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

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