the applicant: all patients in

[9] Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182,780 (Faslodex): development of a novel, "pure" antiestrogen. Cancer. 2000 Aug 15;89(4):817-25.

Trial 0021 and patients in Trial 0020 from countries in which the QOL tool had a validated translation.)

- The statistical reviewer raised the issue of stratification and questioned whether the Cox model was an appropriate method of analysis if the applicant had concerns about imbalance. The reviewer suggested the Log Rank test as an alternate test if patients were not going to be stratified. (Ultimately, both methods were used.)
- The LA intramuscular formulation and diastereoisomer were acceptable to the CMC reviewers. Pharmakokinetic studies of both the i.v and im (LA) formulations were accepted.
- The applicants plan for a hepatic impairment study with the iv formulation was accepted. No specific studies in elderly patients were needed, since the accrual in this population was anticipated to be sufficient for regulatory purposes.

(c) Team meetings/ telecons 4-13-98, 10-4-99, 3-24-00

- Statistical Plans for a double blinded first line registration trial in advanced breast cancer were discussed. The proposed doses were agreed upon.
- The FDA agreed that the approach described by the applicant for blinded independent review of response data from Trials 0020 and 0021 was acceptable, and requested clarification on how discrepancies between responders identified by the investigators and those identified by the computer algorithm will be reconciled. The applicant clarified that discrepancies between responders identified by the investigators and those identified by the computer algorithm would trigger independent review. FDA noted that independent review of Phase 3 data was not required. FDA further stated that a blinded review of data from Trial 0020 would be helpful but was not essential.

(d) Pre NDA meetings 8-3-2000, 11-9-00, 11-15-00,

- The indication sought for FASLODEX is, [redacted]
- The FDA agreed to submission of the NDA without a specific hepatic impairment study. Appropriate labeling will be sought for patients similar to those treated in Trials 0020 and 0021, including those with mild-moderate hepatic impairment related to liver metastases.
- The FDA stated that a combined efficacy analysis of the pivotal trials, Trials 0020 and 0021, would not be acceptable. Trials 0020 and 0021 were designed as stand-alone trials and, therefore, separate analyses should be conducted. Any combined efficacy analysis would be considered exploratory. A combined safety analysis is acceptable.
- Given that the results of Trial 0020 and 0021 did not show fulvestrant superiority over anastrozole in time to progression, the applicant cited previous US regulatory submissions for hormonal treatments for advanced breast cancer (FARESTON [toremifene], October 1995; ARIMIDEX [anastrozole], September 2000) which allowed registration based on non inferiority analysis. These submissions required that the upper 1-sided 95% confidence limit for the hazard ratio for time to progression not exceed 1.25 in order to demonstrate noninferiority; ie, a potential deficiency in time to progression of more than 25% for the experimental treatment should be ruled out.

- The FDA stated that, based on prior regulatory experience with this class of drugs, a non-inferiority analysis of response rate was acceptable. Non inferiority in time to progression could not provide the primary basis for marketing registration since the effect of anastrozole treatment on time to progression was not sufficiently well established.
- FDA further stated that, in terms of tumor response, the 2 regulatory submissions cited above required a deficiency in response rate of greater than 10% to be ruled out in order to demonstrate noninferiority, and that a one-sided 97.5% CI should be used in the non-inferiority analyses.

(e) NDA submitted 3-28-01 electronic document

- CMC supplement submitted July 19, 2001
- 4 month safety update submitted July 20, 2001
- Survival Update submitted Aug 9, 2001
- Survival datasets submitted Aug 28, 2001
- Updated response rates and TTP submitted Sept 13, 2001
- Safety data from trial #25 submitted Oct 18, 2001
- Responses to FDA questions submitted Oct 29, 2001

c. Important Issues with Pharmacologically Related Agents

Safety issues seen with other hormonal treatments for breast cancer include, nausea, hot flashes, fluid retention, weight gain, ocular toxicity, endometrial carcinogenicity, and thromboembolic phenomena.

d. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

i. Pharmacology/Toxicology

(1) Brief Overview of Preclinical Studies

Multiple non-clinical toxicity studies of up to 6 and 12 months duration in rats and dogs, respectively were submitted to support the use of fulvestrant (IM) in the treatment of locally advanced and metastatic breast cancer in post-menopausal women. Studies to determine the

genotoxicity, carcinogenicity, antigenicity and local tissue irritant effects were also submitted. The high doses used in the long-term studies in rats (10 mg/rat/15d for 6 months) and dogs (40 mg/kg/28d for 12 months), based on body surface area conversion were approximately 4 fold higher than the proposed clinical dose of 250 mg/month. Drug exposure ($AUC_{0\text{-}28,\ 30\ days}$) ranged from 4-10 fold and C_{max} ranged from 9-38 fold higher in animals than the values observed in clinical testing.

(2) Absorption and Elimination

Fulvestrant was well absorbed and widely distributed following IM administration in rats. Metabolism was qualitatively similar in rats, dogs, and human with primary route of elimination in feces. Fulvestrant crosses the placenta following single intramuscular doses of 6.0 mg/m^2 in rats and 3 mg/m^2 in rabbits resulting in fetal tissue drug concentrations 2 hours after dosing of 76 and 97% compared to maternal plasma, respectively. Fulvestrant is found in rat milk at levels significantly higher than in rat plasma (12-fold after administration of 12 mg/m^2).

(3) Reproductive toxicity

In all the intramuscularly dosed toxicology studies, effects upon the reproductive tract and other organs sensitive to hormones were observed consistent with the mechanism of action of fulvestrant. In female rats and dogs, atrophy of the uterus, cervix, and vagina with a loss of normal cyclical estrous activity was observed. In the ovary increased late stage and cystic Graafian follicles, loss of mature corpora lutea, and reduced vacuolation of the interstitial cells were observed. There was some evidence of reversibility of these ovarian changes (but not complete recovery) following dose cessation. In male rats, after 6 months dosing, a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides were seen. Changes in the testes and epididymides remained after a 20-week recovery period.

In female rats, fulvestrant ($\geq$0.06 mg/m^2/day) administered prior to mating and until day 7 of gestation, caused a reduction in female fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.006 mg/m^2/day. Restoration of female fertility was evident following a withdrawal period of dosing at 12 mg/m^2/day. Further, a dose of 12 mg/m^2/day during organogenesis resulted in maternal vaginal bleeding, and delay and prolongation of parturition in rats. There was an increase incidence of post-implantation loss in rabbits receiving levels of $\geq$3 mg/m^2/day during organogenesis.

Fulvestrant caused an increased incidence of fetal abnormalities in rats. Tarsal flexure of the hindpaw at 12 mg/m^2/day and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses $\geq$ 0.6 mg/m^2/day were observed when ICI 182,780 was administered during the period of organogenesis. ICI 182,780 also caused an increased incidence of fetal abnormalities in rabbits (backwards displacement of the pelvic girdle, extra 13th ribs, and 27 pre-sacral vertebrae at 3 mg/m^2/day) when administered during the period of organogenesis. This study in rabbits was considered inadequate to fully define possible adverse effects on fetal development due to the lack of maternal toxicity at the highest dose (3 mg/m^2/d) and an incomplete fetal assessment at the low and intermediate doses tested.

(4) Carcinogenicity

ICI 182,780 showed no antigenic, mutagenic, or clastogenic potential. However, in a 2-year carcinogenesis study in female and male rats, an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen.

(5) Safety Issues Relevant to Clinical Use:

(a) Clinical Indications

Both *in vitro*[10] and *in vivo*[11] studies have shown that tumors which eventually develop resistance to ICI 182,780 (fulvestrant) will not subsequently respond to tamoxifen. Thus, a treatment sequence in which ICI 182,780 precedes tamoxifen may not be indicated. This information should be included in the label and has repercussions for indications in which patients may be treated first with ICI 182,780.

(b) Potential Drug Interactions

Preclinical and in vitro data suggest that fulvestrant has minimal potential to be involved in drug interactions based on the inhibition/ induction of human CYP enzymes. In man, fulvestrant is likely to be cleared by a number of metabolic routes with sulfation representing a principal pathway, suggesting that coadministration of fulvestrant with known inhibitors or inducers of hepatic P450 isozymes would not be expected to have significant effect on fulvestrant clearance. Results from pharmacokinetic trials with rifampin, a known CYP inducer, and with midazolam, a known CYP inhibitor, confirmed that coadministration of fulvestrant with these types of agents were unlikely to have a significant effect on exposure to fulvestrant in clinical use.

[10] Brunner N, Boysen B, Jirus S, Skaar TC, Holst-Hansen C, Lippman J, Frandsen T, Spang-Thomsen M, Fuqua SA, Clarke R, MCF7/LCC9: an antiestrogen-resistant MCF-7 variant in which acquired resistance to the steroidal antiestrogen ICI 182,780 confers an early cross-resistance to the nonsteroidal antiestrogen tamoxifen. Cancer Res 1997 Aug 15;57(16):3486-93.

[11] Johnston SR, Lu B, Dowsett M, Liang X, Kaufmann M, Scott GK, Osborne CK, Benz CC, Comparison of estrogen receptor DNA binding in untreated and acquired antiestrogen-resistant human breast tumors. Cancer Res 1997 Sep 1;57(17):3723-7

e. Human Pharmacokinetics and Pharmacodynamics

i. Pharmacokinetics

The pharmacokinetics and disposition of fulvestrant following single doses and multiple once-monthly doses have been characterized both in healthy volunteers and in patients. Table 3 lists the PK studies performed in healthy females:

Table 3: PK Studies in Healthy Female Volunteers

9238HQ/0001	An initial tolerance/PK study of a short acting dose of ICI 182,780 in healthy female volunteers
Design	Randomized, double-blind, placebo-controlled Part 1: parallel-group, ascending dose Part 2: crossover
Purpose	To assess the tolerability and PK of SA im fulvestrant
9238IL/0012	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intravenous dose of 10 mg [^{14}C]-ICI-182,780 in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized, radiolabeled PK study
Purpose	To assess metabolism, excretion, and PK of a single iv dose
9238IL/0029	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intramuscular dose of 18 mg [^{14}C]-ICI 182,780 (ZD9238), short-acting formulation, in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized
Purpose	to assess the metabolism, excretion and PK of a single im dose of 18 mg of [14C]-fulvestrant
9238IL/0038	An open, non-randomized trial to compare the pharmacokinetics of ICI 182,780 (ZD9238) in healthy male, pre-menopausal female and post-menopausal female volunteers
Design	Open, nonrandomized, parallel-group
Purpose	To compare the PK of fulvestrant in healthy men and pre- and postmenopausal volunteers
O-15-11	Phase I Clinical Study of ICI 182,780 - Single intramuscular administration in postmenopausal healthy women
Design	Open-label, single ascending dose levels of 25, 50, 125 and 250 mg
Purpose	To investigate the tolerability, endocrine effect, and PK of a single im injection of LA fulvestrant (Japan)
9238IL/0029	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intramuscular dose of 18 mg [^{14}C]-ICI 182,780 (ZD9238), short-acting formulation, in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized
Purpose	to assess the metabolism, excretion and PK of a single im dose of 18 mg of [14C]-fulvestrant

In clinical use, drug exposure is controlled by the properties of the LA IM injection - the ratio of Cmax to Ctrough for a 5 mL IM injection and a 28-day inter-dose interval is approximately 2.5.

- On a Q 28-day regimen, levels approach approximate steady-state after 3 doses.
- The pharmacokinetics of fulvestrant 250 mg were shown to be similar when administered as either a single 5-ml or as two 2.5-ml injections.
- No clear relationship has been established between efficacy measurements (time to progression, objective response) and pharmacokinetic parameters such as Cmax, Cmin, AUC, and clearance.

- The general pharmacokinetics are:
  - Fulvestrant is rapidly distributed following administration by IV infusion, with plasma concentrations decreasing rapidly in a multiexponential fashion. Estimates of mean terminal elimination half-lives range from approximately 14.0 to 18.5 hours.
  - Fulvestrant is rapidly cleared (>10 ml/min/kg) and renal elimination is low (i.e. <1%).
  - Fulvestrant is extensively metabolized.
- No meaningful differences in the pharmacokinetics are apparent between male and either pre- or postmenopausal female subjects following administration of a single IV dose, nor between male and postmenopausal female subjects following IM administration (irrespective of age).
- Fulvestrant has been shown to be highly bound (99%) to plasma proteins (predominantly lipoproteins) and to have a large steady-state volume of distribution (approximately 3 to 5 L/kg), which suggests that the distribution of the compound is largely extravascular.
- Preclinical studies with human P450 isoenzymes and results from clinical pharmacokinetic trials involving the co-administration of fulvestrant with midazolam or rifampin suggest that
  - Therapeutic doses of fulvestrant have no inhibitory effects on cytochrome P450 enzymes
  - The clinical pharmacokinetics of fulvestrant are unlikely to be affected by P450 inducers or inhibitors.
- There was no apparent effect caused by renal insufficiency or mild hepatic impairment on the pharmacokinetics of fulvestrant. It is possible that in subjects with more severe hepatic impairment, clearance may be reduced. However, because the pharmacokinetics of the LA

IM formulation are controlled by slow drug release, only small changes in plasma fulvestrant concentrations would be anticipated.

- No differences were seen in fulvestrant clearance among Black, Hispanic, native Japanese, or White subjects.
- The 17-keto and sulfone metabolites of fulvestrant found in human plasma, and formed in the rat and the dog (but not in the plasma in these species), show no estrogenic activity. Only the 17-keto compound demonstrates a level of antiestrogenic activity of the same order of magnitude as fulvestrant and its activity is 4.5-fold lower than that of the parent compound.
- A variety of pharmacodynamic endpoints were studied. Generally, the results support that fulvestrant is an estrogen receptor antagonist that acts primarily peripherally.

ii. Pharmacodynamics

Pharmacology studies show that fulvestrant binds to estrogen receptors in a competitive manner, with a high affinity comparable with that of estradiol. Also, the drug's mode of action appears to lead to downregulation of estrogen receptor protein. The applicant claims that, in contrast to all other antiestrogens in clinical use, fulvestrant treatment leads to rapid loss of estrogen receptors and thus is termed an "Estrogen Receptor Downregulator" whose characteristics include a high binding affinity for the estrogen, an absence of stimulatory (estrogen-agonist) activity on estrogen target tissues such as the uterus, and the capacity to block the actions of estrogens and of partial-agonist antiestrogens like tamoxifen. Fulvestrant is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer cells and tamoxifen-resistant cells *in vitro*. Fulvestrant blocks the tropic actions of endogenous and exogenous estrogens in rodents and monkeys, and of tamoxifen in the rat. In a series of *in vivo* xenograft studies, fulvestrant prevents the establishment of tumors from xenografts of human breast cancer cells in nude mice, inhibits the growth of established estrogen-sensitive xenografts and-inhibits the growth of tamoxifen-resistant breast tumors.

Table 4 lists the clinical studies submitted to the NDA examining the effects of fulvestrant on the endometrium of healthy females:

Table 4 : Trials examining effects on the endometrium of healthy females

HQ/0003	An Open, Randomized Study to Examine the Effect of Seven Days Treatment with the Short-Acting Formulation of ICI 182,780 on Endometrial Growth in Premenopausal Women (Patient Volunteers) Scheduled for Hysterectomy for Benign Gynecological Conditions
IL/0036	A Phase I Trial to Assess the Antioestrogen Effect of ICI 182,780 (ZD9238) on the Female Reproductive Tract in Healthy Postmenopausal Female Volunteers
IL/0019	A Randomised, Placebo Controlled, Dose-Ranging Trial Comparing ICI 182,780 With Zoladex™ in Patients With Uterine Fibroids Awaiting Hysterectomy

(1) Clinical Trials in Healthy Postmenopausal Women

(a) Endometrial effects:

In Trial 0036, a Phase I trial to assess the antiestrogenic effect of fulvestrant on the reproductive tract, 30 postmenopausal healthy female volunteers were given single LA im doses of either 125 (n=10), or 250 mg fulvestrant (n=10), or matched placebo (n=10). In the screening phase of the trial, the women were shown to have an estrogen-responsive endometrium by assessing their response to 14 days of treatment with 20 µg ethinyl estradiol. The volunteers were subsequently administered a single fulvestrant injection and after 2 weeks on fulvestrant alone were given 20 µg ethinyl estradiol, once daily for 14 days, as an estrogen challenge.

Endometrial thickness was measured by ultrasound before the trial, during screening, before dosing on Day 1 (baseline), on Days 14 and 28 (ie, at the end of fulvestrant treatment and estrogen challenge, respectively), and at Day 42 (post-trial). Fulvestrant, at a dose of 250 mg, successfully antagonized the normal endometrial stimulatory effect of estrogen. Although this was only a short-term trial, fulvestrant did not demonstrate any agonist effect as evidenced by the absence of any endometrial response over the first 14 days of the trial.

(b) Endocrine effects

In Trial 0004 (Part 2), one group of women were given a single injection of 100 mg fulvestrant plus up to 5 injections of 250 mg fulvestrant (1 per 4 weeks), and a second group of women were given between 2 and 6 injections (ie, for 2 to 6 months) of 250 mg fulvestrant. Plasma concentrations of FSH, LH, and SHBG were measured at 4-weekly intervals. From trial entry to Month 6, FSH levels rose from a mean of 33.1 to 55.7 IU/l, LH concentrations rose from a mean of 27.2 to 42.2 IU/l, and SHBG levels dropped from a mean of 119.8 to 78.6 nmol/l. Although the numbers involved were small (19 patients entered this phase of the trial), the results were reassuring that fulvestrant was having no significant effect on these endocrinology measures as mean values were remaining within the normal ranges, or in the case of SHBG dropped from above normal to within the normal range.

In Trials 0021 and 0020, patients received 125- or 250-mg doses of fulvestrant by injection every month or 1 mg anastrozole (ARIMIDEX™) once daily until progression of disease. The plasma concentrations of estradiol, FSH, LH, and SHBG were measured (in a cohort of patients in each treatment group) every month for the first 3 months and then every 3 months up to and including Month 12. From trial entry to Month 6, FSH levels rose from a mean of 33.1 to 55.7 IU/l, LH concentrations rose from a mean of 27.2 to 42.2 IU/l, and SHBG levels dropped from a mean of 119.8 to 78.6 nmol/l. Although the numbers involved were small (19 patients entered this phase of the trial), the results were reassuring that fulvestrant was having no significant effect on these endocrinology measures as mean values were remaining within the normal ranges, or in the case of SHBG dropped from above normal to within the normal range.

Mean FSH and LH levels rose during the course of the trials from low to more normal postmenopausal values, reaching a plateau approximately 2 to 3 months after the start of treatment. Presumably the low values seen at the start of the trial were secondary to previous tamoxifen therapy. Withdrawal of the tamoxifen resulted in effects at the pituitary level as these rises were seen in both fulvestrant- and anastrozole-treated groups.

Levels of estradiol remained relatively constant throughout the trial in the fulvestrant-treated group, but as expected because of its mode of action, treatment with anastrozole reduced the mean estradiol levels over time. SHBG production is stimulated by estrogen and in both groups SHBG levels fell although the fall was more marked in the anastrozole-treated group.

These results support the concept that fulvestrant lacks agonist properties as both FSH and LH concentrations rose, and SHBG levels fell during the course of treatment.

(c) Conclusions

Fulvestrant, at a dose of 250 mg, appeared to antagonize the normal short term endometrial stimulatory effect of estrogen in a small study of postmenopausal healthy volunteers. In the clinical trials in breast cancer patients previously treated with tamoxifen, mean FSH and LH levels rose during the course of the trials from low to more normal postmenopausal values. It was hypothesized that this effect was attributable to the previous therapy with tamoxifen, however this was not conclusively demonstrated. Levels of estradiol remained relatively constant throughout the trial in the fulvestrant-treated group.

(2) Clinical Trials in Healthy Premenopausal Women

(a) Endometrial effects

In Trial 0003, premenopausal patients with benign gynecologic disease (dysfunctional uterine bleeding, endometriosis, or fibroids) were randomized to receive either 12 mg SA im fulvestrant (n=22), once daily for 7 consecutive days, or to be given no treatment (the observation group [n=11]).

Treatment commenced 4 to 8 days after the start of the last menstrual period. Endometrial thickness was measured by ultrasound at baseline and again after 3 and 6 days of treatment with the patients undergoing hysterectomy either on the last day of treatment or 4 days later.
There was a statistically significant difference between the 2 groups in the change in endometrial thickness from baseline to both Day 3 and Day 6. This was due to an increase in the endometrial thickness in the observation group (as would be expected during a normal menstrual cycle); the endometrial thickness in the fulvestrant-treated group remained at, or close to, baseline. This implies that fulvestrant was successfully antagonizing the effect of endogenous estrogens on the premenopausal endometrium.

In Trial 0019, premenopausal gynecology patients with uterine fibroids due for hysterectomy were randomized to receive either placebo (to fulvestrant or goserelin [n=60]), 50 mg (n=59), 125 mg (n=66), or 250 mg (n=62) fulvestrant (LA im formulation), or 3.6 mg goserelin (n=66). Patients receiving fulvestrant were given 3 im injections over a 12-week period (ie, 1 injection administered every 4 weeks) while patients receiving goserelin received 1 subcutaneous injection every 4 weeks. Patients receiving placebo received either a sham goserelin injection or a matched fulvestrant (1-ml, 2.5-ml, or 5-ml) injection every 4 weeks. The first dose was given on the 1st to 4th day of the patient's menstrual cycle.

Goserelin, a GnRH agonist, has established efficacy in reducing endometrial thickness prior to endometrial ablation. However, it has adverse effects on bone density and treatment is therefore limited to 6 months. It was included in this trial as a positive control.

Endometrial thickness was measured by ultrasound at baseline and following 4, 8, and 12 weeks of treatment. There were no statistically significant differences between any of the fulvestrant doses and placebo on the endometrial thickness after 12 weeks of treatment. The differences between fulvestrant and goserelin were statistically significant at all doses. There was no evidence of a dose-response relationship for fulvestrant.

In addition, endometrial biopsies were taken pre-treatment (during the luteal phase of the menstrual cycle, Days 20 to 24) and pre-surgery after 12 weeks of treatment. The results demonstrated a large increase in the percentage of patients with atrophic/inactive endometrium after treatment with goserelin (5.6% to 50%). This increase was not seen after treatment with any dose of fulvestrant and there was no evidence that fulvestrant had blocked the cyclical effects of estrogen.

(b) Endocrine effects

Trial 003: For the fulvestrant-treated group, the LH levels rose by about 3.5 IU/l from Day 1 to Day 3 and then decreased close to pre-dose levels by Day 7. In the observation group, the mean levels rose by about 5 IU/L between Day 1 and Day 5 and then decreased again.

FSH levels showed a similar pattern in the fulvestrant-treated group with a small increase between Days 1 and 3 and then a return to baseline. In the observation group, the FSH levels decreased over the observation period.

Estradiol levels increased markedly in the fulvestrant-treated group, and far less so in the observation group. SHBG levels remained consistently level in both groups.

In Trial 0019, premenopausal patients with fibroids received fulvestrant (50, 125, or 250 mg), goserelin (3.6 mg), or placebo. Plasma concentrations of estradiol, progesterone, LH, FSH, and SHBG were measured before dosing and again after 12 weeks of treatment (3 injections of fulvestrant/placebo or 3 injections of goserelin depot/placebo). Goserelin reduced FSH, LH, and estradiol levels, with a corresponding reduction in SHBG and progesterone. In the fulvestrant-treated groups, there was no significant effect on FSH, LH, or SHBG. Estradiol levels increased in all 3 fulvestrant treatment groups, although an increase was also noted in the placebo group. Progesterone concentrations also increased with a trend towards a higher increase at the top dose.

The results from these 2 trials in premenopausal women show an absence of, or minimal effect on, the hypothalamic-pituitary axis in a group of women who may be expected to be more sensitive to any effect than postmenopausal women. Postmenopausal women generally have high LH and FSH levels and low estradiol. The effect of additional estrogen antagonism may not therefore have further measurable effect on these parameters. However, in premenopausal women, estrogen antagonism at the ovarian level may result in removal of the negative feedback mechanisms. This can lead to over-stimulation of the hypothalamic-pituitary axis thus dramatically increasing FSH and LH with consequent ovarian hyperstimulation. These effects were not seen with fulvestrant, suggesting that this drug does not seriously disrupt the hypothalamic-pituitary-ovarian axis, and may not cross the blood brain barrier. An absence of effect on SHBG supports the concept that fulvestrant has no estrogenic properties.

(c) Conclusions

Studies in premenopausal women undergoing hysterectomies suggested that fulvestrant reduced the ER index in premenopausal endometrium, and had no observed estrogenic effect on vaginal epithelium as measured by Karyopyknotic Index and Maturation Value Fulvestrant did not appear to have clinically significant effects on the hormones of the hypothalamic-pituitary axis and had no observed stimulatory effects on the ovary, in premenopausal women. There were no changes in cross-linked N-telopeptides and free deoxypyridinoline, both markers of bone resorption, and therefore the applicant concluded that fulvestrant may not cause changes in bone density in premenopausal women.

(3) Clinical studies in Breast Cancer Patients: Effects on Tumor Markers

(a) Description of Clinical studies in breast cancer patients undergoing resection

Table 5: PD Studies on the effects of Fulvestrant on tumor markers

9238IL/ 0002 Phase II efficacy trial LA formulation
A Randomized Study to Evaluate Tolerance, pharmacokinetics, and short term efficacy of seven daily doses of the short acting formulation of ICI 182,780 in women prior to surgery for primary breast cancer
9238IL/ 0018 phase 2 PK, efficacy
A Partially-Blind, Randomised, Multi-centre Trial to Compare the Anti-Tumor 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.

In Trial 0002, postmenopausal women with primary breast cancer were randomized to receive either 6- or 18-mg fulvestrant SA im formulation (n=22 and n=18, respectively), once daily for 7 consecutive days, or were not given any treatment (the observation group [n=19]). A tumor biopsy, was taken before fulvestrant treatment commenced and curative-intent surgery was performed on Day 7 of fulvestrant treatment or after 7 days of observation. Post-treatment histological assessment was carried out on the resected tumor. Fulvestrant treatment caused a large decrease in the ER index of the tumors in a dose-dependent manner. This reduction was such that a number of initially ER-positive tumors no longer expressed ER after treatment. The PgR index also fell after treatment with fulvestrant when compared to the control group.

Trial 0018 was a randomized, partially-blind, parallel-group trial designed to compare the antiestrogenic and antiproliferative effects of a single dose of LA im fulvestrant (50 mg [n=39], 125 mg [n=38], or 250 mg [n=44]) with tamoxifen (20 mg daily for 14 to 21 days [n=36]) or with tamoxifen placebo (n=43), in primary breast tumors in postmenopausal women. Tumor samples were taken before treatment and at surgery which took place 15 to 22 days after the start of randomised treatment. All 3 doses of fulvestrant resulted in a statistically significant decrease in the ER index compared with placebo. The 250-mg dose of fulvestrant also resulted in a statistically significant decrease in the ER index when compared with tamoxifen. There was a dose-related reduction in the ER index in response to fulvestrant. Statistically significant decreases in PgR index were seen with the 125- and 250-mg doses of fulvestrant in comparison with placebo, and all 3 doses of fulvestrant resulted in statistically significantly greater decreases compared with tamoxifen, which resulted in an increase in PgR. Again, the effect appeared to be dose-related. All 3 doses of fulvestrant resulted in statistically significant decreases in the Ki67 labeling index compared with placebo, while no significant effects were noted for the comparisons between fulvestrant and tamoxifen.

(b) Conclusions

Fulvestrant was shown to reduce the ER index of breast tumor cells in postmenopausal women, in some cases with initially ER-positive tumors appearing to become ER-negative after treatment on the basis of immunoreactivity. Fulvestrant reduced the Ki67 labeling index in breast tumor cells, as well as the PgR index in breast tumor cells. Unlike tamoxifen, fulvestrant also reduced the PgR index in breast tumor cells.

Fulvestrant demonstrated anti estrogenic effects on breast cancer tumor cells in human volunteers undergoing resection.

Reviewer comment: This technique can not exclude the possibility that fulvestrant merely makes the receptors less inmmunoreactive, without actually decreasing the amount of receptor present. It is therefore not clear that sufficient evidence has been presented to conclude that fulvestrant represents a new class of drugs to be known as estrogen receptor down regulators.

f. IV. Description of Clinical Data and Sources

i. Overall Data

Data used in the review were primarily from the applicant's clinical trial program, with the exception of historical data used as the basis for establishing the non inferiority margins used in the primary statistical analysis.

ii. Tables Listing the Clinical Trials

(1) Overview of the clinical trial program

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 long acting "LA" depot formulation for intramusculatr injection. Trial 0004, the Phase II efficacy trial, and trials 0020 and 0021, the Phase III controlled trials, were 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) Fulvestrant Clinical Trials included in the NDA

Table 6 : Trials examining effects on the endometrium of healthy females

HQ/0003	An Open, Randomized Study to Examine the Effect of Seven Days Treatment with the Short-Acting Formulation of ICI 182,780 on Endometrial Growth in Premenopausal Women (Patient Volunteers) Scheduled for Hysterectomy for Benign Gynecological Conditions
IL/0036	A Phase I Trial to Assess the Antioestrogen Effect of ICI 182,780 (ZD9238) on the Female Reproductive Tract in Healthy Postmenopausal Female Volunteers
IL/0019	A Randomised, Placebo Controlled, Dose-Ranging Trial Comparing ICI 182,780 With Zoladex™ in Patients With Uterine Fibroids Awaiting Hysterectomy

Table 7: Trials in healthy male volunteers

9238IL/0007	A Trial to Assess the Absorption and Tolerability of Single Oral Doses of ICI 182,780 in Healthy Male Volunteers
9238IL/0008	A Phase I Trial to Assess the Pharmacokinetics and Tolerability of Ascending Oral Doses of ICI 182,780 in Healthy Male Volunteers
9238IL/0017	A Phase I Trial to Assess the Pharmacokinetics, Tolerability and Dose Proportionality of Different, Single Oral Doses of ICI 182,780 in Healthy Male Volunteers
9238IL/0024	A Phase I trial to assess the effect of rifampin on the pharmacokinetics of a single intravenous dose of ICI 182,780 (ZD9238) in healthy male volunteers
9238IL/0026	A Phase I Trial to Assess the Safety, Tolerability and Pharmacokinetics of Single Ascending Intravenous Doses of ICI 182,780 in Healthy Male Volunteers
9238IL/0031	A phase I trial to assess the effect of ICI 182,780 (ZD9238) on the pharmacokinetics of a single oral dose of midazolam in healthy male volunteers
9238IL/0034	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single oral dose of 400 mg [^{14}C]-ICI 182,780 in healthy male volunteers

Table 8: PK Studies in Healthy Female Volunteers

9238HQ/0001	An initial tolerance/PK study of a short acting dose of ICI 182,780 in healthy female volunteers
Design	Randomized, double-blind, placebo-controlled Part 1: parallel-group, ascending dose Part 2: crossover
Purpose	To assess the tolerability and PK of SA im fulvestrant
9238IL/0012	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intravenous dose of 10 mg [^{14}C]-ICI-182,780 in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized, radiolabeled PK study
Purpose	To assess metabolism, excretion, and PK of a single iv dose
9238IL/0029	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intramuscular dose of 18 mg [^{14}C]-ICI 182,780 (ZD9238), short-acting formulation, in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized
Purpose	to assess the metabolism, excretion and PK of a single im dose of 18 mg of [14C]-fulvestrant
9238IL/0038	An open, non-randomised trial to compare the pharmacokinetics of ICI 182,780 (ZD9238) in healthy male, pre-menopausal female and post-menopausal female volunteers
Design	Open, nonrandomized, parallel-group
Purpose	To compare the PK of fulvestrant in healthy men and pre- and postmenopausal volunteers
O-15-11	Phase I Clinical Study of ICI 182,780 - Single intramuscular administration in postmenopausal healthy women
Design	Open-label, single ascending dose levels of 25, 50, 125 and 250 mg
Purpose	To investigate the tolerability, endocrine effect, and PK of a single im injection of LA fulvestrant (Japan)
9238IL/0029	A phase I trial to assess the metabolism, excretion and pharmacokinetics of a single intramuscular dose of 18 mg [^{14}C]-ICI 182,780 (ZD9238), short-acting formulation, in healthy male and healthy post-menopausal female volunteers
Design	Open, nonrandomized
Purpose	to assess the metabolism, excretion and PK of a single im dose of 18 mg of [14C]-fulvestrant

Table 9: Phase 2 studies of PK and efficacy

9238IL/ 0002 Phase II efficacy trial LA formulation	
A Randomized Study to Evaluate Tolerance, pharmacokinetics, and short term efficacy of seven daily doses of the short acting formulation of ICI 182,780 in women prior to surgery for primary breast cancer	
Location	UK
Start/Stop dates	10/91-11/92
Accrual	58 Postmenopausal women with primary breast cancer
Design	Phase 2 open label prior to surgery for breast cancer
Objective	PK, short term efficacy
9238IL/ 0004 Phase II efficacy trial	
An Open, phase 2 study to determine if Partial or Complete Responses can be achieved with a slow release formulation of a pure anti estrogen (ICI 182,780) in post menopausal women with Advanced Breast Cancer who have relapsed on Tamoxifen Therapy	
Location	UK
Start/Stop dates	10/92 – 11/93
Accrual	23 Post menopausal women with advanced breast cancer
Design	Open Label dose finding
Objective	Phase 2 efficacy/tolerability
9238IL/ 0018 phase 2 PK, efficacy	
A Partially-Blind, Randomised, Multi-centre 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
9238IL/ 0039 Phase II PK efficacy	
An Open, Randomised, Multi-centre, 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	18 post menopausal women with advanced breast cancer
Design	Open randomized parallel group
Objectives	PK, tolerability

Table 10: Phase 3 studies of efficacy

9238IL/ 0020 Phase III efficacy	
An Open, Randomised, Multi-centre 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

Table 11 Ongoing Studies in other indications

9238IL/ 0025 Phase III efficacy – first Line	
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

iii. Literature Review

The Applicant included a bibliography as part of the NDA submission. The applicant's bibliography appears to be reasonably complete, based on an FDA Pubmed literature search. Specific references used in this review are included as footnotes.

g. Clinical Review Methods

i. How the Review was Conducted

The phase 3 trials designated as pivotal in this submission were reviewed in detail, with confirmation of response rates by examination of the primary data. Selected case review forms were reviewed. Applicant's results from the single arm efficacy and other trials were presumed to be reasonably accurate, and the primary data was not reviewed.

ii. Overview of Materials Consulted in Review

NDA 21-344 was submitted 3-28-01 in electronic format. NDA supplements were filed on 7-19-01, 7-20-01, 8-9-01, 8-28-01, 10-18-01, 10-19-01, and 9-13-01. The most recent annual report to IND # [redacted] was also included in the materials consulted.

iii. Overview of Methods Used to Evaluate Data Quality and Integrity

Case Review Forms submitted with the NDA were randomly sampled and reviewed for completeness and consistency with the submitted datasets. In addition, clinical inspections have been performed by the Division of Scientific Investigation at the following study sites:

Table 12: DSI audit sites

Center number	Investigator	Address	Number of patients recruited
Trial 9238IL/0021			
0001	C Kent Osborne MD Principal Investigator (Current address)	Director, Baylor Breast Center Baylor College of Medicine One Baylor Plaza, MS BCM 600 Houston, TX 77030	27
0011 Trial 9238IL/0020	[redacted]	[redacted]	54
0084	Dr J Quaresma Albano	Instituto Port ugues De Oncologia De Coimbra Servico De Oncologia Medica AV Byssaia Barreto No 98 3000 Coimbra, Portugal.	37

All DSI inspections showed minor violations but good general compliance with federal regulations. All subjects at the three DSI inspection sites were certified by DSI as able to be used for evaluation of the NDA.

iv. Were Trials Conducted in Accordance with Accepted Ethical Standards

The applicant stated that that the US clinical studies were conducted under the IND in compliance with the Institutional Review Board requirements in 21 CFR 56, and informed consent regulations in 21 CFR 50. Foreign studies were conducted in accordance with the ethical principles stated in the Declaration of Helsinki and in the laws and regulations of the country in which the studies were conducted. There was no information discovered during the review to suggest any violations of ethical standards.

v. Evaluation of Financial Disclosure

Table 13: Summary of financial disclosures

	0020	0021	Total all studies
Total # Investigators*	251	826	1174
No Disclosure (Signed Documents received)	207	564	842
Signed financial disclosure statements received	2	1	5
Did not respond	6	177	185
No Forwarding Information	11	43	58
% Response Rate	90%	95%	93%
No Response	25	41	84

[redacted] investigators out of 1077 in the phase 3 randomized studies admitted to having received significant [redacted] payments from the applicant (see table 12). Over 90% of the investigators responded to the financial disclosure request. There is no evidence to suggest that these financial disclosures suggest any influence on the study findings.

3. Integrated Review of Efficacy

a. Brief Statement of Conclusions

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

The original primary objective was demonstration of superiority of time to progression. Response rate was a secondary endpoint. After data analysis revealed that the original objective was not met, TTP was considered as a secondary endpoint for review, and non inferiority of response the primary endpoint. In the phase 3 efficacy trials, treatment with fulvestrant produced objective response rates comparable to or greater than those achieved with anastrozole, however, superiority of fulvestrant over anastrozole in terms of response rate was not shown. In the pivotal efficacy trials, treatment with fulvestrant produced objective responses in 20.3% in Trial 0020, and in 17% of patients in Trial 0021, per FDA analysis in the ITT population. These rates were comparable to or greater than those achieved with anastrozole which was found to elicit a response rate of 14.9% in Trial 0020 and 17% in Trial 0021. Although superiority was not shown over anastrozole, the 1-sided 97.7% confidence limit for the difference in response rates allows a potential deficiency for fulvestrant of greater than 6.3% to be ruled out in Trial 0021 and greater than 1.4% in Trial 0020. The FDA reviewers concurred with the Applicant's finding that when the non-inferiority margin was 10% for response rate, fulvestrant 250-mg was non-inferior to anastrozole 1-mg with respect to objective response rate whether the analysis was performed on the ITT or PP population for both trials.

Although median time to progression was slightly longer for patients treated with fulvestrant in trial # 21, examination of the Kaplan-Meier curves did not suggest any lasting difference in time to progression between treatment arms. Analysis using Cox proportional hazards model adjusted for covariates suggested that patients with measurable disease only, or worse performance status, appeared to have a somewhat higher risk for progression. Patients whose hormone receptor status was unknown appeared to have a lower risk of progression. In comparing fulvestrant with anastrozole for TTP, differences between the two groups were not significant for any comparison; however, all point estimates favored fulvestrant. 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.

There was no apparent difference in the Kaplan Meier survival curves in trial 20. There was a slight trend in Kaplan-Meier curves in favor of anastrozole in survival analysis in Trial 0021. However, since the data were not mature and the trial was not powered for survival

analysis, no conclusion regarding survival should be drawn. No statistical significant differences between arms were found in other efficacy and QOL endpoints.

b. General Approach to Review of the Efficacy of the Drug

i. Phase 2 studies of efficacy

Studies submitted, but not reviewed in detail:

9238IL/ 0002 Phase II efficacy trial LA formulation	
A Randomized Study to Evaluate Tolerance, pharmacokinetics, and short term efficacy of seven daily doses of the short acting formulation of ICI 182,780 in women prior to surgery for primary breast cancer	
Location	UK
Start/Stop dates	10/91-11/92
Accrual	58 Postmenopausal women with primary breast cancer
design	Phase 2 open label prior to surgery for breast cancer
Objective	PK, short term efficacy
Conclusions: the short acting IM formulation was well tolerated and preliminary evidence suggested biological antagonist but not agonist activity in primary breast tumors	

9238IL/ 0004 Phase II efficacy trial	
An Open, phase 2 study to determine if Partial or Complete Responses can be achieved with a slow release formulation of a pure anti estrogen (ICI 182,780) in post menopausal women with Advanced Breast Cancer who have relapsed on Tamoxifen Therapy	
Location	UK
Start/Stop dates	10/92 – 11/93
Accrual	23 Post menopausal women with advanced breast cancer
design	Open Label dose finding
Objective	Phase 2 efficacy/tolerability
Conclusions: well tolerated. 7/19 evaluable PR's but no CR's	