SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Faslodex. For information on changes after approval please refer to module 8.

1. Introduction

This marketing authorization application concerns Faslodex, solution for injection 250 mg/5ml, which contains the active substance fulvestrant (ICI 182,780, ZD9238). This is a full application for approval of a new active substance. The therapeutic indication for Faslodex is for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant antioestrogen therapy or disease progression on therapy with an antioestrogen. The proposed dose is 250 mg to be administered intramuscularly into the buttock at intervals of 1 month as a single 5 ml injection.

Breast cancer

Breast cancer is the most common form of cancer in women with as many as one in eight women in developed countries being affected by the disease at some point during their lifetime. The aging population is set to give rise to an increase in the prevalence of breast cancer with estimates suggesting an annual rise of 1%, particularly among postmenopausal women.

Treatment of breast cancer is determined by the extent of the disease. Early or localized breast cancer is treated by a combination of surgery and radiotherapy. Adjuvant systemic therapy, consisting of chemotherapy and/or endocrine therapy, in tumours deemed hormone responsive, can prolong the disease-free interval and improve overall survival. However, approximately 30% to 40% of patients with early breast cancer will ultimately relapse, with either local recurrence or distant metastases, and require further systemic treatment for advanced disease (ref: Forbes 1997). Since breast cancer that recurs or progresses after initial treatment is considered incurable, the therapy options available for advanced disease are concerned with disease control and palliation of symptoms (ref: Osborne, 1998). Hormonal therapy has become the treatment of choice in postmenopausal women with hormone sensitive breast cancer. Historically, the selective oestrogen receptor modulator, tamoxifen has been used extensively with success to treat advanced disease (ref: Litherland and Jackson, 1988; Osborne, 1998). Resistance to tamoxifen develops and the mechanism is complex. For postmenopausal women with breast cancer whose disease has recurred or progressed following treatment with tamoxifen or related non-steroidal anti-oestrogen, the choice of additional hormonal treatment lies between aromatase inhibitors (eg, anastrozole, examestane, letrozole) and progestins (eg, megestrol acetate, medroxyprogesterone). Progestins can be poorly tolerated because of adverse effects, notably weight gain, oedema, and thromboembolic complications. As a result, progestins are often reserved as third-line treatment or are avoided if the patient is deemed at risk of these complications. Even though the treatment of advanced breast cancer in postmenopausal women has improved with the introduction of agents such as aromatase inhibitors, these agents still have limitations, and disease management continues to be sub-optimal.

About the product

Fulvestrant is claimed to be the first agent in a new class of anti-oestrogen described by the term Oestrogen Receptor Downregulator (ER Downregulator [ref: Wakeling, 2000]). It is an anti-oestrogen without agonist properties. It blocks the trophic actions of oestrogens without itself having any partial agonist (oestrogen-like) activity on the endometrium of post-menopausal women. Fulvestrant binds to oestrogen receptors (ERs) in a competitive manner with a high affinity comparable with that of oestradiol. Data from pre-clinical studies have shown that fulvestrant is effective against human breast cancer cells and xenografts displaying acquired resistance to tamoxifen or letrozole (ref: Osborne et al, 1994, 1995; Long et al, 2002). A lack of significant issues from single and multiple dose safety studies in animals indicates a potential for a good safety profile. These data have provided a rationale for clinical development of fulvestrant in breast cancer patients whose disease has recurred or progressed following endocrine treatment.

Faslodex is presented as a sterile oily solution in a 5 ml pre-filled syringe. It is a long acting (LA) injection, designed to deliver the required dose of 250 mg of fulvestrant over a 1 month period from a single intramuscular injection into the buttock.

2. Chemical, pharmaceutical and biological aspects

Composition

Faslodex is presented as a sterile oily solution for intramuscular injection containing 50 mg/ml of the active substance fulvestrant. Other ingredients include ethanol, benzyl alcohol, benzyl benzoate and castor oil.

Faslodex is packaged in a single use pre-filled syringe consisting of a siliconised Type I glass barrel fitted with a tamper evident closure/luer lock connector, a siliconised bromobutyl rubber plunger, a bromobutyl/synthetic isoprene rubber tip-cap, a polystyrene plunger rod and a polypropylene back stop. Each pre-filled syringe is enclosed in a black line carton to provide light protection.

Active substance

The chemical name of fulvestrant is 7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl) -nonyl]estra-1,3,5(10)-triene-3,17β-diol. It is is a white crystalline solid compound with very high lipophilicity and extremely low aqueous solubility; it does not ionise except at very high pH. The compound is stable to hydrolysis, but has some susceptibility to oxidation. It contains 6 asymmetric carbon atoms and a stereogenic sulphoxide in the side chain. The active ingredient is a mixture of 2 diastereoisomers: Fulvestrant Sulphoxide A and B, having the same absolute configuration at each of the stereogenic centres in the steroid system but different absolute configurations at the sulphur atom. The ratio of Fulvestrant Sulphoxide A : Fulvestrant Sulphoxide B in fulvestrant is controlled by the clause for optical purity by HPLC.

The synthesis of fulvestrant is a 6-stage process, which will give a mixture of the two diastereoisomers (Fulvestrant Sulphoxide A and B), whose ratio is tightly controlled by HPLC. The route of synthesis has been sufficiently described, and the major steps in the synthesis of Fulvestrant are adequately controlled during the reaction.

There are thirty-four potential synthetic and degradation impurities, which may arise from the route of synthesis. Only 13 of these impurities have been detected in batches of fulvestrant during development. The presence or absence of impurities has been examined by spectroscopy and/or chromatography in all batches used in toxicological or clinical studies.

Active substance specification

The specification of the active substance includes tests for description, identification (IR), assay (HPLC), organic impurities (HPLC), residual solvents (GC), optical purity (HPLC), water content (Karl Fischer titration), sulphated ash, microbial content and endotoxins (LAL).

The limits for the identified and unidentified but specified impurities are justified by toxicological and stability studies. Batch analysis data have been provided for 23 batches of fulvestrant. The analytical results for these batches comply with the proposed specification.

In conclusion it has been proven that the tests and limits in the specification are appropriate for controlling the quality of the active substance.

Stability

Stability studies have been performed on 6 batches of fulvestrant in accordance with ICH guidelines. Samples were stored at 25 ^{o}C/ 60% RH for up to 36 months, 30 ^{o}C/ 60 and 80% RH for 12 months and 40 ^{o}C/ 75% RH for 6 months. Additional sudies were performed for six months under thermal stress (50 and 60^{o}C) and humidity stress conditions (50 and 60 ^{o}C/ 80% RH).

The parameters tested are description, assay, organic impurities (HPLC), degradation products (TLC), specific optical rotation, optical purity, water content, appearance, colour and clarity of solution and melting point. The methods used are the same as those used for routine control of fulvestrant with the

addition of TLC as a complementary technique to HPLC for detection of degradation products. All methods employed were stability indicating.

All parameters evaluated comply with the active substance specification. The stability data presented support the proposed re-tests period for fulvestrant, when stored in a double polythene liner inside an aluminium foil lined fibreboard drum under the specified conditions.

Other ingredients

All materials used are of non-animal origin. Ethanol, benzyl alcohol and benzyl benzoate comply with the Eur. Ph. requirements. The castor oil complies with USP.

Product development and finished product

As already discussed the active ingredient is a mixture of two diastereoisomers. The use of the mixture of these diastereroisomers is justified from the fact that the manufacture of individual diastereoisomers is not practical, their ratio is consistent, adequately controlled and does not change during storage neither in the drug substance or the drug product nor *in vivo* and the individual diastereoisomers have similar pharmacological potency.

Oral delivery has been explored, but this route could not achieve adequate bioavailability. Faslodex has therefore been developed for administration by intramuscular injection.

The goal of the development was to achieve effective and convenient delivery of fulvestrant, using the formulation to control the rate of drug input and reduce the frequency of administration. Achievement of drug solution at the target formulation concentration of 50 mg/ml is the key of this formulation approach. Studies were carried out to measure fulvestrant solubility in a range of oils, esters and alcohols suitable for inclusion in intramuscular injection formulations. It was found that castor oil together with co-solvent (benzyl alcohol, ethanol and benzyl benzoate) were the most suitable to allow a fulvestrant concentration of 50 mg/ml.

The manufacturing process for the finished product follows conventional pharmaceutical practices, which include a solution compounding step, sterile filtration and aseptic filling into syringes followed by stoppering. Processing is carried out under an inert gas (nitrogen) overlay, which has been shown to minimize formation of the oxidative degradation product Fulvestrant Sulphone. Sterility is assured by means of sterilisation by filtration and aseptic processing, as terminal sterilisation by heat or irradiation has been shown to be unsuitable for this product. The critical parameters were identified during development and the manufacturing process has been optimised to ensure control of degradation products and co-solvent levels.

The process validation of Faslodex 50 mg/ml solution for injection has been performed on three commercial batches having the same composition and method of manufacture as the proposed commercial formulation. The process validation criteria were met in all cases and all samples met the pre-defined acceptance criteria.

The batches used in the clinical studies have the same formulation as the product intended for the market.

Product specification

The product specifications include tests by validated methods for the description, assay (HPLC), identification (IR), degradation products (HPLC), sterility, endotoxins (LAL), pre-filled syringe function test, residual solvents (GC) and volume of injection in containers.

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with pharmacopoeial standards (including Ph Eur) and ICH guidelines. The limits for each specification test are supported by data derived from toxicological, biopharmaceutical, and stability studies.

Batch analysis data from 4 pilot and 4 production scale batches of the finished product have been provided. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

Stability of the product

Three primary batches and three supporting batches of Faslodex have been subjected to stability studies using a range of stability conditions: long term (5 ^{o}C) for up to 36 months, accelerated (30 ^{o}C/ 60% RH), thermal stress (30 ^{o}C/ 60% RH and 50 ^{o}C) for up to 6 months, humidity stress (30 ^{o}C/ 80% RH and 40 ^{o}C/ 75% RH) and accelerated (25 ^{o}C/ 60% RH) for up to 12 months. Two of the batches have also been placed under light stress testing according to ICH guidelines.

The parameters studied were description, volume of injection in containers, sterility, degree of coloration of liquid, average weight change, viscosity, assay, degradation products, residual solvents, the content of free fatty acids, water content and optical purity. The tests performed are the same as those used for the release of Faslodex.

Based on the results of the above-mentioned studies it has been concluded that the proposed shelf life for the commercially packaged product under the conditions specified in the SPC is acceptable.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Faslodex is is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is a mixture of two diastereoisomeers with consistent ratio and similar pharmacological activity. It is stable, well characterised and documented. The excipents have been chosen to control the rate of drug input and reduce the frequency of administration. The packaging material is commonly used and well documented. The manufacturing process of the finished product has been adequately described.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Toxico-pharmacological aspects

Pharmacology

Fulvestrant is a competitive inhibitor of oestradiol binding to the oestrogen receptor (ER) with an IC_{50} value of 9.35 x 10^{-9}M. The relative binding affinity to the oestrogen receptor is approximately similar for oestradiol (RBA=1) and fulvestrant (RBA=0.89), and 35 times lower for tamoxifen (RBA=0.025). Multiple changes in ER function in the fulvestrant-ER complex contribute to the blockade of oestrogen action. These changes include impaired receptor dimerisation, disrupted nuclear localisation, an increased rate of receptor degradation, impaired DNA binding and inactivation of activation functions AF1 and AF2. Increased receptor degradation leading to the rapid loss of ER following treatment with fulvestrant occurs in breast cancer cells in culture, in the uterus after *in vivo* treatment and in human breast tumours. Hence, the drug's mode of action appears to lead to downregulation of oestrogen receptor protein. The mode of action on the molecular level thus seem to differ from that of tamoxifen and oestradiol which bind with high affinity to the ER and displaces receptor associated proteins. However, the clinical relevance i.e. in terms of efficacy, of this difference in mode of action is not clear and has to be investigated in patients. It should be emphasised that this discussion involves ERα, while no data is available concerning an eventual interaction between fulvestrant and ERβ. As to date it seems that there is no clear picture about the role of ERβ in breast cancer. According to one reference (Fugua et al 2003) ERβ could serve as an independent marker for malignacy, for instance, the rate of aneuploidy was marginally higher in ERα negative/ERβ positive breast cancer samples suggesting that ERβ positive breast cancers might be more aggressive than other receptor types. It may be speculated that the ERβ could serve as a marker of endocrine therapy resistance. Sub-typing studies have not been carried out but would be welcomed in prospective studies.
Fulvestrant is a reversible inhibitor of the growth of oestrogen-sensitive human breast cancer (MCF-7) cells and tamoxifen-resistant MCF-7 cells *in vitro*. At maximum effect, fulvestrant induced a 80%

reduction in number of MCF-7 cells, whereas tamoxifen induced a 50% reduction in cell number. The Applicant cites studies showing that tamoxifen-resistant cells remain sensitive to the growth inhibitory effect of fulvestrant, whereas fulvestrant-resistant cells are cross-resistant to tamoxifen. Hence, tumors, which have relapsed during fulvestrant treatment, may not respond to treatment with tamoxifen, and this treatment sequence can not be recommended based on non-clinical data.

Moreover, fulvestrant prevents the establishment of tumors from xenografts of human breast cancer cells in nude mice *in vivo*. The efficacy of fulvestrant (single 5 mg s.c. injection) in preventing the growth of tumors from grafts of MCF-7 cells after 4 weeks was comparable to that seen in mice treated daily with a high dose of tamoxifen (10 mg/kg/day p.o.) for 8 weeks.
Fulvestrant is a non-agonist antioestrogen that blocks the uterotrophic action of oestradiol in mice, rats and monkeys without having significant partial agonist oestrogen-like activity. Hence, no adverse effects on the uterus endometrium, or on development of resistance due to agonist effects on the tumour, can be anticipated from the non-clinical data. In monkeys, measurements of plasma fulvestrant showed that inhibition of the trophic effects of oestradiol required drug concentrations in the range 1-2 ng or greater. Extrapolation of this data to humans predicts a monthly i.m. injection of 200 to 300 mg of fulvestrant, which is line with the dose proposed for marketing (250 mg).

Fulvestrant is a racemate showing similar potency as the individual enantiomers in three pharmacodynamic assays. None of the 4 metabolites tested showed any oestrogenic activity. The 17-ketone showed antioestrogenic activity 4-5 fold less potent than fulvestrant.

To conclude, the non-clinical data presented, both *in vitro* and *in vivo,* in animal species considered relevant for pharmacodynamic studies, is consistent with the compound having efficacy in the proposed indication of treatment of advanced breast cancer in women whose disease has progressed following endocrine therapy.

Limited studies did not indicate any significant secondary pharmacodynamic effects of fulvestrant. No interactions with histamine H_2 receptor, β_1, β_2 adrenoreceptors, 5-HT_1 and 5-HT_2 receptors were reported, but a weak non-competitive inhibition of responses mediated by muscarinic, histamine H_1 and adrenergic α_1 receptors was observed. Safety pharmacology studies (see also section on toxicology) in male animals addressed possible effects on the cardiovascular, neurological, respiratory, renal and gastrointestinal systems. Potential interactions with the cardiovascular system were assessed in studies in dog and *in vitro* in sheep Purkinje fibres stimulated at 1 Hz, models and study conditions that can be expected to be relatively insensitive to potential effects. No statistically significant effects were observed. No marked effects of fulvestrant with regard to the CNS were reported. However, in rats fulvestrant was shown to increase locomotor activity, the relevance of this observation is unclear.

Pharmacokinetics

No issues concerning the two diastereomers, sulphoxide A and sulphoxide B that represent fulvestrant in a 45:55 ratio have been identified. Studies indicate these do not undergo interconversion and disposition appears achiral. Fulvestrant has a low oral bioavailability. Absorption after intramuscular doses is good and distribution is wide. The pharmacokinetics of fulvestrant were studied using a short-acting (SA) formulation and the long-acting (LA) formulation. Only the long-acting formulation is intended for clinical use.

Fulvestrant did neither inhibit CYP450 enzymes nor act as an enzyme inducer. Fulvestrant was extensively metabolised with sulphate, glucuronide and ketosulphone derivatives identified as primary metabolites in all species. Metabolism appears complex. After intramuscular injections in rat the metabolism involved oxidation, hydroxylation and conjugation reactions. Oxidative metabolism at C-2 and C-4 position of the A-ring and at the C-17 was suggested to produce a ketone while a similar reaction at the sulphoxide was proposed to produce a sulphone. Parent compound and some metabolites were conjugated at C-2, C-3 and C-4 positions to produce glucuronides and sulphates. The 17-keto compound had pharmacological activity lower than the parent compound while other putative

metabolites tested had no oestrogenic activity. Overall the metabolite profile appeared comparable qualitatively across species.

Fulvestrant is highly protein bound in all species with 98.83% binding using human plasma, indicating a potential for drug displacement interactions. *In vitro* fulvestrant demonstrates non-physiological binding properties and interactions based on displacement do not seem readily studied *in vitro*. In both the albino and pigmented rat, rapid and extensive distribution was evident with highest levels detected in liver, mesenteric lymph nodes and kidney. Distribution into the CNS and the spinal cord seemed limited with the protocol used, a single intramuscular dose of fulvestrant in the SA-formulation. Fulvestrant passes into the milk of lactating rats and crosses the placenta after intramuscular injections in rat and rabbit.

Possible interference with P-gp or any other clinically relevant transporter system (BSEP, MRPs) has been discussed. Fulvestrant is not currently indicated for co-administration with other anticancer agents known to be P-gp substrates or inhibitors. If such developmental programme will be established these potential interactions should be resolved. In non-clinical studies some signals of hepatotoxicity were observed in rat, dog and monkey studies. Although the drug is administered via intramuscular injections it may interfere with different transport proteins and compete with excretion of other exo-/endogenous compounds.

In all species, including humans, the primary excretion route is faecal with less than 2% of label found in urine. Elimination appeared more rapid in rat than in dog and the apparent long elimination half-life was probably due to slow absorption from the injection site.

In rat, day 1 and day 28 AUC values were comparable after daily doses of the SA-formulation. No gender differences were apparent when using the RIA assay. In a 6- month rat study using the LA-formulation and the HPLC assay, higher AUC values were reported after multiple doses than after single doses. There were indications that female rats achieved a higher exposure than males using the LA-formulation and intramuscular injection. In dog, daily intramuscular injections of the SA-formulation as well as monthly injections of the LA-formulation resulted in accumulation as determined by AUC values. Limited data in the dog did not indicate any significant gender differences in exposure.

The systemic exposure and C_{max} in various toxicity studies exhibited significant variations despite similar doses being used. This was partly explained by different analytical methods (LSC RIA and a HPLC MS-MS). Other data indicated very marked interindividual variations in plasma levels after intramuscular doses, e.g. C_{max} levels were 15.5, 38.5 and 135 in three dogs all treated with a single dose of 2 mg/kg. Notwithstanding uncertainties with respect to specificity of the RIA-assay and the origin of some of the great interindividual variations in plasma levels, that could partly be explained by differences in absorption from the injection sites, it can overall be accepted that sufficient exposure was achieved in the pivotal toxicity studies. For the LA-formulation the highest dose levels used (10 mg/rat/15 days) and dog (40 mg/kg/28 days) corresponded to exposure ratios of x4-10 the expected human maximal dose (250 mg/month).

The data indicate overall that from the pharmacokinetic point of view the species used in preclinical studies are valid models to study the toxicological profile of the compound.

Toxicology

The potential of fulvestrant to cause local or systemic toxic reactions when administered by the intramuscular route was investigated in toxicity studies in rat and dog of up to 12 months duration. In addition studies in mouse, rat, dog and monkey are available to assess the potential of fulvestrant to cause pathological effects when administered by oral, intravenous or subcutaneous routes. Most of the studies included saline and vehicle controls and the long-acting (LA) formulation intended for clinical use, was used in the main pivotal toxicity studies. The LA-formulation was composed of fulvestrant (5% w/v), ethanol (10% w/v), benzyl alcohol (10% w/v), benzyl benzoate (15% w/v) and castor oil to 100. The pivotal repeated dose toxicity studies used the intramuscular route and included 1 and 6

month rat studies given total doses of up to 120 mg/rat in a 6-month period. The dog represented the non-rodent species and the highest dose given in the pivotal 12-month study was 40mg/kg/28 days. The maximum doses were limited by solution characteristics of the formulation and the maximum volume that could possibly be administered by the intramuscular route. The selection of the high dose was justified and corresponded to approximately x8 (dog) and x40 (rat) on a monthly dose basis, or approximately x4-11 on a systemic exposure basis. The studies are overall considered sufficient for evaluation of the toxicological profile of fulvestrant.
Safety pharmacology studies (see also section on pharmacology) indicated a limited potential of fulvestrant to interfere with the function of major organ systems. The studies all used male animals and addressed possible effects on the cardiovascular, neurological, respiratory, renal and gastrointestinal system. Locomotor activity in male rats was increased by intramuscular doses of 20 mg/kg, the relevance of which is unclear. Single dose pharmacokinetic studies indicated very limited passage into the CNS using the SA-formulation. However, there were some indications in repeated dose toxicity studies such as pituitary effects that suggest fulvestrant and/or metabolites have the capacity to either directly or by secondary hormonal activity, interact with the CNS. In the literature it is reported that fulvestrant may have effects on the brain such that the effect of oestrogens is blocked in the hippocampus, but not in the frontal cortex. Further, neuroprotective effects of oestradiol were blocked by fulvestrant in a model of stroke-like ischemic injury in female rats. In view of the proposed new principle of action and in case of future extended indications it would be of interest to clarify the potential effects of fulvestrant on the central nervous system based on known, expected hormonal actions.

Myocardium is a target tissue for oestrogens. Potential interactions with the cardiovascular system were assessed in studies in the dog and *in vitro* in sheep Purkinje fibres stimulated at 1 Hz. No statistically significant effects of fulvestrant doses up to 20 mg/kg (LA-formulation) in anaesthetized dogs monitored up to 120 minutes post-dose, were observed. Heart rate was somewhat increased. In an *in vitro* study in sheep Purkinje fibres stimulated at 1 Hz, no effects on QT intervals was reported. Both test systems and study conditions can be expected to be relatively insensitive to potential effects. In an intravenous tolerance study in dogs there was evidence of transient cardiovascular effects and clinical signs of panting and flushing were recorded. ECG measurements in the 12-month dog study did not show any effects. It is reported in literature data that fulvestrant can block the inhibitory effect of oestradiol at concentrations that inhibit oestradiol metabolism to precursors of methoxyoestradiols on human coronary vascular smooth muscle cells. Fulvestrant has been shown to activate large conductance Ca(2+) activated K(+) (BK(Ca)) channels in smooth muscle cells further suggesting potential for interactions on the vascular level. Further retrospective characterisation with respect to the cardiovascular system is not warranted in the context of the present application concerning treatment of advanced or metastatic breast cancer.

Toxicity studies with repeated administration indicate that with the possible exception of effects on the kidney, apparently restricted to males, adverse effects could mainly be attributed to the pharmacological activity. Increased kidney weights and vacuolation was noted in male mice and an increased incidence of chronic progressive nephropathy was reported in male rats in the 2-year carcinogenicity study. In the event of an extended use these changes should be further evaluated as to the mode of action. Moreover, in the 12- month study in dogs, 6 animals were stated to have arteritis **(**or vasculitis**)**, considered unrelated to treatment, affecting a variety of organs. The Applicant has discussed the reasons why arteritis was not considered related to treatment, and attributed changes as related to an underlying disorder, precipitated by treatment and specific for the strain of Beagle dogs used. In the 6 month study the incidence of arteritis did not seem increased in treated dogs while in the 12 month study lesions in the urinary bladder vessels affected 3 of 6 dogs with arteritis or vasculitis. Although arteritis might not be a specific drug induced effect, a treatment related effect can not be excluded. The potential of fulvestrant to exacerbate or induce these kinds of changes is likely a late effect with doubtful significance for the general safety profile of the compound in the present indication.

A high dose female dog in the 12-month study was noted for multifocal hepatic granuloma. In other studies occasional decreases in spleen weight was observed possibly secondary to anti-oestrogenic pharmacology and indicative of immunological effects. There are theoretical mechanisms for

immunotoxicity due to fulvestrant, but these likely are not relevant for the target population. It is accepted that immunotoxicology studies are not conducted but in case of future extended indications these issues might be reconsidered. Fulvestrant had no antigenic potential in studies in guinea-pig and mouse.

Histopathological changes related to treatment with fulvestrant were recorded in the uterus (uterine atrophy affecting endometrium and myometrium), cervix (atrophy, increased stromal density), vagina (atrophy, increased stromal density and organ reduced in size), ovaries (disturbance in the maturation of the Graafian follicle, formation of follicular cysts, degenerate corpora lutea, cystic and haemorrhagic), adrenal glands (atrophy in males, zona fasciculata of the cortex), and pituitary gland (atrophy, increase in the number of castration cells). These effects seemed primarily related to the pharmacologic activity of fulvestrant. The increase in red blood cell parameters recorded in some studies in females likely also as suggested was related to the anti-oestrogenic activity. In the majority of toxicity studies a no effect level could not be established, but effects recorded were mostly local reactions or changes related to the pharmacological activity of the compound. The Applicant suggests that fulvestrant has no effect on bone density at relevant doses in rat. *In vitro* studies reported in the literature have shown that fulvestrant may reverse oestrogen-induced expression of proteins central to osteoclast formation and function. However, fulvestrant did not impair the long-term bone-protective effects of testosterone in young orchidectomized male rats.

The local tolerance of fulvestrant (5% w/v) was studied in rabbit and dog. Local reactions were dependent on the vehicle used, but severity and frequency increased with increasing concentrations of fulvestrant. Adverse local reactions appeared dependent also on species, site of administration and frequency of administration. In rat 1 and 6 month studies injection site fibrosis was evident. In the 2-year rat carcinogenicity study changes consisted of local inflammation, plantar epithelial ulceration and multiple cysts at times associated with mild local inflammation and degeneration or atrophy of skeletal muscle. In the 6-month dog study myositis, present also after a 6-month withdrawal period, and necrosis was evident. In the 12 month dog study changes at the injections site were described as "multifocal inter and intrafasicular granulomatous foreign body response."

Fulvestrant was evaluated for genotoxic activity in the Ames test, the mouse lymphoma test, in the chromosomal aberration test using human lymphocytes and in the rat micronucleus test after a single oral dose of 2000 mg/kg. All tests were negative for genotoxic potential. In a 2-year rat carcinogenicity study an increase in the incidence of ovarian granulosa cell tumours in females and in Leydig cell tumours in low and mid dose males were observed. The incidence of mammary gland and pituitary gland tumours was decreased. No carcinogenic activity that could not be associated with the pharmacological activity was identified. Literature data indicate that fulvestrant treatment of mice may increase serum levels of LH consistent with a hormone-mediated increase in male tumour incidence. Tamoxifen, another anti-oestrogen, has been shown to be hepatocarcinogenic in the rat. In contrast fulvestrant did not induce liver cancers in rat, but the incidence of altered eosinophilic foci in liver was increased in males.

Reproduction toxicity studies in rat and rabbit were conducted. Fulvestrant was given by intramuscular injections prior to mating, through mating and implantation and through weaning. Fertility in female rats was reduced and embryonic survival decreased at doses ≥ 0.01 mg/kg/day. Following a 29-day withdrawal period fertility and embryonic survival was restored. Male fertility was not specifically studied, but repeated dose toxicity studies indicated loss of spermatozoa and epididymides degeneration. In a rat study that included administration during organogenesis, live foetuses were decreased at a dose of 2 mg/kg/day. The number of foetuses with torsal flexure was increased. A NOEL of 0.001 mg/kg/day in rat was identified for female fertility and embryonic survival, foetal survival and development. Rabbits treated with 1mg/kg/day had no live foetuses and at 0.25 mg/kg/day post-implantation loss increased. Foetal development was not affected. An increased incidence of foetal variations was noted at 0.25 mg/kg/day.

In a rat post natal development study pup survival was lower after maternal treatment with fulvestrant. Pregnancy in F1 animals was not affected by maternal treatment, but pre-implantation loss was increased. There were no effects on fertility, sperm counts or gonadal histopathology of F1 males.

Separate studies showed that fulvestrant passes into milk of lactating rats. The lack of effect of potential exposure to an oestrogen receptor antagonist during neonatal life contrasts with the findings from the oestrogen receptor knockout mice that are infertile and have testis degeneration. Faslodex should not be used during pregnancy and lactation, and this is reflected in the SPC with a contraindication for pregnancy and in breast-feeding.

4. Clinical aspects

The fulvestrant clinical study programme was primarily designed to evaluate the efficacy and safety of fulvestrant in the treatment of advanced breast cancer in postmenopausal women and the pivotal study data was provided by 2 Phase III studies examining the efficacy of fulvestrant for the key endpoints of time to progression, objective response rate, and time to death. The programme comprises the following studies:

- 2 Phase III pivotal efficacy studies (Studies 0020 and 0021)
- 2 Phase II efficacy studies (Studies 0004 and O-15-22)
- 18 Clinical pharmacology studies

(Studies 0001, 0002, 0003, 0007, 0008, 0012, 0017, 0018, 0023, 0024, 0026, 0029, 0031, 0034, 0036, 0038, 0039 and O-15-11)

Scientific Advice was sought from the CPMP in 1997.

Clinical pharmacology

Pharmacokinetics

Eighteen clinical pharmacology studies, involving premenopausal and postmenopausal healthy female volunteers and male volunteers have been performed. Pharmacokinetic data has also been collected in two phase II and two phase III studies. Specific studies in special populations have not been performed. The influence of decreased renal function and demographic factors on the pharmacokinetics of fulvestrant was evaluated in a population pharmacokinetic analysis of data from phase III studies.

Absorption

After administration of Faslodex 250 mg intramuscularly (LA formulation), fulvestrant is slowly absorbed. Maximum plasma concentrations are reached after about 7 days. Single dose studies have demonstrated that absorption continues for more than one month and that the terminal half-life is about 50 days. Repeated administration once a month results in an approximately 2-3 fold accumulation. Steady state is reached after about 6 months with the major part of the accumulation achieved after 3-4 doses. At steady state there was an approximately 2-fold difference between mean C_{max} and C_{min}. Unfortunately, a more frequent dosing than once a month has not been tested. With more frequent dosing during the first months, steady state (and potentially more effective concentrations) could be reached earlier, possibly resulting in better efficacy.

Absolute bioavailability has not been determined. The bioavailability has roughly been estimated to about 90-100% by between study comparison. The variability in exposure after the first dose of an i.m. Administration of the LA formulation is large. CV% was between 25 and 70% for $AUC_{0\text{-}28d}$ and between 28 and 83% for C_{max} suggesting a large variability in absorption rate. Considerably lower variability in exposure is observed at steady state, CV% about 15%. The exposure was approximately proportional to dose in the studied range 50 to 250 mg. Dose proportionality above the intended dose has not been studied. Results from phase III studies suggest time independent pharmacokinetics.

Distribution

Fulvestrant has a high volume of distribution, V_{ss} is 4.1±1.6 l/kg. The plasma concentration declines in a tri-exponential fashion with rapid distribution into peripheral tissues. In vitro studies demonstrated high protein binding, 99%, with lipoproteins being the major binding component.

Elimination

Fulvestrant is eliminated mainly by metabolism, and to a smaller extent by biliary excretion unchanged. The major route of excretion is via the faeces with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11±1.7 ml/min/kg, suggesting that it is a drug with high extraction ratio. The metabolism of fulvestrant includes ketone and sulphone metabolites, 3-sulphate, 3- and 17-glucuronides. In plasma, fulvestrant was the largest component. Identification of metabolites in plasma was not possible due to low concentrations of radioactive material. Characterisation of radioactivity in faeces demonstrated at least 15 components after iv dosing, none of which amounted to more than 10% of the dose and over 20 components following im administration. Only 28% of the extracted radioactivity (24% of the dose) was identified after im administration. Although enzyme hydrolysis and mass spectroscopic analysis showed that a number of the metabolites were probably sulphate and/or glucuronide conjugates of unchanged [^{14}C]-fulvestrant and its ketone and sulphone metabolites, the identity and potential activity of a large part of the metabolites is not known. The applicant has concluded that fulvestrant is extensively metabolised, primarily by routes analogous to those of endogenous oestradiol and is excreted in the faeces. None of the identified metabolites are likely to contribute to a significant extent to drug activity.

Target population

A population pharmacokinetic analysis on data from two phase III studies resulted in similar or somewhat lower estimate of clearance than observed in other studies. Based on this analysis, the estimated steady state exposure in the target population is AUC 328±48 ng·d/ml, C_{max} 15.8±2.4 ng/ml and C_{min} 7.4±1.7 ng/ml.

Special populations

The influence of decreased renal function and demographic factors on the pharmacokinetics of fulvestrant was evaluated in the population pharmacokinetic analysis of data from phase III studies. The population included subjects with mild and moderate, but not severe renal impairment, and covered an age range of 33-89 years and a weight range of 40-127 kg. The population analysis did not identify any covariate influencing the clearance of fulvestrant to any significant extent.

Interactions

An *in vitro* inhibition study showed no relevant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. Other CYP450 isoenzymes were not studied and the applicant intends to evaluate the influence of fulvestrant on CYP2A6, 2C8 or 2E1 as a post-authorisation commitment. The lack of inhibition of CYP3A4 was confirmed in an *in vivo* interaction study with midazolam. CYP3A4 was the only enzyme identified as having a capacity to metabolise fulvestrant *in vitro*. Interaction studies with rifampicin (CYP3A4 inducer) and ketokonazole (CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics.

The potential for interaction with sulphate conjugation, drugs that influence hepatic blood flow and protein binding displacement appears to be low.

Pharmacodynamics

The pharmacodynamic study programme was designed to demonstrate both the antioestrogenic potential of fulvestrant and also to confirm the absence of oestrogen agonist activity in postmenopausal women in various oestrogen-sensitive target organs.

Following a single dose of short-acting (Study 0002) or long-acting (Study 0018) fulvestrant, there was evidence of dose-dependent down-regulation of oestrogen receptor (ER) and effect on the ER pathway as evidenced by a reduced expression of PgR, and a decrease in the Ki67 (an anti-proliferative marker) labelling index in postmenopausal women with primary breast cancer. Only the 250 mg dose showed a statistically significant reduction in ER index compared to tamoxifen.

The effects of one dose of fulvestrant (250 mg) on tumour markers were also studied in premenopausal women with ER-positive primary breast cancers in Study 0041. Fulvestrant did not exert any statistically significant anti-tumour or anti-proliferative effect as evaluated by effects on the ER, PgR and Ki67 labeling indices.

Short-term studies of 2 weeks' treatment with the long-acting formulation in post-menopausal women showed that fulvestrant antagonised the effect of exogenous and endogenous oestrogen stimulation, as judged by ultrasound measurement of endometrium thickness. Fulvestrant did not have any effect on endometrial thickness or fibroid volume in pre-menopausal women after 12 weeks of treatment while goserelin had a statistically significant effect on both indices.

In postmenopausal women, fulvestrant (including long-term treatment in the phase 3 studies) did not appear to have significant effects on gonadotropins, which tended to increase, but remained within normal postmenopausal limits. This, and the decrease in SHBG, was interpreted as indirect evidence of an absence of a (significant) oestrogen agonist activity. These results, however, were not conclusive, partly because of the high attrition rate of the study participants and partly because of methodological issues.

The relationship between fulvestrant plasma concentration and effect was evaluated in studies 0018, 0036 and the two-phase III studies. The PK/PD evaluations in studies 0018 and the phase III studies did not show any evidence for a relationship between fulvestrant plasma concentration and effect. However, in study 0036, increased concentrations were related to a better anti-oestrogenic effect.

Discussion on clinical pharmacology

Valid information regarding impact of hepatic impairment on fulvestrant pharmacokinetics is lacking, and use in severe hepatic impairment has been contraindicated (see SPC). Use in mild and moderate hepatic impairment should be approached with caution. The applicant has committed to conduct an open label, phase I study to compare the pharmacokinetics of a single 18 mg short-acting intramuscular dose of fulvestrant in patients with hepatic impairment to controls with normal hepatic function.

Very limited data are available on the effects of fulvestrant on endometrium thickness and no data are available regarding endometrium morphology. While these short-term data cannot exclude the possibility of adverse effects of long-term treatment on the endometrium and ovaries, the lack of agonist activity of fulvestrant means that further evaluation of endometrial safety could be included in post-marketing clinical studies. Based on the 12-week study of biochemical markers of bone resorbtion in pre-menopausal women, no conclusion can be drawn on the effect of long-term fulvestrant on bone density in post-menopausal women. The applicant committed to further evaluate endometrial and bone safety.

A clear deficiency of the clinical development program is the lack of dose finding studies. While the results of an uncontrolled Study 0004 were presented as the basis for selecting the 250 mg dose for the pivotal studies, efficacy data were collected at the 250 mg dose without any comparative efficacy data at the lower doses. A dose higher than 250 mg monthly was not studied. As stated by the Applicant, there were formulation issues that restricted concentrations greater than 50 mg/ml, and practical standards in-patient care that limit intramuscular injection volume. The question is whether a shorter dosing interval or a regime involving two injections to deliver a higher dose could have been investigated. Results from Study 0036 on post-menopausal endometrium discussed above and the two pivotal studies were consistent in showing that 250 mg fulvestrant had a larger effect size than the 125 mg dose, and the possibility of an even larger effect size with a higher dose can not be excluded. Furthermore, study of dynamic markers in Study 0018 did not conclusively show that the effect of 250 mg fulvestrant was larger than tamoxifen, and as will be discussed later.Moreover, the population pharmacokinetic analysis evaluated the relationship between pharmacokinetic parameters and response using estimated pharmacokinetic parameters after the first dose and at steady state. The absorption rate is highly variable and time to reach steady state is up to 6 months. Many patients progress in their disease before steady state has been reached. From the evaluations provided (first dose and steady state only), no conclusions can be drawn regarding actual concentration prior to and at time of progression. Nor can conclusions be drawn regarding if there is a difference in plasma concentration between patients progressing in their disease and patients responding to therapy at different time points on the way to steady state. If the high initial variability in exposure and long time until steady state is reached are potential reasons for treatment failure, a better response could be obtained by a more optimal posology, e.g. with more frequent dosing during the first months. The Applicant has committed to conduct a phase III study comparing the 250 mg monthly dose with a 500

mg monthly dose in combination with a loading dose in the second line treatment setting. Using simulation models, the proposed dosage in the new study seems appropriate.

Clinical efficacy

Main clinical studies

The efficacy of fulvestrant was investigated in two randomised multicentre controlled clinical trials, Studies 0020 and 0021, in comparison to the selective aromatase inhibitor anastrozole in postmenopausal women with locally invasive advanced or metastatic breast cancer (Table 1). Study 0020 was an open trial conducted in Europe while Study 0021 was a double-blind trial conducted in North America. The 250 mg dose was administered as a single intramuscular injection in the European study while two serial injections, one per buttock, were administered in the North American study, in accordance with the North American nursing guidelines on intramuscular injections. The studies were otherwise similar in design and a combined analysis was prospectively defined. These two studies were initially designed to study both 125 mg and 250 mg monthly dose groups. Study of the 125 mg group was terminated early because of insufficient evidence of activity in the first 30 patients enrolled across the two trials as prospectively defined. These patients were either withdrawn from the trial or were permitted to continue on the 125 mg dose, but not to increase to the 250 mg dose. Both studies were originally designed to investigate the potential superiority of fulvestrant over anastrozole but the results did not reach statistical significance. A switch to a claim of non-inferiority was made and analysis performed using a non-inferiority margin that was assigned retrospectively by an independent expert group.

Table 1 Summary of efficacy studies

Study ID	Design	Subjects	No.	Dosage
Phase III				
9238IL/0020 83 centres Europe	Multicentre, open-label, randomised, parallel-group Efficacy and safety; and PK	Postmenopausal women with advanced breast cancer who relapsed or progressed following prior hormonal therapy	541	Fulvestrant 250 mg LA im injection monthly Anastrozole 1 mg orally daily Discontinued fulvestrant 125 mg
9238IL/0021 84 centres North America	Multicentre, double-blind, randomised, parallel-group Efficacy and safety; and pharmacokinetics (PK)	Postmenopausal women with advanced breast cancer who relapsed or progressed following prior hormonal therapy	473	Fulvestrant 250 mg LA im injection monthly with daily oral placebo Anastrozole 1 mg orally daily with placebo im injection monthly Discontinued fulvestrant 125 mg
Phase II efficacy studies				
9238IL/0004 2 centres UK	Open-label, uncontrolled Phase II study in 2 parts: Part 1: Single dose Part 2: Up to 6 monthly doses	Part II: Post-menopausal women with advanced breast cancer who had relapsed on tamoxifen	23	Part 1: Fulvestrant 50 mg as a single LA im injection (5 ml) Part 2: Fulvestrant LA im injection: 100 mg x 1, then 250 mg every 28 days (4 pts) or 250 mg every 28 days (19 pts) up to 6 months
O-15-22 13 centres Japan	Open-label, multicentre uncontrolled Phase II study	Postmenopausal women who had relapsed on tamoxifen (or toremifene) therapy	30	Fulvestrant LA im (5 ml) 250 mg
SZ0001 8 centres Europe	An open, multicentre, non-comparative European Phase II Investigator Initiated study	Post-menopausal women with advanced breast cancer who had failed on prior therapy with non-steroidal or steroidal aromatase inhibitors.	42	250 mg LA im monthly

Methods

Study participants and eligibility criteria. Eligible patients were postmenopausal women with hormone sensitive locally invasive advanced or metastatic breast cancer who had progressed following hormonal therapy for advanced disease or had relapsed after adjuvant endocrine therapy with a non-steroidal anti-oestrogen. Breast cancer had to be confirmed histologically or cytologically. Each patient had to have at least 1 measurable or evaluable lesion in order to be eligible for inclusion.

Evidence of hormone sensitivity was defined as (a) at least 12 months of adjuvant hormonal therapy before relapse, (b) tumour remission or stabilisation after at least 3 months of hormonal therapy before progression, or (c) a tumour status of oestrogen-receptor positive (ER+) or progesterone-receptor positive (PgR+). Patients with a tumour status of ER negative or ER unknown were permitted to enter the studies as long as they fulfilled either criteria (a) or (b).

In addition, selection criteria included a World Health Organisation (WHO) performance status of 0 (fully active), 1 (ambulatory, able to do light work or pursue a sedentary occupation), or 2 (ambulatory, capable of self-care but unable to work) (ref: WHO 1979) and a life expectancy of greater than 3 months. Patients were to be excluded from study participation if they had serious concurrent medical illnesses or laboratory abnormalities that would compromise safety or interfere with the collection or interpretation of efficacy and safety data. Patients were also to be excluded in case of previous treatment with the following: fulvestrant or aromatase inhibitors; two or more regimens of endocrine therapy for advanced disease (excluding oophorectomy, ovarian radiation, or luteinizing hormone-releasing hormone [LH-RH] analogue therapy), radiation or chemotherapy within 4 to 6 weeks of baseline tumour assessment; or oestrogen replacement therapy (within 4 weeks of randomisation [Study 0021], ongoing at entry [Study 0020]); or investigational drug therapy within 4 weeks of randomisation.

Treatments. In both studies, patients received monthly intramuscular long-acting fulvestrant at 250 mg or 125 mg, or the selective aromatase inhibitor anastrozole at 1 mg orally per day. Patients also received, in addition to active treatment, either placebo tablets or placebo injections to maintain blinding to treatment in study 0021. Study 0020 was an open study while Study 0021 was double-blind.

Frequency of clinical assessments. Patients were assessed at baseline and monthly for 3 months and 3-monthly thereafter for 12 months or until withdrawal or progression of disease or death.

Objectives and endpoints. The primary objective was to compare time to disease progression. The secondary objectives were to compare the objective response rate, duration of response, time to treatment failure, time to death, symptomatic response, quality of life, tolerability (local and systemic) and pharmacokinetic assessment.

Time to disease progression was defined as the number of days from date of randomisation until date of objective disease progression (as first documented), or until death from any cause, whichever occurred first. The date of progression was determined using the earliest of dates where there was an increase in size of more than 25% for a measurable lesion, progression of an evaluable non-measurable lesion or a new lesion as indicated by the investigator. For patients who had not progressed at the time of data cut-off, data were right censored for analysis purposes to last assessment date. Objective tumour assessments were first completed in the 4 weeks that preceded the first administration of study treatment. Post-treatment assessments were then repeated every 3 months (±2 weeks) until disease progression. Patients with physically assessable soft-tissue lesions were also assessed monthly for the first 3 months of treatment. The treatment was continued until objective evidence of disease progression or other events requiring treatment withdrawal. Patients were followed up for survival until death. The disease was designated as measurable; evaluable but not measurable; or neither measurable nor evaluable. Patients taking bisphosphonate treatment could enter the trial and their bone lesions could be evaluated for disease progression but not for tumour response. The radiological data were read locally.

Measurable disease was defined as lesions that were clinically measurable in 2 perpendicular axes with at least 1 dimension being greater than or equal to 2.5 cm or measurable using imaging in 2 perpendicular axes with both dimensions being greater than or equal to 1.0 cm. Up to 4 measurable lesions [largest and most clearly defined] were assessed per patient and monitored throughout the

study. Assessment of tumour response was made for both measurable and non-measurable disease based on response categories defined according to the Union Internationale Contre Le Cancer (UICC) criteria for Complete response, partial response, stable disease or disease progression.

Time to treatment failure was defined as the time between randomisation and the earliest occurrence of disease progression, withdrawal of study treatment for any reason, or death from any cause. Patients who have not failed treatment at data cut off would be right-censored at the most recent date of assessment. Time to death was defined the number of days from randomisation to death. This was analysed in the same way as the time to progression. Patients who were alive at data cut off will be right-censored at the latest date they were known to be alive. Duration of response was calculated for those who had a best response of complete response or partial response. Symptomatic response comprising analgesic use, global pain score and performance status was summarised without statistical analysis.

QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B), consisting of the FACT-G 'general' QOL tool for cancer patients and the Breast Cancer Sub-scale (BCS) questionnaires.

Sample size. The estimation of sample size was based on the primary end point of time to progression. Assuming a median time to progression for anastrozole of 140 days (ref: Buzdar 1996), 490 events were considered necessary to detect a hazard ratio of greater than or equal to 1.43 or less than or equal to 0.70, at a significance level of 5% with 90% power. Given that both studies had an estimated accrual time of 24 months, with 6-month follow-up periods, patient requirements were 196 patients per treatment group per study or at least 588 patients per study. When the 125-mg treatment group was dropped, 196 patients would be required in each of the remaining 2 groups, and the analysis would be performed when at least 340 end point events had occurred across each of the remaining 2 groups. Patients were randomised 1:1:1 into Faslodex 125 mg, Faslodex 250 mg or anastrozole 1 mg.

Statistical analyses

The primary analysis was a Cox proportional-hazards model with baseline covariates (age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxics and use of bisphosphonates for bone disease), based on the ITT population (on the basis of randomised treatment for all randomised patients, regardless of treatment actually received). Secondary analyses were conducted for a subset of patients who did not significantly violate or deviate from the protocol (also known as the per-protocol population), by treatment received, and for the ITT population with data unadjusted for baseline effects. Secondary analyses were used to assess whether the conclusions from the primary analyses were robust.

Time to progression (TTP) was summarised by trial treatment using the Kaplan-Meier method. The treatment comparisons was performed using the Cox proportional-hazards model, adjusting for baseline prognostic covariates:. The Log-Rank test was used to provide a comparison of treatment groups without adjusting for potential prognostic factors. A global test for treatment-by-baseline covariate interactions was performed.

Objective responders were patients with a best objective response of complete response or partial response. A logistic regression model was used for analysis of objective response rate and covariates were included in the model. Objective response rates would also be assessed for a subgroup of patients excluding patients with bone only disease treated with biphosphonates.

The effects of centre and treatment-by-centre interaction were not investigated. Additionally, no analyses were performed for individual centres or for any centre sub-grouping. Except where noted, all significance levels were 2-sided.

As prospectively planned, data from Studies 0020 and 0021 were combined for an overall evaluation of fulvestrant effects at the 250-mg dose

Results

A total of 1014 patients from 83 centres in North America and 83 centres in Europe, Australia,and South Africa were randomised to treatment in Studies 0020 and 0021 (Figure 1 and 2). Of these,428 patients were randomised to monthly treatment with fulvestrant 250 mg (Study 0021, 206 patients; Study 0020, 222 patients), 423 to daily treatment with anastrozole 1 mg (Study 0021, 194 patients; Study 0020, 229 patients), and 163 to monthly treatment with fulvestrant 125 mg (Study 0021, 73 patients; Study 0020, 90 patients).

Nearly all patients who were randomised to either fulvestrant 250 mg or anastrozole 1mg received the allocated treatment and were included in the intention to treat analysis as shown in the following flow chart. Only one patient was lost to follow-up. The major reason for withdrawal was objective disease progression.

Fig 1. Flow chart of participants (Study 20)

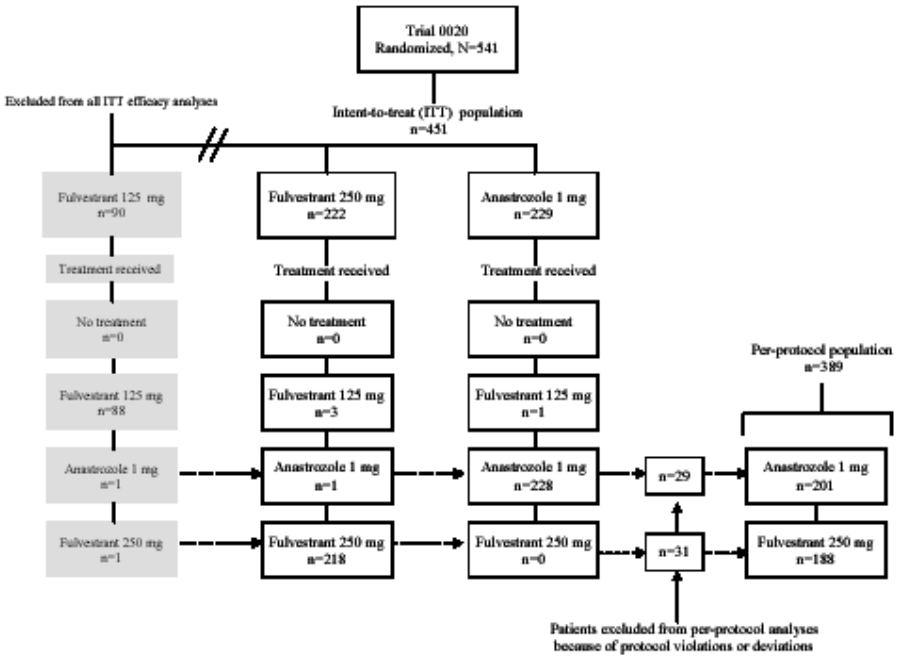
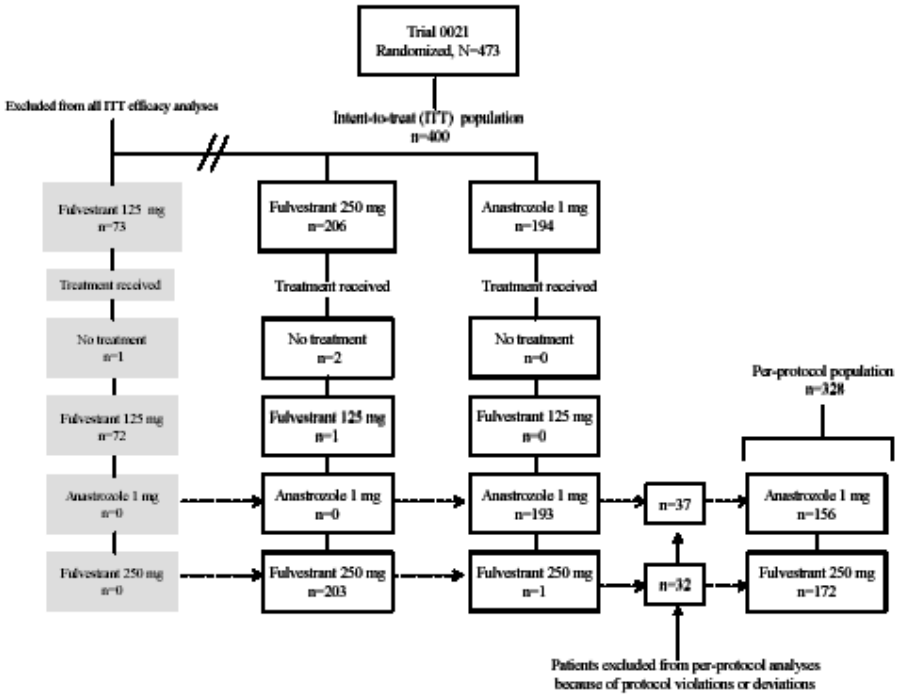


Fig 2. Flow chart of participants (Study 21)



Baseline characteristics

Baseline patient and tumour characteristics are shown in Tables 2 - 7. The median age for patients randomised to anastrozole in Study 0021 was 61 years, compared with a median age of 64 years for patients randomised to fulvestrant (both studies) and 65 years for patients randomised to anastrozole in Study 0020. The mean weight in each of the treatment groups was about 70 kg and the North American patients were 3 to 5 kg heavier than the European patients. The most common previous hormonal therapy was tamoxifen in all groups: 95% of the fulvestrant group and 96 % of the anastrozole group in study 0021 and 97% and 98% in the fulvestrant and tamoxifen groups, respectively (Table 3). The other hormonal agents used were droloxifene, goserelin, idoxifen, megestrol, and toremifene in isolated cases.

Table 2. Demographic characteristics by randomised treatment (Study 0020)

Table 1 Age, weight, and race of patients, by individual efficacy study and studies combined

Demographic characteristic	Study 0021				Study 0020				Combined studies			
	Fulvestrant 250 mg N=206[a]		Anastrozole 1 mg N=194[a]		Fulvestrant 250 mg N=222[a]		Anastrozole 1 mg N=229[a]		Fulvestrant 250 mg N=428		Anastrozole 1 mg N=423	
Age (y)												
Mean	63		62		63		64		63		63	
SD	11		12		10		11		11		11	
Median	64		61		64		65		64		64	
Minimum	33		36		35		33		33		33	
Maximum	89		94		86		89		89		94	
Age distribution, n (%)												
<45	12	(5.8)	12	(6.2)	8	(3.6)	8	(3.5)	20	(4.7)	20	(4.7)
≥45 to <65	96	(46.6)	102	(52.6)	107	(48.2)	103	(45.0)	203	(47.4)	205	(48.5)
≥65 to <75	61	(29.6)	48	(24.7)	74	(33.3)	77	(33.6)	135	(31.5)	125	(29.6)
≥75	37	(18.0)	32	(16.5)	33	(14.9)	41	(17.9)	70	(16.4)	73	(17.3)
Weight (kg)												
Mean	71.7		72.7		68.9		67.8		70.2		70.0	

Demographic characteristic	Study 0021				Study 0020				Combined studies			
	Fulvestrant 250 mg N=206[a]		Anastrozole 1 mg N=194[a]		Fulvestrant 250 mg N=222[a]		Anastrozole 1 mg N=229[a]		Fulvestrant 250 mg N=428		Anastrozole 1 mg N=423	
SD	14.7		16.3		13.0		11.8		13.9		14.3	
Median	72.1		70.7		67.0		67.0		69.1		68.0	
Minimum	36.8		43.1		40.9		40.0		36.8		40.0	
Maximum	126.8		134.0		123.5		110.0		126.8		134.0	
Race, n (%)												
White	177	(85.9)	157	(80.9)	214	(96.4)	218	(95.2)	391	(91.4)	375	(88.7)
Black	20	(9.7)	24	(12.4)	0		0		20	(4.7)	24	(5.7)
Hispanic	8	(3.9)	10	(5.2)	0		1	(0.4)	8	(1.9)	11	(2.6)
Asian/Oriental	0		1	(0.5)	1	(0.5)	2	(0.9)	1	(0.2)	3	(0.7)
Other[b]	1	(0.5)	2	(1.0)	7	(3.2)	8	(3.5)	8	(1.9)	10	(2.4)

[a] For Study 0021 weight calculations: N=199, fulvestrant group; N=185, anastrozole group.
For Study 0020 weight calculations: N=214, fulvestrant group; N=221, anastrozole group.
[b] Includes mixed race and race unknown.
SD Standard deviation.

Table 3. Previous treatment history, by individual study and studies combined

Breast cancer history	Study 0020		Study 0021		Combined studies	
	Fulvestrant 250 mg N=222	Anastrozole 1 mg N=229	Fulvestrant 250 mg N=206	Anastrozole 1 mg N=194	Fulvestrant 250 mg N=428	Anastrozole 1 mg N=423
Previous treatment, n (%)[a]						
Surgery	204(91.9)	200(87.3)	194(94.2)	182(93.8)	398(93.0)	382(90.3)
Cytotoxic chemotherapy	94(42.3)	98(42.8)	129(62.6)	122(62.9)	223(52.1)	220(52.0)
Radiotherapy						
Loco-regional	128(57.7)	125(54.6)	99(48.1)	91(46.9)	227(53.0)	216(51.1)
For metastatic disease	40(18.0)	47(20.5)	68(33.0)	53(27.3)	108(25.2)	100(23.6)

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

Table 4. Receptor status at study entry, by individual study and studies combined

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

ER Oestrogen receptor; PgR Progesterone receptor.

Table 5. Previous hormonal treatment and tumour remission, relapse during adjuvant hormonal treatment, and WHO status, by individual study and studies combined

Breast cancer history	Study 0021		Study 0020		Combined studies	
	Fulvestrant 250 mg N=206	Anastrozole 1 mg N=194	Fulvestrant 250 mg N=222	Anastrozole 1 mg N=229	Fulvestrant 250 mg N=428	Anastrozole 1 mg N=423
Previous hormonal treatment for advanced disease, n (%)	110(53.4)	97 (50.0)	126 (56.8)	129 (56.3)	236 (55.1)	226(53.4)
Tumour remission <3 mo	6 (2.9)	10 (5.2)	7 (3.2)	6 (2.6)	13 (3.0)	16 (3.8)
Tumour remission ≥3 mo	104(50.5)	87 (44.8)	119 (53.6)	123 (53.7)	223 (52.1)	210(49.6)
Relapse during adjuvant hormonal treatment, n (%)	122(59.2)	116 (59.8)	121 (54.5)	119 (52.0)	243 (56.8)	235(55.6)
Relapse after <12 mo	16(7.8)	13 (6.7)	10 (4.5)	9 (3.9)	26 (6.1)	22 (5.2)
Relapse after ≥12 mo	106(51.5)	103 (53.1)	111 (50.0)	110 (48.0)	217 (50.7)	213(50.4)
WHO performance status, n (%)[a]						
0	90(43.7)	84 (43.3)	104 (46.8)	104 (45.4)	194 (45.3)	188(44.4)
1	94(45.6)	95 (49.0)	93 (41.9)	98 (42.8)	187 (43.7)	193(45.6)
2	21(10.2)	15 (7.7)	25 (11.3)	27 (11.8)	46 (10.7)	42 (9.9)

[a] WHO status unknown for 1 fulvestrant-treated patient in Study 0021
WHO World Health Organization; mo Month.

Table 6. Metastatic disease at entry, by individual efficacy study and combined

Disease at entry	Study 0020		Study 0021		Combined studies	
	Fulvestrant 250 mg N=222	Anastrozole 1 mg N=229	Fulvestrant 250 mg N=206	Anastrozole 1 mg N=194	Fulvestrant 250 mg N=428	Anastrozole 1 mg N=423
Sites of metastatic disease,[a] n (%)						
Breast	21 (9.5)	30 (13.1)	8 (3.9)	8 (4.1)	29 (6.8)	38 (9.0)
Skin and soft tissue	40 (18.0)	35 (15.3)	43 (20.9)	41 (21.1)	83 (19.4)	76 (18.0)
Bone	115 (51.8)	117 (51.1)	90 (43.7)	85 (43.8)	205 (47.9)	202 (47.8)
Viscera[b]						
Liver involvement	48 (21.6)	56 (24.5)	47 (22.8)	45 (23.2)	95 (22.2)	101 (23.9)
Lung involvement	56 (25.2)	60 (26.2)	63 (30.6)	60 (30.9)	119 (27.8)	120 (28.4)
Lymph nodes	78 (35.1)	83 (36.2)	58 (28.2)	56 (28.9)	136 (31.8)	139 (32.9)
Other[c]	27 (12.2)	18 (7.9)	22 (10.7)	8 (4.1)	49 (11.4)	26 (6.1)
Extent of metastatic disease, n (%)						
Soft tissue only	11 (5.0)	8 (3.5)	12 (5.8)	13 (6.7)	23 (5.4)	21 (5.0)
Bone only	38 (17.1)	40 (17.5)	47 (22.8)	43 (22.2)	85 (19.9)	83 (19.6)
Viscera only	30 (13.5)	41 (17.9)	39 (18.9)	45 (23.2)	69 (16.1)	86 (20.3)
Lymph node only	22 (9.9)	21 (9.2)	15 (7.3)	17 (8.8)	37 (8.6)	38 (9.0)
Mixed	121 (54.5)	118 (51.5)	92 (44.7)	74 (38.1)	213 (49.8)	192 (45.4)
Unknown	0	1 (0.4)	1 (0.5)	2 (1.0)	1 (0.2)	3 (0.7)

[a] And recurrent disease; patients may be in more than one category.
[b] Defined as liver or lung metastatic, or recurrent, disease.
[C] Include ascites, lymphoedema, pleural effusion and other non-measurable, non-evaluable metastases.

Patients underwent bone scan at entry followed by X-rays if hot spots had been identified. The number of patients found to have metastatic lesions in each of the treatment groups was higher than identified at baseline. The number of patients found to have metastatic bone lesions and the use of phosphonates in each of treatment groups is displayed in Table 7.

Table 7. Patients with metastatic bone lesions and use of bisphosphonates

	Study 0020		Study 0021	
	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
Metastatic bone lesions	103 (68%)	105 (70%)	129 (79%)	117 (77%)
Bisphosphonates	26 (11.8%)	17 (7.5%)	62 (30%)	66 (34%)

Primary end- point -Time to Progression TTP

Patients were followed up for a median of 439 days in Study 0020 (min 0, max 901) while the median was 510 days in Study 0021 (min 0, max 1093). A follow-up of zero could be due to withdrawal of consent at base-line visit. The first patient was recruited into Study 0020 on 11 June 1997 and the last on 8 September 1999 with a data cut-off date of 31 December 1999. The first patient was recruited into Study 0021 on 15 May 1997 and the last on 13 August 1999. At the data cut-off dates, 374 events and 339 events had occurred in Study 0020 and Study 0021, respectively. A summary of TTP results is shown in Table 8-9 and Figure 3.

The two individual studies showed that similar proportion of patients progressed. The combined data showed that, 355 (82.9%) of 428 patients in the fulvestrant group and 358 (84.6%) of 423 patients in the anastrozole group, had disease progression. Tumour progression during treatment was the most common progression event, accounting for progression in 77.6% of the fulvestrant group and 79% of the anastrozole group. Death as a progression event occurred in less than 5% in each group.

Table 8 Time to progression: Primary analyses, by individual study and studies combined

Assessment	**Study 20**		**Study 21**		**Combined analysis**	
	F	**A**	**F**	**A**	**F**	**A**
	(n=222)	**(n=229)**	**(n=206)**	**(n=194)**	**(n=428)**	**(n=423)**
Time to Progression (TTP):						
Proportion of patients progressed	82%	83%	83%	86%	83%	85%
TTP days	166	156	165	103	166	126
Estimated hazard ratio (HR)[a]	0.98		0.92		0.95	
95.14% confidence interval for HR	(0.80-1.21)		(0.74-1.14)		(0.82-1.10)	
p-value	0.84		0.43		0.48	

F fulvestrant 250 mg administered intramuscularly monthly. A anastrozole 1 mg administered orally daily.
[a] Expressed as the ratio of fulvestrant to anastrozole; i.e. hazard ratio (HR) <1 favours fulvestrant.

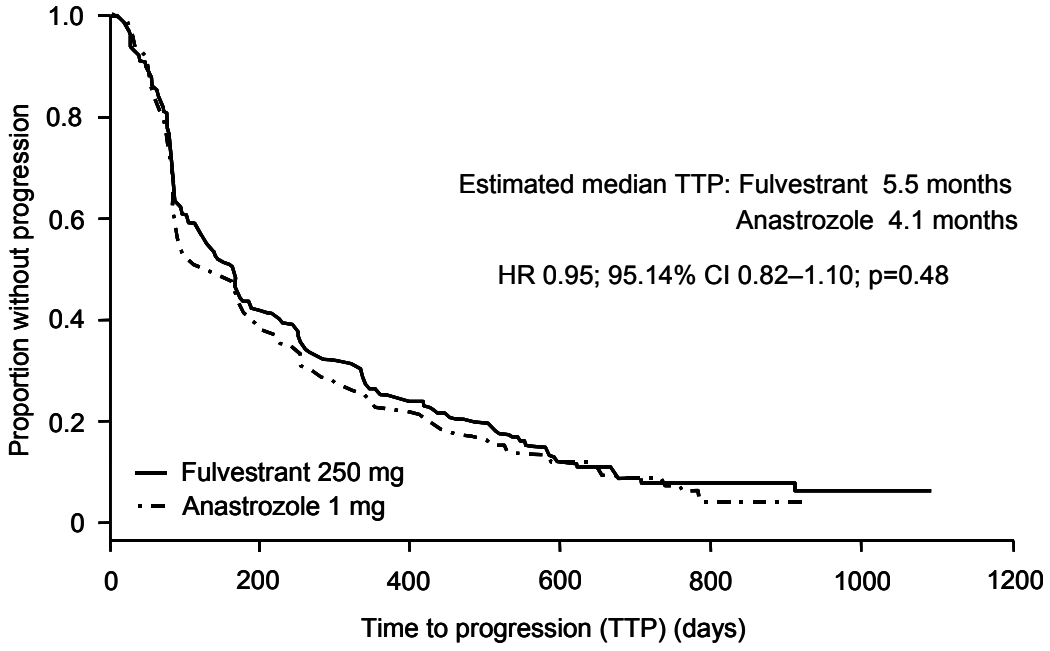
Results of the per protocol analyses were consistent with those of the primary analysis in the percentages of patients who had progressed. Combined data for the per-protocol population showed that 85.3% (307 patients) in the fulvestrant group and 86.0% (307 patients) in the anastrozole group had progression, with most patients progressing during treatment (fulvestrant group, 83.3% [300 patients]; anastrozole group, 82.6% [295 patients]). The hazard ratios for these analyses are presented in table 9.

Table 9. Time to progression: secondary analyses, by individual study and studies combined

Secondary populations by study	Hazard ratio[a]	95.14% CI[b,c]	p-value
Study 0020			
Per-protocol, adjusted[d]	0.97	0.78 to 1.21	0.7888
ITT, unadjusted	0.94	0.76 to 1.15	0.5210
Study 0021			
Per-protocol, adjusted[d]	0.95	0.74 to 1.21	0.6602
ITT, unadjusted	0.88	0.71 to 1.10	0.2594
Studies combined			
Per-protocol, adjusted[d]	0.95	0.81 to 1.11	0.5138
ITT, unadjusted for baseline covariates	0.91	0.78 to 1.05	0.2076
ITT, adjusted[d] with study as a stratified variable	0.95	0.82 to 1.10	0.4789

[a] Fulvestrant/anastrozole. [B] CI Confidence interval (lower limit to upper limit): 95.14% CI accounts for the interim analysis.
[c] The upper limit of the 95.14% CI corresponds to the one-sided 97.57% CI for non-inferiority.
[d] For baseline covariates. ITT Intention to treat.

3.1 Figure 3. Kaplan-Meier plot for time to progression (Studies 0020 and 0021 combined)



Secondary endpoint - Objective tumour response

Overall, 20 (4.7%) patients in the fulvestrant group compared with 11 (2.6%) in the anastrozole group achieved a complete response (CR), and 62 (14.5%) in the fulvestrant group compared with 59 (13.9%) in the anastrozole group achieved a partial response (PR). These differences between treatments for objective response were not statistically significant. The results of the per protocol analyses were consistent with those of the primary ITT analysis. Results are summarised in Tables 10-11.

Table 10. Tumour response by individual study and combined– ITT population

Assessment	Study 20		Study 21		Combined analysis	
	F (n=222)	A (n=229)	F (n=206)	A (n=194)	F (n=428)	A (n=423)
Tumour response:						
Response rate (CR+PR)	20.7%	15.7%	17.5%	17.5%	19.2%	16.5%
Estimated odds ratio[b]	1.38		1.01		1.21	
95.14% confidence limit for odds ratio	(0.84-2.29)		(0.59-1.73)		(0.84-1.74)	
p-value	0.20		0.96		0.31	
Estimated difference in response rates[c]	+4.8%		+0.2%		+2.8%	
95.14% confidence limit for difference in response rates	(-2.2%, +14.2%)		(-6.3%, +9.3%)		(-2.3%, +9.0%)	

F fulvestrant 250 mg administered intramuscularly monthly. A anastrozole 1 mg administered orally daily.
[b] Odds ratio >1 favours fulvestrant 250 mg. [c] Difference in response rates >0 favours fulvestrant 250 mg.
n Number of patients. CR Complete response. PR Partial response

Table 11. Objective tumour response: secondary analyses

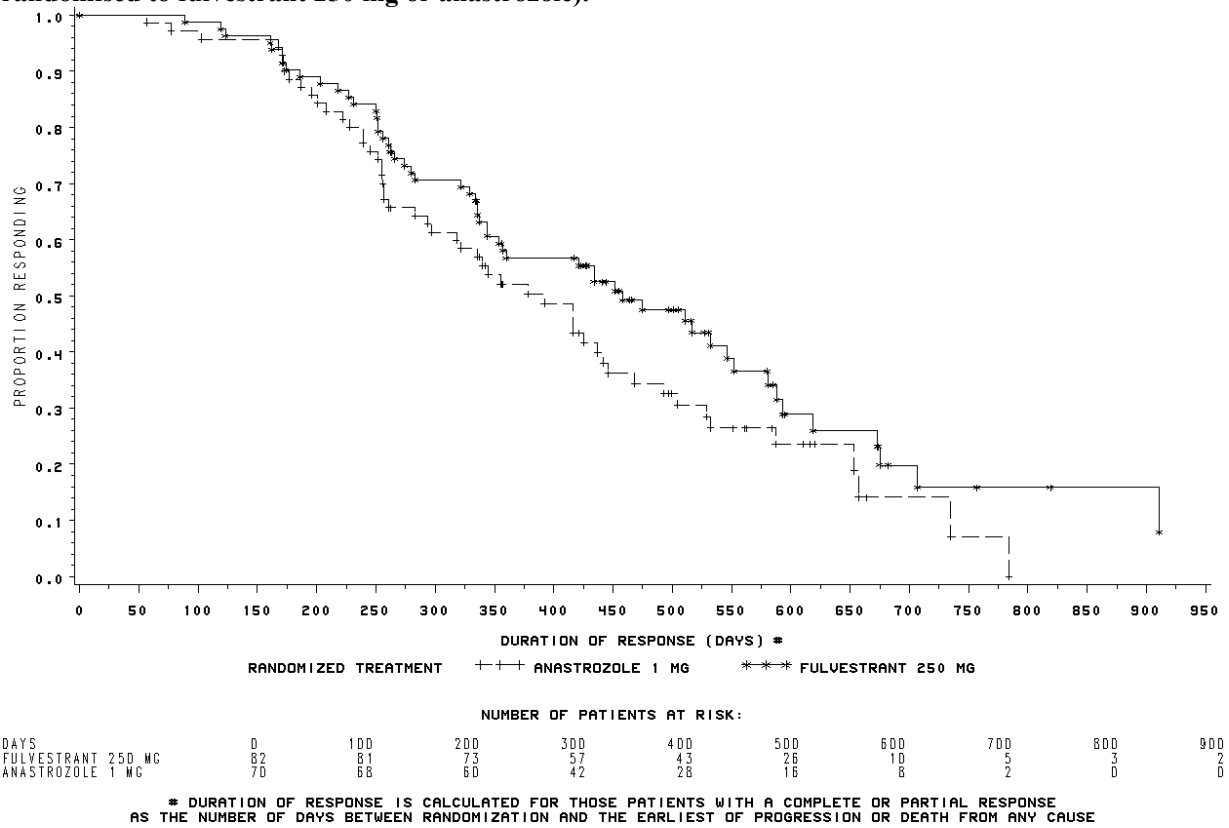
Population	Odds ratio	95.14% CI[a,b] (odds ratio)	Difference in response rates[c]	95.14% CI[a,b] (difference in response rates)	p-value
Study 0020					
Per protocol, adjusted[d]	1.54	0.91 to 2.64	6.50%	-1.25% to 17.08%	0.1087
ITT, unadjusted	1.40	0.86 to 2.29	5.00%	-1.83% to 14.17%	0.1684
Study 0021					
Per protocol, adjusted[d]	1.05	0.58 to 1.91	0.76%	-6.43% to 11.26%	0.8622
ITT, unadjusted	1.00	0.59 to 1.68	-0.05%	-6.34% to 8.77%	0.9895
Studies combined					
Per protocol, adjusted[d]	1.33	0.90 to 1.97	4.21%	-1.43% to 11.39%	0.1550
ITT, unadjusted	1.20	0.84 to 1.71	2.63%	-2.27% to 8.75%	0.3170

[a] CI Confidence interval (lower limit to upper limit); 95.14% CI accounts for interim analysis.
[b] The lower limit of the 95.14% CI corresponds to the one-sided 97.57% CI for non-inferiority.
[c] Estimated; fulvestrant rate minus anastrozole rate. [d] For baseline covariates.

Duration of objective response

Within and across studies, median durations of response from date of randomisation and from date of objective response were consistently greater among patients in the fulvestrant groups (Figure 4). Overall, for the 82 patients in the fulvestrant group who had objective tumour responses, the median duration of response was 458 days (approximately 1 year, 3 months), and for the 70 patients in the anastrozole group who had objective tumour responses, the median duration of treatment was 392 days (approximately 1 year, 1 month), a difference of 2 months.

Figure 4. Kaplan-Meier plots for duration of response from randomisation until objective disease progression (Studies 0020 and 0021 combined –patients included: all patients randomised to fulvestrant 250 mg or anastrozole).



NUMBER OF PATIENTS AT RISK:

DAYS	0	100	200	300	400	500	600	700	800	900
FULVESTRANT 250 MG	82	81	73	57	43	26	10	5	3	2
ANASTROZOLE 1 MG	70	68	60	42	28	16	8	2	0	0

DURATION OF RESPONSE IS CALCULATED FOR THOSE PATIENTS WITH A COMPLETE OR PARTIAL RESPONSE AS THE NUMBER OF DAYS BETWEEN RANDOMIZATION AND THE EARLIEST OF PROGRESSION OR DEATH FROM ANY CAUSE

Survival

The results are summarised in Table 12-13, and Figure 5. The protocol required analysis of time to death was delayed until sufficient events had occurred. For Study 0020, 167 (75.2%) patients randomised to the fulvestrant 250 mg group and 173 (75.5%) patients randomised to the anastrozole 1 mg group had died. The estimated median time to death was 67 days longer for patients in the fulvestrant group, compared with patients in the anastrozole group. In Study 0021, 140 (68.0%) patients randomised to the fulvestrant 250 mg group and 127 (65.5%) patients randomised to the anastrozole 1 mg group had died. The estimated median time to death was 67 days longer for patients in the anastrozole group, compared with patients in the fulvestrant group.

Combining both studies, 307 (71.7%) patients randomised to the fulvestrant 250-mg group and 300 (70.9%) patients randomised to the anastrozole 1-mg group had died. The estimated ITT median time to death was similar for patients in the fulvestrant group compared with patients in the anastrozole group (833 vs. 839 days). The estimated hazard ratio for fulvestrant 250 mg in relation to anastrozole 1 mg was 1.01 with a 2-sided 95% confidence interval of 0.86 to 1.19 (p=0.87).

Table 12. Number of deaths and time to death for patients in Studies 0020 and 0021, separately and combined: ITT population

Assessment	Study 20		Study 21		Combined analysis	
	F (n=222)	A (n=229)	F (n=206)	A (n=194)	F (n=428)	A (n=423)
Time to death						
Proportion of patients progressed	167 (75.2)	173 (75.5)	140 (68.0)	127 (65.5)	307 (71.7)	300 (70.9)
Median days to death	803.0	736.0	844	911	833.0	839.0
Estimated hazard ratio (HR)[a]	0.97		1.03		1.01	
95% confidence interval for HR	0.78 to 1.21		0.81 to 1.32		0.86 to 1.19	
p-value	0.8166		0.7852		0.8707	

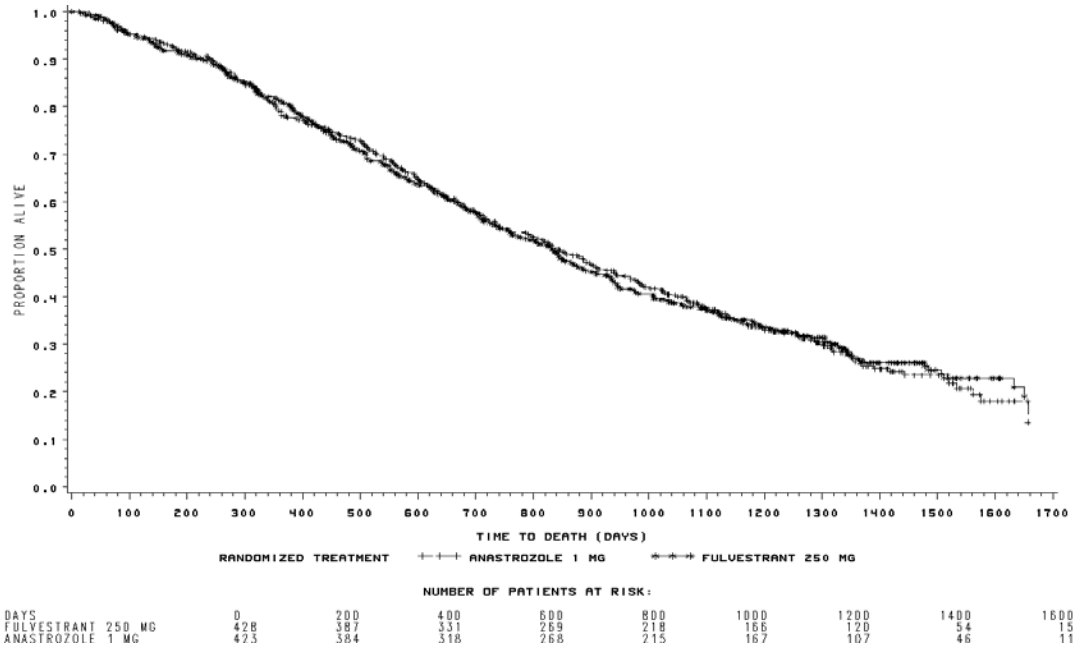
[a] Fulvestrant/anastrozole.

Table 13. Secondary analyses of time to death for patients in Studies 0020 and 0021, separately and combined

Population	Hazard ratio[a]	95% CI[b]	p-value
Study 0020			
Per-protocol, adjusted[c]	0.96	0.75 to 1.22	0.7160
ITT, unadjusted for baseline covariates	0.96	0.78 to 1.19	0.7015
Study 0021			
Per-protocol, adjusted[c]	0.99	0.75 to 1.30	0.9419
ITT, unadjusted for baseline covariates	1.05	0.83 to 1.34	0.6638
Studies 0020 and 0021 combined			
Per-protocol, adjusted[c]	0.98	0.82 to 1.17	0.8045
ITT, unadjusted for baseline covariates	1.00	0.85 to 1.17	0.9733
ITT, adjusted[c] with study (trial) as a stratified variable	1.01	0.86 to 1.19	0.8628

[a] Fulvestrant/anastrozole. [b] CI Confidence interval (lower limit to upper limit).
[c] For baseline covariates. ITT Intention to treat.

3.2 Figure 5. Kaplan-Meier probability of time to death (Studies 0020 and 0021 combined – all patients randomised to fulvestrant 250 mg or anastrozole 1 mg)



Interim analyses

There were 2 planned interim analyses. The first was the review of the effect of the 125 mg monthly dose after treating 30 patients (across Studies 0020 and 0021) for a minimum of 3 months because there was no previous response data at this dose. The second interim analysis was performed after 170 end point events in each of the studies were recorded across the remaining 2 treatment groups.

Data review of the fulvestrant 125 mg dose group

The objective was to assess whether 125 mg fulvestrant would produce a response in 10% of the target population. Had the dose produced a 10% or greater response rate, a 95% chance that 1 or more objective tumour responses would be obtained in 29 successive patients was estimated. At the time of the review, 1 (3.3%) patient had withdrawn, 9 (30%) had stable disease, and 20 (66.7%) had disease progression. Randomisation to the 125-mg dose group was dropped from both studies on 29 April 1998 because no tumour responses were observed. These patients were switched from fulvestrant 125 mg to the most appropriate subsequent therapy as determined by the individual investigator and patient, and no further efficacy data were collected.

Although no tumour responses were observed among the first 30 patients randomised to fulvestrant 125 mg followed-up for a minimum of 3 months, further examination of tumour response data up to 29 April 1998 indicates tumour shrinkage of 50% or greater; i.e. tumour response, in 4/161 (2.5%) of patients in this treatment group.

Final analyses and switch from superiority to non-inferiority

Superiority was not demonstrated and treatment with fulvestrant was retrospectively assessed for non-inferiority, compared with anastrozole, for the pre-defined efficacy end points of time to progression, objective response, and time to treatment failure. The Applicant convened a group of independent clinical and statistical experts in breast cancer to discuss the design of a potential clinical study programme to demonstrate non-inferiority of a new hormonal agent for post-menopausal women with advanced breast cancer, when compared with standard therapy. These participants were selected also on the basis of lack of previous connection with the clinical development of fulvestrant, and, at the time of the forum, no knowledge of the results from the fulvestrant Phase III clinical programme.

The participants reached a consensus that “it would be reasonable to use anastrozole as the reference arm”. Anastrozole was the first, and remains the most widely prescribed, third generation non-steroidal aromatase inhibitor, and was selected as the active comparator in both studies. Based on the

historical performance of anastrozole, when previously compared with megestrol acetate in two published studies using similar patient population as the fulvestrant program, this corresponded to a median TTP of approximately 5 months.

In the absence of data for placebo, the group speculated that the median TTP for 'no treatment' would be approximately 3 months. The group then indicated that at least one half of the presumed benefit for the new agent should preserve anastrozole over 'no treatment'. The 2-sided 95% confidence interval for the TTP hazard ratio should allow a median TTP of less than 4 months for the new agent to be ruled out. This corresponds to a maximally acceptable hazard ratio of 5/4 = 1.25 for the new agent in relation to anastrozole. Continuing this line of reasoning, a hazard ratio of 3/5 = 0.60 for anastrozole in relation to 'no treatment' would apply. The Applicant also justified the choice of non-inferiority margin by citing that a similar margin of 0.25 was used in the assessment of toremifene for approval as a regulatory precedent. The Applicant used *post-hoc* comparisons of time to progression using fulvestrant 250 mg or anastrozole with fulvestrant 125 mg to support the speculated effect of no treatment proposed by the independent expert group (Table 14).

Table 14 Results for Time to Progression comparisons with fulvestrant 125 mg (Studies 20 and 21 combined)

Comparison	Hazard ratio	Confidence interval	p-value
Fulvestrant 250 mg – Fulvestrant 125 mg	0.59	(0.44 – 0.80)	<0.001
Anastrozole 1 mg – Fulvestrant 125 mg	0.63	(0.47 – 0.84)	0.002

Table 15 illustrates the TTP results from the 'Intention to Treat' and 'Per Protocol' analysis populations (Studies 20 and 21 combined)

Table 15 Results from Intention to Treat and Per Protocol populations

Analysis Population	Fulvestrant (n)	Anastrozole (n)	Hazard Ratio	Confidence Interval	p-value
Intention To Treat	428	423	0.95	(0.82 – 1.10)	0.48
Per Protocol	360	357	0.95	(0.81 – 1.11)	0.51

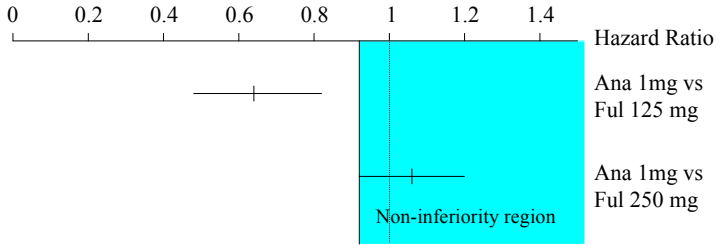
It can be concluded that non-inferiority of fulvestrant 250 mg is demonstrated even for the most conservative estimation for the following reason. Using the upper confidence limit of anastrozole over "no treatment" of 0.84, the non-inferiority margin for 50% of the least benefit of anastrozole over "no treatment" is set as 0.92. As the lower confidence limit of anastrozole over fulvestrant 250 is 0.91 (1/1.10), this lies just to the right of the non-inferiority margin as shown in Figure 6.

Figure 6. Non-inferiority margin and estimatimated hazard ratio for time to progression

Anastrazole 1mg vs Fulvestrant 125 mg: HR 0.63 (95%CI 0.47; 0.84)

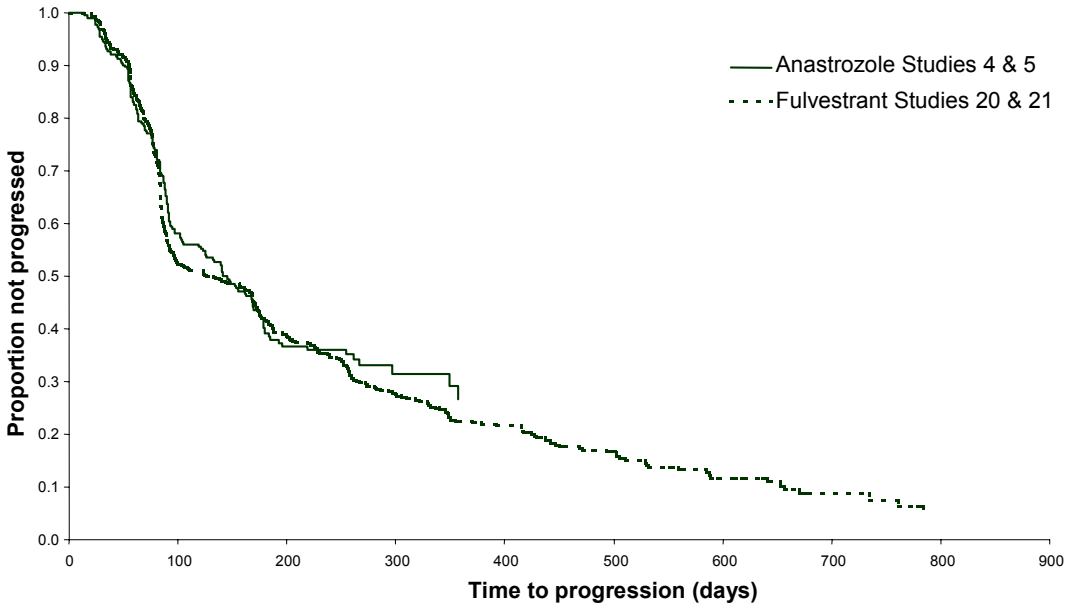
Non-inferiority margin: 50% of the least benefit (upper 95% CI-limit) of Anastrzole vs Fulvestrant 125mg: 0.92

Anastrazole 1mg vs Fulvestrant 250mg: HR 1.05 (95%CI 0.91; 1.22)



Furthermore, the performance of the anastrozole arm in this program is comparable to historical performance. The Kaplan-Meier plot for Time to Progression from the combined analysis of the two registration studies, in which anastrozole 1 mg was compared with megestrol acetate, is superimposed on the corresponding plot for anastrozole 1 mg in the combined analysis of both studies in the fulvestrant Phase III clinical programme in Figure 7. Although this type of visual assessment is subject to the limitations of cross-study comparisons, there appears to be no evidence that the performance of anastrozole in the fulvestrant Phase III clinical programme is inconsistent with the anticipated performance of the drug, based on historical data.

Figure 7. Performance of anastrozole 1 mg in historical setting (Studies 4 and 5 versus megestrol acetate) and in the fulvestrant phase III clinical programme (Studies 20 and 21)



Clinical benefit: Patients designated as responders (complete response or partial response) plus those with a best response of stable disease for 24 or more weeks (calculated from the date of randomisation) were considered to have achieved clinical benefit. Combined data showed that a similar proportion of fulvestrant-treated patients [186 (43.5%)] achieved clinical benefit compared with anastrozole-treated patients [173 (40.9%)]. Median duration of clinical benefit (time between randomisation and first observation of progression) was 20 days longer for patients in the fulvestrant group (combined data) compared with that for patients in the anastrozole group.

Time to treatment failure: The estimated median time to treatment failure (combined data) was 31 days longer for patients in the fulvestrant group (141 days) compared with patients in the anastrozole group (110 days); however, time to treatment failure was not statistically significantly different between treatment groups (p=0.6149).

Quality of life: QOL was assessed using the Functional Assessment of Cancer Therapy-Breast questionnaires. QOL was maintained for patients who received treatment. Time to deterioration in QOL (combined data) was not statistically significantly different between treatment groups (p=0.6051). The median times to deterioration in QOL were 186 and 191 days for patients in the fulvestrant and anastrozole groups, respectively. The pattern of deterioration appeared to follow that for progression, suggesting that deterioration in QOL was a function of disease progression rather than treatment. The similarity in QOL measures between Studies 0020 and 0021 shows that the use of an injection versus an oral treatment does not lead to an adverse effect on QOL.

Supportive studies

There were three supportive non-comparative efficacy studies, namely 0004, SZ001 and O-15-22, involving small number of patients.

Study 0004 was a dose-exploring, non-comparative Phase II efficacy study. In Study 0004, three doses of fulvestrant-50, 100, and 250 mg-were evaluated in a dose-escalating fashion. Among patients who received the 250-mg dose (n =19), 7 had partial responses and 6 had stable disease for at least 6 months.

Study O-15-22 was an open, non-comparative, Japanese Phase II bridging study involving 30 postmenopausal Japanese women with advanced breast cancer, who had relapsed on tamoxifen (or toremifene) therapy after initial response to the therapy. For the primary endpoint of objective tumour response, the response rate was 23.3%, with supportive data provided by the secondary endpoints of clinical benefit, time to progression, duration of response, and time to response.

Study SZ0001 (currently ongoing), is an open, multicentre, non-comparative European Phase II investigator initiated study, with 46 subjects recruited to date in postmenopausal women with advanced breast cancer who had failed on prior therapy with non-steroidal or steroidal aromatase inhibitors (anastrozole, letrozole or aminoglutethimide). Preliminary analyses of data from 32 eligible patients, indicated the following responses: partial response 6%, stable disease 28%, progressive disease 66%, and clinical benefit 34%.

Other studies

Study 0025 compared 250 mg fulvestrant with tamoxifen as *first* line treatment in post-menopausal women with advanced breast cancer. A total of 587 patients were randomised in this double-blind study. The results showed that fulvestrant had anti-tumour effect but neither superiority nor non-inferiority of fulvestrant 250 mg relative to tamoxifen could be concluded for the primary endpoint time to progression. The hazard ratio for time to progression was 1.18 (95% CI 0.98 to 1.44). Statistically significant differences in the secondary endpoints, time to treatment failure and clinical benefit, favoured tamoxifen. The criterion for non-inferiority of fulvestrant relative to tamoxifen was met for objective response rate. The hazard ratio for objective response rate was 0.87 (95% CI 0.61 to 1.14). The study was not sufficiently mature to assess survival at the time of data cut-off.

Study 0042 was a study that compared fulvestrant with tamoxifen as neoadjuvant treatment in post menopausal women with primary breast cancer. This study was terminated early after enrolling three patients on ethical grounds because results from the 0025 study showed that equivalence to tamoxifen could not be claimed.

Discussion on clinical efficacy

The efficacy of fulvestrant was investigated in two randomised multicentre controlled clinical trials, Studies 0020 and 0021, in comparison to the selective aromatase inhibitor anastrozole in postmenopausal women with locally invasive advanced or metastatic breast cancer. All patients were accounted for and followed up in the two pivotal studies. Combined analysis of the two trials showed that both treatment groups were comparable with respect to baseline data. 355 (82.9%) of 428 patients in the fulvestrant group and 358 (84.6%) of 423 patients in the anastrozole group, had disease progression. Tumour progression during treatment was the most common progression event, accounting for progression in 77.6% of the fulvestrant group and 79% of the anastrozole group. Death as a progression event occurred in less than 5% in each group. The per protocol analyses confirmed that the most conservative estimate of time to progression for patients treated with fulvestrant 250 mg was unlikely to be more than 11% higher than that for patients treated with anastrozole. The difference in median time to progression in the two arms in the two studies was noted but the hazard ratios were similar and the Kaplan-Meier plots for the two arms were similar and the point differences observed at the medians were not sustained.

Both studies were originally designed to investigate the potential superiority of fulvestrant over anastrozole but the results did not reach statistical significance. A switch to a claim of non-inferiority was made and analysis performed using a non-inferiority margin that was assigned retrospectively. The non-inferiority criterion 0.25 as proposed by the Applicant is acceptable based on an independent definition of delta using published data and the approval of toremifene using a delta of 0.25 as regulatory precedent. The choice of 0.25 as the margin is also consistent with the EMEA Concept Paper (CPMP/EWP/2158/99) on the choice of delta. The true effect of placebo in this setting is unknown but the Sponsor was able to use post-hoc analysis of the effect of fulvestrant 125 mg to justify the speculated placebo effect, even though fulvestrant 125 mg was unlikely to be worse than no treatment. Because of an absence of dose-finding studies, these two studies were initially designed to study both 125 mg and 250 mg monthly dose groups. Study of the 125 mg group was terminated early because of the lack of objective response in the first 30 patients enrolled across the two trials after prospectively defined interim data analysis.

It can be concluded that non-inferiority of fulvestrant 250 mg is demonstrated even for the most conservative estimation for the following reason. Using the upper confidence limit of anastrozole over "no treatment" of 0.84, the non-inferiority margin for 50% of the least benefit of anastrozole over "no treatment" is set as 0.92. As the lower confidence limit of anastrozole over fulvestrant 250 is 0.91 (1/1.10), this lies just to the right of the non-inferiority margin.

Combining both studies, the estimated ITT median time to death was similar for patients in the fulvestrant group compared with patients in the anastrozole group (833 vs. 839 days). The per protocol analyses were consistent with the primary ITT analysis and the death rate for fulvestrant was unlikely to be more than 19% higher than that of the anastrozole treatment group. The hazard ratios for the individual studies and the combined analysis were approximately 1 and the Kaplan-Meier curves were similar. As the two studies were not designed to show superiority with respect to survival, there was limited power to detect treatment difference in time to death.

Overall, 20 (4.7%) patients in the fulvestrant group compared with 11 (2.6%) in the anastrozole group achieved a complete response (CR), and 62 (14.5%) in the fulvestrant group compared with 59 (13.9%) in the anastrozole group achieved a partial response (PR). These differences between treatments for objective response were not statistically significant. A trend in favour of fulvestrant was obtained in the open study but not in the double-blind study. The odds ratios were 1 or larger in the individual and combined studies, in favour of fulvestrant although none of these results reached statistical significance. The per protocol analysis of the combined results was consistent with the ITT analysis and the objective response rate obtained from fulvestrant was unlikely to be 2.3% below that of anastrozole.

For both treatments, numerical comparisons between subgroups suggested a greater objective response among patients with history of previous hormonal treatment, patients without visceral disease, and patients with measurable disease only, although the latter should be considered cautiously given the small number of patients. Median duration of response from the date of randomisation and from date of objective response were consistently longer among patients in the fulvestrant groups compared with

those in anastrozole groups (2 months and 28 days longer, respectively, favourable to fulvestrant). There were too few patients younger than 45 years to perform any age comparisons.

Clinical safety

A total of 1559 subjects, male and female, received fulvestrant at various doses and of these subjects 1149 were postmenopausal women with breast cancer. In the 2 pivotal studies, a total of 423 postmenopausal women were exposed to monthly injections of the LA formulation of fulvestrant 250 mg; this corresponds to a median treatment duration of approximately 6 months, but some patients were given treatment for up to approximately 5 years. An overview of the adverse events in the two main clinical trials is presented in Table 16.

Table 16 Overview of adverse events in the 2 pivotal controlled efficacy studies

	Study 0020		**Study 0021**	
	Fulvestrant 250 mg N=219 n (%)	**Anastrozole 1 mg N=230 n (%)**	**Fulvestrant 250 mg N=204 n (%)**	**Anastrozole 1 mg N=193 n (%)**
All adverse events	188 (85.8)	199 (86.5)	198 (97.1)	181 (93.8)
Drug-related adverse events	93 (42.5)	78 (33.9)	109 (53.4)	95 (49.2)
Deaths due to adverse events	4 (1.8)	5 (2.2)	1 (0.5)	3 (1.6)
Adverse events leading to withdrawal	8 (3.7)	6 (2.6)	5 (2.5)	6 (3.1)
Serious adverse events	41 (18.7)	37 (16.1)	41 (20.1)	31 (16.1)

[a] Categories are not mutually exclusive. n = Subset of subjects. N = Total number of subjects exposed.

There were a total of 39 adverse events that resulted in death in the entire clinical development program. Five deaths occurred in the fulvestrant arm compared to 8 in the anastrozole arm in the pivotal trials. All causes, in descending frequency, included heart failure, myocardial infarct, arrhythmia, pulmonary embolus, infections, cerebrovascular disease, and isolated cases of renal failure, hypercalcemia, haemorrhage and radiation injury.
Serious adverse events regardless of association with treatment were reported in 82 (19.4%) of the fulvestrant group compared with 68 (16%) of the anastrozole group. Apart from nausea, vomiting, dehydration, pneumonia or pathological fractures that occurred in more than 5 patients in either one of the two treatment groups, a difference in the profile between fulvestrant and anastrozole can not be concluded. However, although drug-related pulmonary embolism was equally uncommon (0.5%) in both groups, deep thrombophlebitis/pulmonary embolus was reported as SAE in a slightly higher number of patients in the fulvestrant group: pulmonary embolism fulvestrant N=5 (1.2%) versus anastrozole N=2 (0.5%); deep venous thrombosis fulvestrant N=5 (1.2%) versus anastrozole N=3 (0.7%). As many of these patients had predisposing factors, a treatment-related effect can not be concluded nor excluded.

The commonest adverse events affecting both fulvestrant and anastrozole treatment groups were nausea, asthenia, pain vasodilatation, and headache. These were consistent with the effects of oestrogen deprivation. In general, there were small differences in incidences between the two groups except for a 50% higher incidence of joint disorders in the anastrozole group. Joint disorders are known to be associated with the use of aromatase inhibitors.

Table 17. Adverse events and intensity of events that occurred at an incidence of ≥5% during treatment or the specified follow-up period in the 2 pivotal controlled efficacy studies

Body system and adverse event[a]	Fulvestrant 250 mg N=423 n (%)		Anastrozole 1 mg N=423 n (%)	
	All intensities	Severe	All intensities	Severe
Body as a whole	295 (69.7)		291 (68.8)	
Asthenia	104 (24.6)	5 (1.2)	118 (27.9)	12 (2.8)
Pain	86 (20.3)	9 (2.1)	95 (22.5)	12 (2.8)
Headache	70 (16.5)	9 (2.1)	75 (17.7)	5 (1.2)
Back pain	68 (16.1)	7 (1.7)	65 (15.4)	7 (1.7)
Abdominal pain	54 (12.8)	4 (0.9)	56 (13.2)	7 (1.7)
Injection-site pain[b]	48 (11.3)	1 (0.2)	29 (6.9)	0
Pelvic pain	47 (11.1)	6 (1.4)	42 (9.9)	7 (1.7)
Flu syndrome	36 (8.5)	2 (0.5)	30 (7.1)	1 (0.2)
Chest pain	32 (7.6)	1 (0.2)	24 (5.7)	5 (1.2)
Fever	32 (7.6)	3 (0.7)	29 (6.9)	2 (0.5)
Accidental injury	23 (5.4)	0	26 (6.1)	4 (0.9)
Cardiovascular system	135 (31.9)		136 (32.2)	
Vasodilatation	78 (18.4)	4 (0.9)	79 (18.7)	1 (0.2)
Hypertension	23 (5.4)	1 (0.2)	24 (5.7)	1 (0.2)
Digestive system	228 (53.9)		211 (49.9)	
Nausea	119 (28.1)	10 (2.4)	114 (27.0)	6 (1.4)
Vomiting	64 (15.1)	8 (1.9)	52 (12.3)	6 (1.4)
Constipation	59 (13.9)	2 (0.5)	50 (11.8)	3 (0.7)
Diarrhoea	59 (13.9)	1 (0.2)	59 (13.9)	1 (0.2)
Anorexia	42 (9.9)	1 (0.2)	48 (11.3)	1 (0.2)
Haemic and lymphatic systems	66 (15.6)		62 (14.7)	
Anaemia	25 (5.9)	2 (0.5)	24 (5.7)	3 (0.7)
Metabolic and nutritional disorders	91 (21.5)		89 (21.0)	
Peripheral oedema	46 (10.9)	3 (0.7)	48 (11.3)	0
Musculoskeletal system	123 (29.1)		134 (31.7)	
Bone pain	76 (18.0)	8 (1.9)	65 (15.4)	6 (1.4)
Myalgia	19 (4.5)	0	21 (5.0)	2 (0.5)
Arthritis	16 (3.8)	3 (0.7)	29 (6.9)	3 (0.7)
Nervous system	161 (38.1)		157 (37.1)	
Insomnia	35 (8.3)	0	42 (9.9)	0
Dizziness	34 (8.0)	4 (0.9)	31 (7.3)	1 (0.2)
Paresthesia	30 (7.1)	1 (0.2)	37 (8.7)	1 (0.2)
Depression	27 (6.4)	0	33 (7.8)	1 (0.2)
Anxiety	23 (5.4)	0	20 (4.7)	1 (0.2)
Respiratory system	172 (40.7)		151 (35.7)	
Pharyngitis	73 (17.3)	0	53 (12.5)	0
Dyspnoea	68 (16.1)	5 (1.2)	57 (13.5)	9 (2.1)
Cough increased	52 (12.3)	2 (0.5)	51 (12.1)	1 (0.2)
Sinusitis	16 (3.8)	0	22 (5.2)	0
Skin and appendages	102 (24.1)		109 (25.8)	
Rash	39 (9.2)	2 (0.5)	38 (9.0)	0
Sweating	22 (5.2)	2 (0.5)	24 (5.7)	0
Urogenital system	85 (20.1)		80 (18.9)	
Urinary tract infection	29 (6.9)	0	20 (4.7)	0

[a] A patient may have had more than 1 adverse event. n = Subset of patients. N =Total number of patients.

[b] In Study 0020 treatment was not blinded, patients on anastrolzole did not receive placebo injections, and fulvestrant 250 mg was delivered in a single 5-ml injectins. In Study 0021 where 2x2.5 ml injections (1 in each buttock) were administered monthly to patients in both fulvestrant 250 mg and anastrozole (placebo injections) groups. The incidence of injection-site events in Study 0021 was higher comopared to Study 0020. It is presumed to be due to the greater number of injections (2 per visit for all patients) in Study 0021.

Fulvestrant injections were reasonably well tolerated. 11% of the fulvestrant group reported pain at the injection site but these cases were typically mild to moderate in intensity. There was one patient who withdrew because of pain. So far, only one case of local necrosis requiring debridement has been reported in a diabetic patient for whom there was some doubt on whether the injection was administered correctly into the muscle.

Immunogenicity events had not been specifically studied. Two cases of angioedema had been reported, one in the clinical trial program and another post-marketing. A total of 5 cases of urticaria have been reported in the post-marketing program.

The shift tables on haematology, biochemistry and liver enzymes from baseline to withdrawal showed similar trends for changes in both treatment groups. A few cases of leucopenia were reported in patients who received cytotoxics treatment soon after withdrawal from treatment and that would have been the more likely cause. Analyses of AST, ALT in those patients with or without liver metastases did not point to any significant hepatotoxic risk for fulvestrant. The currently available data do not suggest any significant diabetogenic potential for fulvestrant.

The switch from tamoxifen was followed by changes in total cholesterol, LDL-cholesterol and lipoprotein A increased in both the fulvestrant group and anastrozole group and that was not unexpected.

There were no drug interactions of note reported in the clinical trial program.

Discussion on clinical safety

The total number of patients exposed to fulvestrant in the clinical trial programme is sufficient for preliminary assessment of safety in view of the proposed therapeutic indication. However, due to the patient population with advanced breast cancer, the median duration of exposure is not high (approximately 6 months). Many potential risks of treatment (such as cardiovascular undesirable effects, including venous thromboembolism, adverse effect on bone density, effects on ovaries and endometrium) may not be readily assessable based on the database.

The number of deaths due to adverse events was too low to allow comment on difference between groups but patients who died in the fulvestrant group were younger than those in the anastrozole group. The cause of death was reported heart arrest, heart failure, ventricular arrhythmia and pulmonary embolism in the four cases of cardiovascular death in the fulvestrant group.

Concerning the observed serious adverse events, both arterial and venous thromboembolic events should be kept under observation in the post-marketing program. The applicant has committed to provide cumulative review of these adverse events, within the post-marketing surveillance program. Cumulative review will also be provided for cardiovascular events (arrhythmia, heart failure, ischaemic heart disease), hypersensitivity, fractures and osteoporosis, and local reactions.

The Applicant proposed to assess the effect of fulvestrant on the endometrium in the neoadjuvant setting and this is supported. In view of the mechanism of action of fulvestrant, the study duration of 4 months is acceptable.

A negative effect on bone mineral density with long-term fulvestrant treatment is considered to be likely because of its antioestrogenic effect. The recently published randomised trial of letrozole in postmenopausal women after 5 years of tamoxifen therapy for early-stage breast cancer reported a numerically increarse in the rate of new-onset osteoporosis in the letrozole group (5.8%) in comparison with placebo (4.5%, p=0.07) (Goss et al., 2003). The Applicant committed to study biochemical markers of bone turnover in the neoadjuvant setting. It is agreed that it would be difficult to interpret changes in bone mineral density in the metastatic disease setting. A warning has been included in the SPC that . Due to the mode of actions of fulvestrant, there is a potential risk of osteoporosis.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the benefit risk balance of the product.

Non-clinical pharmacology and toxicology

Fulvestrant is a non-agonist antioestrogen and has no other discernible pharmacological effects. The mode of action appears related to estrogen receptor downregulation. The non-clinical data presented is consistent with the compound having efficacy in the proposed indication of treatment of advanced breast cancer in women whose disease has progressed following endocrine therapy.

Fulvestrant has low acute and chronic toxic potential. The pivotal toxicology studies have been conducted in appropriate species and have shown that there are no major issues of concern from a pre-clinical perspective. Overall, adverse findings can be considered to be linked to the pharmacological mode of action. In the present set of non-clinical studies no toxicological findings can be identified that may be considered real safety issues.

Clinical documentation

Pharmacology

The pharmacokinetics of fulvestrant has been studied appropriately. Two follow-up measures are related to influence of hepatic impairment on fulvestrant pharmacokinetics and potential for inhibition of CYP2A6, CYP2C8 and CYP2E1.

The optimal dose and regimen of fulvestrant in terms of benefit/risk is still not clarified but the applicant has committed to resolve this through a post-marketing study.

Efficacy

The overall conclusion on efficacy is that fulvestrant 250mg monthly treatment is non-inferior to anastrozole 1mg daily treatment in postmenopausal women with locally advanced or metastatic breast cancer whose disease has progressed following hormonal therapy or had relapsed after adjuvant endocrine therapy with an anti-oestrogen. This second-line indication is restricted to those patients with ER positive breast cancer, consistent with the mechanism of action of fulvestrant and the analysis of results according to ER status.

Safety

The available safety data suggest that fulvestrant LA im 250 mg once a month has an acceptable safety profile in the context of the proposed therapeutic indications. Data on endometrial and bone safety are limited, and further evaluation is required as post-marketing studies. The absence of safety data in patients with hepatic impairment, especially in view of expected major impact of hepatic impairment on fulvestrant pharmacokinetics, requires further investigations. Hypersensitivity reactions (angioedema and urticaria), cardiovascular reactions (including arterial and venous thromboembolism, arrhythmia and heart failure), cerebrovascular events and hepatic adverse drug reactions must continue to be closely monitored with reporting of cumulative incidences. Adverse effect on bone density and fractures with long-term use is not unexpected and monitoring of these events should also be undertaken. The applicant has committed to a post-marketing surveillance programme to monitor these events.

Benefit/risk assessment

Fulvestrant 250mg monthly treatment is non-inferior to anastrozole 1mg daily treatment in postmenopausal women with locally advanced or metastatic breast cancer whose disease has

progressed following hormonal therapy or had relapsed after adjuvant endocrine therapy with an anti-oestrogen. This second-line indication is restricted to those patients with ER positive breast cancer, consistent with the mechanism of action of fulvestrant and the analysis of results according to ER status.

The optimal dose and regimen of fulvestrant in terms of benefit/risk is still not clarified. In response to the CPMP's list of outstanding issues, the Applicant has proposed a new study (0064) to compare the 250mg monthly dose with a 500mg monthly dose in combination with a loading dose in the second-line treatment setting. The Applicant has also submitted an outline to a neoadjuvant study (0065) and it is agreed that this study will provide useful and relevant information on the relationship between exposure, ER receptor down-regulation and efficacy. The results of both of these studies will be submitted as post-marketing commitments.

The dose comparison study was discussed within the CPMP therapeutic advisory group in oncology. The advisory group considered that proposed new study to compare the 250 mg monthly dose with a higher dose in combination with a loading dose in a second-line indication is considered useful. The study should be adequately powered to detect a risk reduction, which is considered clinically meaningful.

While the available safety profile of the 250mg monthly dose is acceptable in the context of the proposed therapeutic indication, data on endometrial and bone safety are limited, further evaluation has therefore been included in the proposed post-marketing clinical studies. The Applicant's proposal to commit to further investigate endometrial safety and bone safety as part of a neoadjuvant study is acceptable. Due to limited experience, hypersensitivity reactions, cardiovascular reactions (including arterial and venous thromboembolism, arrhythmia and heart failure), cerebrovascular events, and hepatic ADRs will be closely monitored in a post-marketing surveillance program.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Faslodex in the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant antioestrogen therapy or disease progression on therapy with an antioestrogen was favourable.