European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/14045/2009

ASSESSMENT REPORT

FOR

FABLYN

International Nonproprietary Name: lasofoxifene

Procedure No. EMEA/H/C/000977

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Pfizer Limited submitted on 10 January 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for FABLYN, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 May 2007.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the USA. The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Steffen Thirstrup
Co-Rapporteur: Pieter de Graeff

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 10 January 2008.
- The procedure started on 30 January 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 April 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 April 2008.
- During the meeting on 27-30 May 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 30 May 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2008.
- A GCP inspection related to clinical trial protocol A2181002 was requested by the CHMP and was carried out at one site in Argentina and one site in Romania. The final integrated Inspection Report was issued on 25 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 September 2008.
- During the CHMP meeting on 22-25 September 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 20 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 6 November 2008.
- During the CHMP meeting on 17-20 November 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP on 19 November 2008.
- During the CHMP meeting on 17-20 November 2008, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP list of outstanding issues on 26 November 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 4 December 2008.

- During the meeting on 15-18 December 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to FABLYN on 18 December 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 12 December 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Osteoporosis is a systematic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures cause substantial clinical and economic burden for society. Vertebral and hip fractures have been, for many years, associated with increased morbidity and mortality. More recently, an association has been shown between increased mortality and a collective group of other major nonvertebral fractures (i.e. pelvis, distal femur, proximal tibia, multiple ribs and proximal humerus). Hip, vertebral, forearm and humeral fractures also reduce, to various extents, health-related quality of life with deleterious effects lasting up to several years after the fracture event.

Primary or involutional osteoporosis develops as a result of excessive age-related bone loss. Age and menopause are the two main determinants of osteoporosis. The cessation of ovarian production of oestrogen, at the time of the menopause, results in an accelerated rate of bone loss in women.

The aim of the pharmacological intervention is to decrease the incidence of fractures. Several compounds with original modes of action have been approved for the treatment of postmenopausal osteoporosis after demonstration of an anti-fracture efficacy at the level of the axial skeleton (spine) or appendicular skeleton (all non-vertebral, major non-vertebral, or hip). These products include bisphosphonates with daily or intermittent dosing formulations, selective oestrogen receptor modulators, calcitonin, active vitamin D metabolites, teriparatide, and strontium ranelate. Hormone replacement therapy (HRT) has been shown to reduce the risk of fracture, but increases the risk of breast cancer and cardiovascular diseases.

Lasofoxifene belongs to the class of selective estrogen receptor modulators (SERMs). SERMs exert selective agonist and antagonist effects on different estrogen target tissues and are chemically diverse and act by binding to the α and β isoforms of the estrogen receptor (ERα or ERβ), which have distinct functions in cells. The resultant conformational change and receptor dimerization allows interaction with coregulators and promoter regions on DNA.

The EMEA/CHMP Guideline on the Evaluation of Medicinal products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95), in its current version (Revision 2), is applicable for this application. EMEA/CHMP scientific advice has not been obtained by the applicant for the development programme.

The application for marketing authorization is a so called “full application” meaning that a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants’ own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies has been submitted.

FABLYN is available in film-coated tablets containing lasofoxifene tartrate, equivalent to 500 micrograms lasofoxifene. The recommended dose is one 500 microgram tablet daily taken any time of day without regard to food and beverage intake. Supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

The claimed indication at time of application read as follows: “FABLYN is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A significant reduction in the

incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated (see section 5.1)."

The approved indication is:

> "FABLYN is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated (see section 5.1).
>
> When determining the choice of FABLYN or other therapies, including estrogens, for a postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits (see section 5.1)."

2.2 Quality aspects

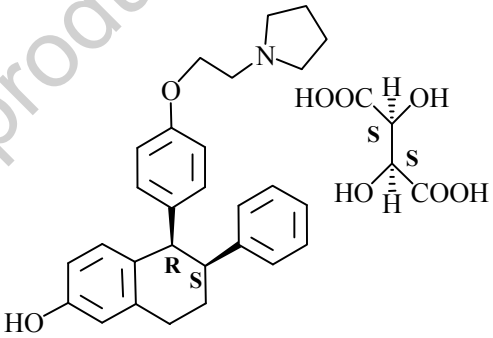
Introduction

FABLYN is presented as film-coated tablets containing lasofoxifene tartrate, equivalent to 500 micrograms lasofoxifene. Other ingredients are cellulose microcrystalline, lactose anhydrous, silica (colloidal anhydrous), croscarmellose sodium, magnesium stearate. The film tablet coat contains hypromellose, titanium dioxide, lactose monohydrate and glycerol triacetate and sunset yellow FCF aluminium lake (E110).

The tablets are packed in PVC blisters sealed with aluminium foil or HDPE bottles.

Active Substance

Lasofoxifene has the chemical name 6S-Phenyl-5R-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalen-2-ol, 2S,3S–Dihydroxy-succinic acid, and the structural formula is the following:



Lasofoxifene tartrate is a nonhygroscopic, white to off-white solid and its aqueous solubility is pH dependant. The polymorphic form is form A, no other forms have been discovered during development.

- Manufacture

The synthesis of lasofoxifene tartrate drug substance consists of five steps.

Adequate information on the starting materials and reagents and solvents were provided, including specifications, methods and where relevant also validations. Specifications have been set for the intermediates, starting materials and reagents. The impurities are discussed. Methods and where relevant validations have been provided

Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

- Specification

The active substance specifications include tests for appearance, identification (HPLC, IR or NIR), assay (HPLC), tartaric acid content (HPLC), water content, heavy metals, residue on ignition (Ph Eur), residual solvents (GC), purity (HPLC), chiral purity (HPLC), particle size.

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Batch analysis data of a number of batches of active substance were provided. The results are within the specifications and consistent from batch to batch.

- Stability

Three batches were packed in the double LDPE anti-static liners in stainless steel drums and stored according to ICH guidelines for up to 60 months at 5 °C/60% RH and 25 °C/60% RH, up to 12 months at 30 °C/60% RH and up to 6 months at 40 °C/75% RH. Site specific stability studies were also performed, with data available up to 48 months for three batches at 5 °C/60% RH, 25 °C/60% RH and 30 °C/60% RH, and up to 6 months at 40 °C/75% RH.

The stability parameters investigated were appearance, water content, assay, achiral purity, chiral purity and particle size.

In addition photostability and degradation studies were performed.

The results justify a retest period proposed by the company in the intended packaging.

Medicinal Product

- Pharmaceutical Development

During development, several immediate release oral forms were developed and for tablets several strengths were formulated. The active substance is compatible with the excipients which were shown by compatibility studies and finished product stability. A bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation. The manufacturing process was justified and no critical process steps were identified.

The excipients used in the tablet core are cellulose microcrystalline, lactose anhydrous, silica (colloidal anhydrous), croscarmellose sodium, magnesium stearate, and the film tablet coat contains hypromellose, titanium dioxide, lactose monohydrate and glycerol triacetate and sunset yellow FCF aluminium lake (E110).

All excipients chosen are well-known and comply with the Ph Eur, except for sunset yellow FCF aluminium lake. The choice and function of the excipients in the formulation were described.

FABLYN is packaged in HDPE bottles or in PVC / Aluminium blisters. The packaging material components have been sufficiently described and the specifications established are in compliance with EU Guideline on plastic immediate packaging materials where relevant.

- Adventitious agents

Except for lactose anhydrous and lactose monohydrate no excipients are of animal or human origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as

those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products'.

- Manufacture of the Product

The proposed commercial manufacturing process is considered as conventional but it is regarded as a non-standard process as the active substance is present in a low amount. Sufficient experience from manufacture of low dose products has however been demonstrated.

The manufacturing process was validated by a number of studies for the major steps of the manufacturing process. The manufacturing process has adequately been validated and is satisfactory. The in process controls are adequate for this pharmaceutical form.

The batch analysis data show that the product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for description, identification (HPLC, TLC), assay (HPLC), uniformity of dosage units (Ph Eur), water content, dissolution, individual degradation products (HPLC), total degradations products (HPLC), and microbial purity (Ph Eur).

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for the intended purpose.

Batch analysis data on several commercial scale batches confirm satisfactory uniformity of the product at release.

- Stability of the Product

Three production scale batches were stored at 30°C/65% RH for 36 months and at 40ºC/75% RH for 6 months in the proposed market packaging materials. Five bottle/fill configurations were tested at the 30°C/65%RH condition.

Parameters investigated were appearance, assay, chiral purity, degradation products, water content and dissolution. Microbial purity has been tested for in one batch (both packagings) at the 12 month and 36 month time point.

In addition, one production batch was stored for photostability and under stress conditions.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

A comprehensive nonclinical toxicity study programme was conducted prior to and in parallel with the clinical program. These studies included a battery of both *in vitro* and *in vivo* genotoxicity studies, safety pharmacology studies, acute and repeated dose oral studies, rodent carcinogenicity studies, and developmental and reproductive toxicity studies.

All the pivotal toxicity studies were conducted in compliance with GLP regulations. The safety pharmacology studies were not conducted in compliance with GLP in accordance with the current guideline. Nevertheless, the GLP-compliant repeat-dose toxicity studies are regarded as sufficient for the safety assessment due to the lack of treatment-related effects in the CNS and respiratory functions together with the low cardiotoxic potential of lasofoxifene.

Pharmacology

- Primary pharmacodynamics

Lasofoxifene has high affinity for both ER-α (IC_{50} = 1.08 nM) and ER-β (IC_{50} = 4.41 nM), whereas the metabolites of lasofoxifene showed a significantly reduced affinity to the estrogen receptors (IC_{50} of minimal 33.7 nM and 79.9 nM, respectively). Although limited, the *in vitro* data suggest that lasofoxifene has mixed agonistic and antagonistic actions. Crystallographic evidence indicates that the tissue selective actions of lasofoxifene can be explained by the conformational changes induced in the estrogen receptor.

In vitro, lasofoxifene inhibited osteoclastogenesis by inducing apoptosis of osteoclast precursors in a dose-dependent manner.

The pharmacological effect of lasofoxifene has been studied in three prevention studies in the OVX rats: 4-week, 8-week and 12-month. In general, OVX induced elevation of the bone biomarkers (osteocalcin and deoxypyridinoline), reduction of trabecular bone content/density (as measured by pQCT and histomophometry) and reduction of bone strength. Lasofoxifene partially prevented the OVX-induced changes. Generally, effects were without apparent dose-response relationship as all dosages gave similar effects.

The effect of lasofoxifene was also investigated in a 24-month prevention study in OVX monkeys. Lasofoxifene partially inhibited OVX-induced increase in bone turnover and bone loss (spine BMD and hip BMD). The effect of lasofoxifene on bone strength and bone structure (histomorphometry) was less obvious. Most effects of lasofoxifene on bone parameters were observed in cancellous bone while little effect was observed on endocortical bone.

- Secondary pharmacodynamics

Lasofoxifene is not expected to interact with several different types of receptor systems at therapeutic plasma concentrations since 1) the selectivity towards the ERs as compared to a number of other receptors is more than 20-fold, 2) the plasma protein binding of lasofoxifene is high (>99%), and 3) the mean peak concentration observed in humans treated with the proposed clinical dose of lasofoxifene are at least 16-fold lower than the IC_{50} values determined for these receptor systems.

The *in vivo* effect of lasofoxifene on reproductive tissues, mammary tissues, serum cholesterol and body weight gain is described in the following:

<u>Effect of lasofoxifene on reproductive tissues</u>
In immature rats treated with lasofoxifene, uterine weights did not differ from vehicle-treated controls with the exception of lasofoxifene at the 10 μg/kg/day dose. In contrast to lasofoxifene, ethynyl estradiol (EE) significantly increased uterine wet and dry weight in immature rats by over 200% and

57%, respectively. In OVX immature rats, short-term treatment with lasofoxifene (0.01 and 0.1 µg/kg/day PO) significantly increased uterine and vaginal wet weights, uterine and vaginal epithelial thickness and cell proliferation in both uterus and vagina over the vehicle-treated control, but to a much lower extent than the significant increases seen with estradiol. Treatment with the lowest dose of lasofoxifene only significantly increased vaginal thickness and cell proliferation in both epithelial cells and stromal cells of the uterus. Results obtained following treatment with lasofoxifene are almost similar to those found after treatment with raloxifene. In contrast to OVX controls and estradiol and other SERM-treated rats, lasofoxifene (0.1 µg/kg/day) significantly increased mucopolysaccharide production from the epithelial cells of the vagina which may explain the increase in vaginal wet weight. The applicant claims that this lasofoxifene-induced increase in mucopolysaccharide production is one of the unique beneficial effects that differentiate lasofoxifene from estrogen and other SERMS. Mucopolysaccharide is a protein-polysaccharide complex containing up to 95% of polysaccharide, which is composed of mucin and glycogen. Treatment with lasofoxifene enhances vaginal epithelial cell differentiation, resulting in increased mucus and glycogen synthesis. This is known to contribute to the reduction in vaginal pH as glycogen is broken down by lactobacilli to form lactic acid in the vaginal cavity. This pH change provides a protective environment against pathogenic microorganisms and may contribute to the improvement in vaginal health. However, the applicant has not provided evidence supporting this claim.

In adult rats, short-term treatment (8 weeks) with lasofoxifene slightly but significantly increased both uterine and vaginal weights in OVX rats when compared with OVX controls, but was significantly less than in sham controls. When lasofoxifene and estradiol were co-administered to OVX rats, lasofoxifene inhibited the hypertrophic effects of EE in the uterus, indicating that lasofoxifene is an ER antagonist in the uterus, and does not stimulate uterine epithelial cell proliferation, as do estrogens and tamoxifen. Following long-term treatment, uterine and vaginal wet weights in OVX rats did not significantly differ from OVX controls, but were significantly less than in sham controls. Histological examination of the uteri revealed that lasofoxifene prevented OVX-induced uterine epithelial atrophy, whereas other results were more identical to OVX controls.

Four-week treatment of aged intact female rats with lasofoxifene at doses as high as 73.3 µg/kg/day had no significant effects on uterine weight and uterine histology.

Long-term treatment of OVX monkeys with lasofoxifene (1 and 5 mg/kg/day PO) produced only minor uterine changes, such as simple endometrial hyperplasia, endometrial cystic changes and endometrial stromal fibrosis. Lasofoxifene had no effect on the vagina of OVX monkeys following 2 years of treatment.

Effect of lasofoxifene on mammary tissue

Lasofoxifene at the highest dose (10 mg/kg PO or SC) significantly inhibited growth of the human MCF-7 breast tumor grown as a xenograft in athymic mice and with comparable efficacy and potency as tamoxifen. In the N-methylnitrosourea (NMU)-induced rat mammary carcinoma model, lasofoxifene significantly reduced tumor incidence, tumor multiplicity and tumor volume compared to vehicle-treated rats. Similar to tamoxifen, lasofoxifene is effective in both preventing and treating mammary carcinoma in rats.

In OVX primates, long-term treatment with lasofoxifene did not induce any proliferative changes in mammary glands.

Effect of lasofoxifene on total serum cholesterol

In rats, short-term treatment (28 days) with lasofoxifene significantly reduced the OVX-induced increase in total serum cholesterol in a dose dependent manner, whereas in monkeys, only minimal differences between the OVX and lasofoxifene groups were found following 12, 18 and 24 months of treatment. The lack of significance in this latter study is most likely related to the initial high cholesterol diet and the change in diet at only 40 weeks.

Effect of lasofoxifene on body weight gain
Lasofoxifene inhibited OVX-induced body weight gain in both rats and monkeys.

- Safety pharmacology programme

An overview of the safety pharmacology studies conducted with lasofoxifene is given in Table 1.

Table 1 Results from the safety pharmacology studies

Organ System Evaluated (Study Report No.) GLP-status	Species/ Number/ Group	Method of Administration / Dose	Results	NOAEL
CENTRAL NERVOUS SYSTEM				
Irwin's test incl. locomotor activity, reflexes, muscle tone, autonomic system function. (General pharmacology evaluation) Non-GLP	CD-1 mice/ 3♂/group	0.01, 0.032, 0.1, 0.32, 1, 3.2, 10 mg/kg PO	No treatment-related effects	10 mg/kg PO
Proconvulsant/anti-convulsant effects following pentylenetetrazol (PTZ)-injection (General pharmacology evaluation) Non-GLP	CD-1 mice/24-26/group	20, 200, 2000 µg/kg PO	No treatment-related effects	2000 µg/kg PO (corresponding to a plasma concentration of 23 ng/mL)
CARDIOVASCULAR SYSTEM, RESPIRATORY SYSTEM				
Vascular smooth muscle (General pharmacology evaluation) Non-GLP	Isolated aorta from guinea pigs/2	*In vitro*/ 1 nM-10 µM	No treatment-related effects on basal tension or on norepinephrine-stimulated contraction	10 µM
Heart muscle (General pharmacology evaluation) Non-GLP	Isolated atria from guinea pigs/2	*In vitro*/ 1 nM-10 µM	**1 µM:** 5% inhibition of the basal heart rate **10 µM:** 25% inhibition of the basal heart rate	100 nM
Heart muscle (General pharmacology evaluation) Non-GLP	Isolated left atria from Hartley guinea pigs/2	*In vitro*/ 1, 3, 6, 10 µM	Up to approximately 35% inhibition of the maximal response at all concentration with no apparent concentration-response relationship	ND
Cardiovascular functions (General pharmacology evaluation) Non-GLP	M. fascicularis primates/ 3/sex/group	1 mg/kg PO	No treatment-related effects	1 mg/kg PO (corresponding to a plasma concentration of approximately 24 ng/ml)
Cardiovascular and respiratory functions (General pharmacology evaluation) Non-GLP	SD rats/ 6 ♂/group	2 mg/kg PO	No treatment-related effects	2 mg/kg PO
RENAL SYSTEM, GASTROINTESTINAL SYSTEM				
Renal function (General pharmacology evaluation) Non-GLP	SD rats/ 12 ♂/group	20, 200, 2000 µg/kg PO	No treatment-related effects	2000 µg/kg PO
Intestinal smooth muscle (General pharmacology evaluation) Non-GLP	Isolated ileum from guinea pigs/2	*In vitro*/ 1 nM-10 µM	**10 µM:** 94% inhibition of histamine-stimulated tension	1 µM

Organ System Evaluated (Study Report No.) GLP-status	Species/ Number/ Group	Method of Administration / Dose	Results	NOAEL
Intestinal smooth muscle (General pharmacology evaluation) Non-GLP	Isolated longitudinal ileum from guinea pigs/3	*In vitro*/ 1, 10 µM	**10 µM:** 58% inhibition of Ca^{2+}-induced contraction	1 µM
Gastrointestinal transit (General pharmacology evaluation) Non-GLP	SD rats/ 5 ♂/group	20, 200, 2000 µg/kg PO	No treatment-related effects	2000 µg/kg PO
OTHER ORGAN SYSTEMS				
Smooth muscle (General pharmacology evaluation) Non-GLP	Isolated uterus from rats/2	*In vitro*/1 nM-10 µM	**10 µM:** 28% inhibition of oxytocin-induced contraction	1 µM

Effects on the cardiovascular system were apparent in cynomolgus monkeys in both the 3-month and 1-year studies. These consisted of lower heart rates (≥5 mg/kg, both sexes) and blood pressure (15 mg/kg, males only), and increased (~ 10%-50% increase over controls) QT intervals on ECG tracings (≥5 mg/kg, both sexes). Using the NOAEL of 1 mg/kg/day obtained in these studies, the animal:human safety margins were approximately 3-8 at the maximal recommended human dose (MRHD). The applicant re-examined the studies and found the increases in the QT interval was likely due to decreased heart rate. Taking all data into account the safety margins were considered adequate and the potential for cardiac toxicity was considered low.

No other relevant treatment-related effects were observed during the safety pharmacology studies at therapeutic relevant concentrations/dosages.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interactions were not investigated. Two pharmacology studies were performed to assess if efficacy could be enhanced by combination therapy using lasofoxifene with estradiol or parathyroid hormone 1-34 (PTH). Lasofoxifene showed addition/synergic effect in combination with PTH but not with EE. Combination treatment with bisphosphonates has not been investigated. Nevertheless, further studies were not considered necessary.

Pharmacokinetics

Analytical methods
A LC-API/MS/MS method, which was validated for the pivotal pharmacokinetic and toxicokinetic studies, was used.

Absorption
Following oral administration, the bioavailability of lasofoxifene was moderate in rats (33-42%) and monkeys (25-55%). In monkeys, a high inter-animal variability was observed in the oral bioavailability. Intravenous studies have not been conducted in humans. Thus, the absolute bioavailability and the apparent volume of distribution cannot be estimated for humans. The half-life was relatively short in rats (~3-5 h) and monkeys (~7-11 h) as compared to humans (116-150 h). The total blood clearance of lasofoxifene was around 50-80% of the hepatic blood flow in the respective species (rat and monkey). The apparent volume of distribution of lasofoxifene after IV administration was 6 L/kg in rats and 18 L/kg in cynomolgus monkeys. These values are up to approximately 25-fold the volume of the total body water in the respective species indicating extravascular distribution of lasofoxifene. This is supported by the findings of the whole body autoradioluminography studies in rats. Following IV administration, the decline of drug plasma concentrations was biphasic in rats while

the decline seemed to be monophasic in monkeys. No apparent gender-related differences or accumulation were observed during the repeat-dose toxicity studies.

Distribution
Tissue distribution was studied in rats. Radioactivity was widely distributed to tissues, which is consistent with the high apparent volume of distribution. In pigmented rats, lasofoxifene distributed well to the eye, e.g., the highest amount of radioactivity and the longest half-life were observed in the uvea. Radioactivity was not observed in the uvea of albino rats indicating the uveal binding observed in this study is associated with binding to melanin present in the eye of pigmented rats. Other tissues with radioactivity were various glands (adrenal, lacrimal, salivary), well-perfused tissues (lung, spleen, pancreas) and those associated with metabolism and excretion (liver, kidney and GI tract). In pigmented rats but not in albino rats, radioactivity was detected in the brain, bone and bone marrow suggesting strain differences in distribution. No apparent gender differences were observed.

Lasofoxifene-related radioactivity was observed in liver, lung, intestinal tissue and whole body of foetuses indicating placental transfer. Exposures were similar to that of the dams, at least for the tissue investigated (intestinal tissue and lung).

In the mouse, rat, monkey and human, lasofoxifene had no preferential binding to whole blood constituents indicating that plasma can be used for monitoring of lasofoxifene.

Lasofoxifene is highly bound (>99.8%) to plasma proteins in all species (mouse, rat, monkey and human). Lasofoxifene binding to HSA (~97%) is slightly more extensive than to AGP (~84%).

Metabolism
Lasofoxifene was readily metabolized in humans. In addition to unchanged drug, a total of 3 metabolites in plasma (M7, M9, M17), 5 metabolites in urine (M7, M9/M21, M17, M23/24), and 6 metabolites in faeces (M9/M21, M10-12, M15, M17) were detected by LC/MS. The major pathways were due to conjugation with glucuronic acid or sulfuric acid. The other pathways were due to oxidations on the phenyl tetraline moiety and the pyrrolidine ring.

The human metabolites were all identified in the rat and/or the monkey. Using the percentages of the dose for each metabolite in humans at the clinical dose (0.5 mg once a day) and extrapolating to the NOAEL for the mouse, rat and monkey, the applicant has estimated the relative body burden of each metabolite. The results of this exercise show that at dosages causing no adverse toxicological effect, animals are exposed to a significantly greater amount of each lasofoxifene metabolite than is present in humans at the clinical dose.

There were no apparent sex-related qualitative differences in the profile of metabolites in mice, rats and monkeys.

One metabolite is a catechol. Some catechols are known to be carcinogenic. However, this is an intermediate that, according to the applicant, is quickly conjugated with glucuronic or sulphuric acid or methylated by catechol-O-methyl transferase. It can be assumed that the catechol intermediate may be primarily formed in the liver, as it is formed after oxidative metabolism by CYP enzymes, which are mainly present in the liver. As there appears to be no indication for liver toxicity this agrees with the explanation of the applicant that M21 is probably quickly conjugated, i.e. before it can exert toxicity.

Excretion
The excretion of [^{14}C]-lasofoxifene was investigated in the animal species used in toxicology studies and in healthy male human volunteers following oral administration. The major route of excretion in all species including humans was the faeces (>66%) presumably via the bile. The urinary excretion was less than 11% in all species. Lasofoxifene is excreted in milk; the concentration in milk was similar to that observed in maternal plasma.

Pharmacokinetic Drug Interactions
Potential interactions of lasofoxifene with other drugs have been investigated in several studies, though the following observations are made:

- It is acknowledged that it is unlikely that lasofoxifene inhibits the metabolism of other drugs via inhibition of CYP enzymes. The lowest IC50 value (0.21 µM for CYP2E1) is considerably higher than the Cmax value anticipated during normal drug use (3.6 ng/ml or 0.009 µM). No studies have been performed to investigate whether lasofoxifene induces the metabolism of other drugs, or that other drugs induce the metabolism of lasofoxifene. However, based on the metabolism pathways for lasofoxifene, it can be predicted that inducers will have some effect on the exposure to lasofoxifene.
- It is also acknowledged that it is unlikely that lasofoxifene affects the free concentration of warfarin (on average bound for 99.26% in study DM1997-336156-027) or propranolol (on average bound for 76.5% in study DM1997-336156-027).
- The *in vitro* binding of lasofoxifene to cholestyramine has been investigated to evaluate potential drug interactions. The binding to lasofoxifene was about 34%, and to lasofoxifene glucuronide about 59-66%. The applicant considers this to be low to moderate binding suggesting that an *in vivo* drug interaction is unlikely. However, lasofoxifene probably undergoes enterohepatic circulation (excreted in the gastrointestinal tract as glucuronide in the bile, and subsequently partly reabsorbed in the small intestine). Especially during enterohepatic circulation, the drug will probably be absorbed as glucuronide, which has a higher binding to cholestyramine than the parent drug. Therefore, interactions cannot be excluded with the presently described *in vitro* binding of lasofoxifene and lasofoxifene glucuronide to cholestyramine. *In vivo* data on the interaction between lasofoxifene and cholestyramine are discussed in the section Clinical aspects / Pharmacokinetics.

Toxicology

- Single dose toxicity

The minimal lethal dose of lasofoxifene was 1000 mg/kg in mice and >2000 mg/kg in rats following single oral administration. Following single IV administration, the minimal lethal dose was 300 mg/kg in mice and >100 mg/kg in rats. Convulsions were noted in IV-dosed mice (300 mg/kg), and tremors were apparent in orally dosed mice (1000 and 2000 mg/kg) and rats (2000 mg/kg).

- Repeat dose toxicity (with toxicokinetics)

Repeated–dose toxicity studies consisted of a 2-week, 3-month and 1-year oral dose studies in rats and monkeys. In addition, 10-day range-finding, oral dose study was performed in monkeys.

Rats
In the 2-week and 3-month studies, lasofoxifene produced changes at all doses ≥1 mg/kg/day that were consistent with the pharmacologic activity of SERMs, including a decrease in body weight gain, prostate and pituitary weights, along with enlarged ovaries secondary to cysts and granulosa hyperplasia, uterine atrophy, and vaginal mucification. Clinical pathology changes in male and female rats included effects on hematology (decreases in erythroid and white cell indices) and serum chemistry (decreased serum cholesterol, total protein, albumin, globulin). The increased levels of alkaline phosphatase (at ≥1 mg/kg/day) and alanine aminotransferase (at 100 mg/kg/day) and decreased levels of 5`nucleotidase (at ≥1 mg/kg/day) could not be related to changes in liver weight or to microscopic liver damage. Changes considered related to treatment but inconsistent with pharmacologic activity included salivation (≥10 mg/kg/day), and specific serum chemistry parameters (creatinine, glucose) in males and females. In the 2-week studies, additional microscopic changes noted at 200 and 500 mg/kg consisted of slight dermatosis, thymic atrophy, splenic lymphoid depletion, and bone marrow depletion. In the 3-month study in monkeys, thymic atrophy was observed in males at ≥1 mg/kg/day and a decrease in circulating eosinophils at 15 mg/kg/day. In view of these findings, it is not clear whether lasofoxifene could interact with the immune system. Studies on the immunotoxicity of lasofoxifene have not been performed.

In the 1-year rat study, similar pharmacological effects and effects on liver enzymes were observed. Microscopically, liver damage has not been observed. In two females (one each in the 1 and 100 mg/kg/day dose), the hyperplastic change of the ovarian granulosa cells had progressed to a benign granulosa cell tumour. In addition, ovarian amyloidosis was present in 13/15 and 8/15 females at 20 and 100 mg/kg/day, respectively. These ovarian findings might be related to a lasofoxifene-mediated, estrogenic effect on the mitogenic activity of granulosa cells. Splenic hematopoiesis in males at ≥20 mg/kg/day was considered to be a compensatory response to the slight decreases in erythroid parameters (red blood cell count, hemoglobin and hematocrit), consistent with the estrogenic effect of the compound. A slightly higher level of fibrinogen in serum was noted in both sexes at all doses. Eosinophil counts were reduced in animals at the high dose. The slightly higher white cell indices (white blood cell counts, neutrophils, lymphocytes) in the high-dosed females at 100 mg/kg/day did not correspond to any microscopic evidence of inflammation in the tissues examined.

In rats, the NOAEL values were 10 mg/kg/day and 1 mg/kg/day in the 3-month and 1-year studies, respectively, with $AUC_{(0\text{-}24)\ unbound}$ values of 15.7 and 2.7x the $AUC_{(0\text{-}24)\ unbound}$ at the MRHD, respectively. The NOAELs in both studies were based primarily on increased hepatic serum transaminases. However, NOAEL values are not relevant here, since pharmacological effects noted on the ovary, pituitary and prostate organ weights, lowering of cholesterol, uterine atrophy, and vaginal mucification are considered to be adverse.

Monkeys
In 10-day non-pivotal and the 2-week pivotal study, the dose-limiting toxicity was apparent at doses of ≥25 mg/kg/day as evidenced by emesis and/or inappetence. These changes essentially subsided upon lowering the high dose to 15 mg/kg/day.

In the 3-month and 1-year pivotal studies, pharmacologically-related effects on the reproductive system were observed in females at all dose levels ≥1 mg/kg/day (abnormal menstruation, decreased uterine weight, increased ovarian weight, ovarian cysts) and in males at 15 mg/kg/day (testis atrophy with tubular giant cells, atrophy accessory glands). Effects were also noticed on hormonal/endocrine-dependent organs in males at ≥ 1 mg/kg/day (mastopathy and ectasia of the mammary gland, decreased adrenal weight) and females at 15 mg/kg/day (decreased pituitary weight). The incidence and severity of these effects did not progress with increased duration of dosing. In the 1-year study, increased serum estradiol and testosterone levels were observed in males at all doses ≥ 1 mg/kg/day. The increased creatinine and blood urea nitrogen levels in males at 1 µg/kg/day were not associated with changes in kidney weight or renal pathologic findings.

In the 3-month study in monkeys, uterine adenomysosis was observed in one of the three females at 15 mg/kg/day. This finding was ascribed to pharmacologic activity of the compound, but the CHMP considers it as an adverse effect. In view of the fact that two uterine sarcomas were observed in clinical trials, information should be provided on the underlying mechanism and the clinical relevance of this finding.

Treatment related findings that were inconsistent with pharmacology were effects on the cardiovascular system and neuromuscular system in the 3-month and 1-year study. These effects consisted of lower heart rates with corresponding longer RR and QT intervals at ≥5 mg/kg/day and lower blood pressure, and tremors at 15 mg/kg/day. The cardiovascular changes were not progressive, and were not associated with any other evidence of cardiovascular effects. The significance of these ECG effects was, however, not clear. Whilst studies to assess the potential of lasofoxifene to delay cardiac repolarization (QT prolongation) were missing, the applicant re-examined the *in vivo* studies and found the increases in the QT interval correlated with decreased heart rate.

Effects on the hematopoietic system consisted of thymic atrophy in males at ≥1 mg/kg/day (3-month, and 1-year study), slightly lower red cell parameters (red blood cell count, hemoglobin, hematocrit) in females at ≥1 mg/kg/day (2-week study) and at ≥5 mg/kg/day (1-year study). Increased reticulocyte counts at 5 mg/kg/day and decreased eosinophil counts and increased APTT times (1.14-1.32X) at 15 mg/kg/day in the 1-year study.

In cynomolgus monkeys, the NOAEL was 1 mg/kg/day in both the 3-month and 1-year studies with $AUC_{(0\text{-}24)\ unbound}$ values of 5.5-12 and 9.5-12.2x the $AUC_{(0\text{-}24)\ unbound}$ at the MRHD, respectively. This NOAEL is based on the decreased heart rates and tremors observed at the intermediate and high dose groups. However, NOAEL values are not relevant here, since the CHMP considers pharmacological effects of the compound as adverse.

- Genotoxicity

The mutagenicity studies demonstrate that lasofoxifene does not induce microbial or mammalian cell gene mutations *in vitro*. An increase in chromosomal abnormalities was produced *in vitro* in a lymphoblastoid cell line, but not with cultures of human lymphocytes. No chromosomal damage occurred following *in vivo* treatment of mice with lasofoxifene. No DNA adducts were detected in the livers of rats following *in vivo* treatment.

The impurities CP-335,992 and CP-324,098 presumably have a low genotoxic potential, which is addressed with the limits in the specification.

- Carcinogenicity

Two-year carcinogenicity studies were performed in rats and mice. In mice, increases in adrenal cortical tumours, ovarian tumours, and epithelial polyps in the uterus were observed. In theory, these tumours could all arise through a rodent specific mechanism in which LH levels are increased due to a pharmacological effect of lasofoxifene. The increases in LH however, have not been observed at doses which induced tumour formation. The applicant has addressed this issue and it has been assessed that increased LH levels were plausible mainly based on the evidence of LH/FSH secreting gonadotrophs in the pituitary gland.

In rats, increases in ovarian and renal tumours (in males only) were observed. The mechanism responsible for the induction of ovarian tumours might also be an increase in LH levels. However, increases in LH levels were observed at higher doses than those that caused induction of these tumours. Therefore, the same applies to rats as it does to mice, ovarian tumour incidence is increased before increases in LH levels are measured.

An increase in renal tumours in the male rats has been observed. The applicant proposed that this could be due to a male rat specific expression of ERα versus ERβ. The applicant suggests that the kidney of the male rate mainly express the ERα and to a lesser extent ERβ. This would result in cell proliferation and tumour induction. The applicant submitted a summary of expression data in different species; the full report will be provided as follow-up measure including raw data and a re-evaluation of the ER-α/ER-β ratios on an individual basis rather than on mean values. Furthermore, the proposed mechanism behind the tumours implies that tissues which lack ERβ might be prone to disturbed proliferation and ultimately tumour formation when exposed to lasofoxifene. Thus the applicant will elaborate in a follow-up measure on the ERα/ERβ ratio in human tissues other than the kidney and the implication hereof in relation to the risk of developing cancer. Furthermore, the monitoring for the carcinogenic potential of lasofoxifene is included in the Risk Management Plan.

- Reproduction Toxicity

Following PO administration, lasofoxifene showed adverse effects on fertility and early embryonic development at low doses (0.001 mg/kg/day) in rats. It was not possible to establish NOAELs neither on male and female fertility. Lasofoxifene is only for use in post-menopausal women.

Following PO administration, lasofoxifene showed adverse effects on embryo-fœtal development at low doses in two species. Lasofoxifene showed slight increase in malformations (imperforate anus and shortened tail) in addition to flexions of hind limbs and paws, decreased implantations and increased resorptions. All together, lasofoxifene showed reproductive and developmental toxicity presumably associated with the pharmacodynamic activity, which is addressed in the SPC.

- Local tolerance

The local tolerance studies performed with lasofoxifene are summarised in Table 2.

Table 2 Results from the local tolerance studies

Species/test system Number/Group	Method of Administration/ Dose	Results	Conclusions
SENSITIZATION: MAGNUSSON AND KLIGMAN MAXIMAMIZATION TEST (98-1186-35, GLP)			
Guinea pigs: 10♀	Induction: 0.1 mL intradermal injection 1%w/v in propylene glycol (max. dose – not irritating) followed by 0.8 g topical induction (a week later). Challenge: 0.4 g topically.	No toxicity. No signs of sensitization potential. Positive control DNBC gave skin reaction in 7/10 animals after challenge.	Not sensitizing
DERMAL TOXICITY (98-1186-37, GLP)			
NZ white rabbits/3♂ and ♀	2000 mg/kg under occlusive dressing for 24 hr.	After 24 hours: erythema (score 1) in 2/6 animals and score 2 in 1/6 animals. Absent after 1-2 days	No dermal irritation as far as tested.
EYE IRRITATION (98-1186-37, GLP)			
NZ white rabbits/1♂ and 2♀	0.1 mL of lasofoxifene powder in the conjunctival sac.	Severe conjunctival reddening, chemosis, iritis and corneal opacity. Reverisible.	Eye irritating

NZ – New Zealand
DNBC - 1-Chloro-2,4-dinitrobenzene

Lasofoxifene was not sensitizing when tested in the M&K maximization test. A dermal toxicity test was performed, but not a dermal irritation test. Lasofoxifene was not toxic after dermal application and no severe effects were observed at the application site. An eye irritation test with powder resulted in severe eye irritation. Since lasofoxifene is intended to be administered orally no further dermal studies are required

- Other toxicity studies

Immunotoxicity
Non-clinical studies to predict the immunotoxicity have not been conducted. Some signals of effects on the immune system were detected in the 3-month repeat-dose toxicity studies in rats and in the 3-month monkey study. These have been assessed as coincidental and not relevant for humans. Furthermore, clinical data do not indicate any immunotoxicity of lasofoxifene.

Impurities
The proposed specification concerning the impurities CP-324,098 and CP-335,992 has not been qualified with the present data. It is acknowledged that the genotoxic potential of the impurities CP-324,098 and CP-335,992 is low. This issue has been satisfactorily addressed with the limits in the specification.

Ecotoxicity/environmental risk assessment

Based on the provided information a risk for the aquatic compartment was determined. Risk for groundwater and sewage treatment plants are acceptable. The risk assessment for soil is not needed. However, the risk assessment for the sediment compartment could not be completed. The applicant committed to submit study reports on determination of bioconcentration factor and a sediment toxicity study with Hyalella sp., Lumbriculus sp. or Chironomus sp as a follow-up measure.

Deviations from guidelines in the adsorption/desorption have been identified and the applicant was asked to clarify this, together with re-formation of the active ingredient form the human metabolite in the PEC surface water refinement. The applicant was also requested to reanalyse the submitted full-life cycle test in fish. Finally, a further Tier B risk characterization or risk mitigation measures might be warranted pending the results of the reanalysed full-life cycle test. The applicant provided a commitment to address these issues as follow-up measures within defined timelines.

2.4 Clinical aspects

Introduction

Lasofoxifene has been studied for the treatment of osteoporosis in postmenopausal women at increased risk of fracture in six phase 2 studies and four phase 3 studies. The applicant provided data concerning osteoporosis, including clinical dose-response studies. In addition data were provided concerning breast cancer risk and breast density. Furthermore, phase 2 and phase 3 studies are reported on vulvar and vaginal atrophy endpoints. The overall clinical study programme is summarized in table 3; the phase 2/3 program comprised over 20,000 subject-years of exposure to lasofoxifene.

Table 3 Phase 2/3 Studies by Study Objective

Objective	Study
Phase 2 Studies	
Treatment of osteoporosis	A2181037 (JADE)
Prevention of osteoporosis	218-101, 218-101E, 218-102, 218-103, A2181042 (LACE)
Vulvar and vaginal atrophy	A2181012
Female sexual dysfunction	A2181014, A2181015, A2181016 and A2181021
Phase 3 Studies	
Treatment of osteoporosis	A2181002 (PEARL)
Prevention of osteoporosis	A2181003 and A2181004 (OPAL) A2181030 (CORAL)
Vulvar and vaginal atrophy	A2181031, A2181032

The main study for the osteoporosis indication is study A2181002 (PEARL). Furthermore, study A2181037 (JADE) provides supportive evidence. The key features of these studies are summarized in table 4.

Table 4 Studies Included in the Summary of Clinical Efficacy

Study	Length and Design Features	Patient population	Treatment* (daily dose)	Location	N
A2181002 (PEARL)	5 years with a 3 year interim; double-blind, placebo-controlled	Postmenopausal (≥5 years) women aged 60-80 years, with screening T-score ≥ -4.5 and ≤ -2.5 (lumbar spine or femoral neck)	Lasofoxifene 0.25 mg 0.5 mg placebo	32 countries in Africa, Asia, North, Central and South America, Australia, and Europe	8556
A2181037 (JADE)	1 year; double-blind, placebo-controlled	Postmenopausal (≥3 years) women aged ≤80 years, with screening T-score ≥ -4.5 and ≤ -2.5 (lumbar spine)	Lasofoxifene 0.025 mg 0.25 mg 0.5 mg placebo	Japan, Korea, Taiwan	497

N = number of subjects treated.
* All subjects received supplements of calcium and vitamin D.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A routine GCP inspection at two sites of the pivotal study A2181002 (PEARL) was performed and major GCP non-compliance with regard to safety data generation was identified. Overall conclusions from the inspected sites were that safety data were not systematically verifiable and the assessments of the causality were questionable. Since these findings did cast doubts on the reliability of the safety data provided with the application, the applicant was asked to explain and justify the approach for the generation of safety data in the study, and to discuss the impact on the overall safety database of FABLYN. Based on the information provided by the applicant, the CHMP concluded that the inspection findings have neither resulted in underreporting of (serious) adverse events, nor in a limitation to the detection of safety signals.

Pharmacokinetics

The phase 1 programme consisted of 23 studies to evaluate the pharmacokinetic and pharmacodynamic properties of lasofoxifene in healthy volunteers, bioequivalence of the commercial formulation and relative bioavailability of earlier formulations, routes of metabolism and excretion, drug interactions, the effects of food and hepatic impairment on pharmacokinetics, and the pharmacokinetics in Japanese versus Caucasian women. The studies were conducted predominantly in postmenopausal women.

Bioequivalence with respect to rate and extent of absorption of lasofoxifene between the uncoated and film-coated commercial 0.25 mg and 0.5 mg lasofoxifene tablets used in the clinical phase 3 studies has been demonstrated.

- Absorption

Absorption of lasofoxifene appeared to be slow with tmax values of 6-12 hours. Exposure of lasofoxifene at steady-state following 0.5 mg administration was 3.6 ng/ml for Cmax and 79 ng.h/ml for AUCτ. Based on the mass balance data it can be estimated that at least 50% of the lasofoxifene dose is absorbed. Food does not affect the bioavailability of lasofoxifene. Thus, lasofoxifene can be dosed without regard to the timing of meals as stated in the SPC.

- Distribution

Lasofoxifene is highly bound to plasma proteins >99% but binding is independent of the dose (0.25 – 20 mg). No effect of lasofoxifene on the protein binding of propranolol and warfarin was observed *in vitro*. However, the effect of warfarin and propranolol on the protein binding of lasofoxifene was not determined. Volume of distribution was estimated to 1235 L in a phase 1 study and confirmed by Population PK analysis.

- Elimination

A long terminal elimination half-life (6 days) was observed in both single and multiple-dose studies, and is consistent with the low clearance (~ 105 mL/min) of lasofoxifene. Conventional studies and popPK analysis indicate a moderate intra- and inter-subject variability of lasofoxifene. Clearance of lasofoxifene occurs predominantly by metabolism. Metabolites have been identified in plasma, urine and faeces. Lasofoxifene can be metabolised by multiple pathways: conjugation with glucuronic acid and sulfuric acid, hydroxylation at the phenyl tetraline moiety, methylation of the catechol intermediates by catechol-O-methyl transferase, and oxidation at the pyrrolidine ring. It is not likely that any of the circulating metabolites contribute to the pharmacologic activity of lasofoxifene.

In vitro studies have identified that CYP3A4/5 and CYP2D6 were the primary CYP450 isoforms involved in the oxidative metabolism of lasofoxifene. It is estimated that direct conjugation accounts

for 49% of the pathways of metabolism for lasofoxifene, the transferases involved have not been identified. The major circulating metabolites M7 (+M9) is formed by direct glucuronidation.

Lasofoxifene was predominantly excreted as metabolites in the faeces and only 6% of the administered dose is excreted in the urine. Excretion of unchanged lasofoxifene was 22% (of 66% recovered) in the faeces and <2% (of 6% recovered) in the urine, respectively. The excretion of radioactivity occurred over a prolonged period of time with approximately 20% excreted from days 11 to 24 post dose. Furthermore, the mass balance study indicated a substantial first pass metabolism and an extensive enterohepatic circulation of lasofoxifene because Cmax of total radioactivity was reached at 4 hours, while tmax for lasofoxifene was 12 hours, and secondary peak concentrations of lasofoxifene were observed. The enterohepatic circulation may explain the apparent slow absorption of lasofoxifene and the long elimination half-life.

- Dose proportionality and time dependencies

Lasofoxifene exhibits linear pharmacokinetics with respect to dose and time. The pharmacokinetics of lasofoxifene are dose proportional over the dose range of 0.01 to 100 mg indicating that metabolism of lasofoxifene is not saturated. Steady-state pharmacokinetics of lasofoxifene are consistent with expectations from single dose pharmacokinetics indicating that lasofoxifene does not inhibit or induce its own metabolism.

- Special populations

Population pharmacokinetic analysis predicted age, weight and creatinine clearance as covariates of lasofoxifene clearance. The effects on the pharmacokinetics of lasofoxifene were < 35% difference in AUC by any of these variables. These effects are not considered to be clinically meaningful. Race and gender had no effect on the pharmacokinetics of lasofoxifene. The pharmacokinetics of lasofoxifene have not been studied in children, which is acceptable given the proposed indication.

Lasofoxifene is predominantly cleared by metabolism. Lasofoxifene and metabolites are mostly excreted in the faeces. Therefore, renal impairment is not expected to affect the pharmacokinetics of lasofoxifene to a great extent. This was supported by the population pharmacokinetic analysis which estimated a 20% increase in AUC in patients with mild and moderate renal impairment as low as 32 mL/min. The effect of severe renal impairment on lasofoxifene exposure has not been determined. This has been addressed in the SPC adequately.

Information on the effects of hepatic impairment was derived from a phase 1 study in 6 healthy subjects, in 6 subjects with mild and 6 subjects with moderate hepatic impaired function. The effect of severe hepatic impairment on lasofoxifene exposure was not determined. The effect of liver impairment appears to be low because AUC of lasofoxifene was increased by only 38% in subjects with moderate hepatic impairment. No effect on the plasma protein binding of lasofoxifene was apparent. Lasofoxifene is predominantly cleared by metabolism and is likely to undergo extensive enterohepatic circulation. An increased incidence of treatment-related cholelithiasis was observed in the lasofoxifene treated population. Therefore, especially bilirubin concentrations may affect pharmacokinetics and safety of lasofoxifene. The subject with the highest serum bilirubin levels had the highest AUC value approximately 80% higher than the mean AUC of healthy subjects but there are not enough data to correlate bilirubin with pharmacokinetics of lasofoxifene. The subjects with Child-Pugh B grade hepatic impairment were too heterogeneous to draw conclusions. In the phase 3 studies, patients with liver function test >1.5 ULN were excluded. Therefore, safety has not been evaluated in patients with moderate and severe impaired liver function.

- Pharmacokinetic interaction studies

Clinical interaction studies with the CYP inhibitors ketoconazole, paroxetine and fluconazole increased the total exposure of lasofoxifene with 20%, 35% and 1%, respectively. These results are consistent with the *in vitro* data indicating that CYP3A4 and CYP2D6, but not CYP2C9, play a role in lasofoxifene metabolism. Considering the relatively small magnitude of these interactions, no dosage adjustment is necessary for co-administration of CYP3A4 or CYP2D6 inhibitors. The effect of CYP3A4 inhibitors in poor metabolisers of CYP2D6 was not studied. However, the potential effect of CYP3A4 inhibitors in poor CYP2D6 metabolisers was assessed using an acknowledged

pharmacokinetic model. Considering the safety profile of the compound the expected rise in AUC is not considered clinically relevant.

Lasofoxifene at steady-state had no effect on the PK parameters of methylprednisone (CYP3A4), R-warfarin (CYP3A4), S-warfarin (CYP2C9), chlorzoxazone (CYP2E1), dextromethorphan (CYP2D6) and digoxin (MDR1 P-glycoprotein). Although the pharmacokinetics of warfarin were not altered by lasofoxifene, mean PT AUC and PTmax for warfarin during administration of lasofoxifene were approximately 8% and 16% (3.4 sec) lower, respectively, than for warfarin alone. The 90% confidence intervals for the mean PTmax and PT AUC ratios were both within the 80% to 125% range but did not include 100%. Overall it can be concluded that the potential of lasofoxifene to inhibit or induce cytochrome P450 enzymes is low.

The effect of concomitant CYP inducing agents on the pharmacokinetics of lasofoxifene has not been investigated. As the cytochrome P450 system is involved in metabolism of lasofoxifene, CYP inducing agents may potentially increase lasofoxifene metabolism and significantly decrease lasofoxifene plasma concentrations and consequently may reduce efficacy, this is addressed in the SPC.

Direct conjugation accounts for ~50% of metabolism of lasofoxifene and the major circulating metabolites M7 (+M9) is formed by direct glucuronidation. Lasofoxifene could be metabolised by several UGT isoforms including UGT1A1 and 1A4 as well as 1A3, 1A6, 1A8, 1A9 and 1A10. Thus UGT polymorphism status is not considered likely to influence safety or efficacy.

Aqueous solubility of lasofoxifene is pH dependent with a drop in solubility between pH 5.4 (146µg/ml) and pH 6.5 (0.6 µg/ml). Concomitant administration of lasofoxifene with proton pump inhibitors, H2 antagonists or antacids may therefore alter solubility and bioavailability of lasofoxifene and may lead to reduced efficacy. The applicant was requested to evaluate whether PPIs affect the pharmacokinetics of lasofoxifene. This will be done with a population PK analysis using available data from the completed phase 2/3 studies and will be provided as a follow-up measure.

- Pharmacokinetics using human biomaterials

In vitro studies have identified that CYP3A4/5 and CYP2D6 were the primary CYP450 isoforms involved in the oxidative metabolism of lasofoxifene. In vitro studies with human recombinant UGT isoforms indicate UGT1A1, 1A3, 1A4, 1A6, 1A8, 1A9 and 1A10 can catalyze the direct conjugation of lasofoxifene.

In vitro inhibition studies showed that CYP 2E1 (IC50 0.21 µM) and 2D6 (IC50 4.2µM) isoforms were the most sensitive to inhibition by lasofoxifene (Cmax steady-state ~9 nM). Therefore, *in vitro* data indicated that lasofoxifene is unlikely to inhibit drug-metabolizing CYP enzymes at clinically relevant concentrations.

Pharmacodynamics

- Mechanism of action

SERMs mediate their biologic activity through the ER whereby binding results in differential activation of estrogenic pathways in some tissues and blockade of others. In competitive binding assays, lasofoxifene demonstrated high affinity binding to both the ERα (IC50 = 1.08 nM) and ERβ (IC50 = 4.41 nM). Lasofoxifene is thought to exhibit tissue-selective agonist activity on the skeleton and could also exhibit activity on serum cholesterol, coagulation factors, the breast, the endometrium, the vulva and vagina.

- Primary and secondary pharmacology

The effects of lasofoxifene treatment on exploratory pharmacodynamic biomarker endpoints (LDL-C, HDL-C, LH, FSH, urinary NTX, etc.) were assessed in 5 studies: 218-001, 218-002, 218-004, A2181011, A2181025. A principal objective of these studies was to select target doses for the Phase 3

osteoporosis program with a final goal of identifying the lowest dose that produced the optimum efficacy on multiple surrogate endpoints (e.g., bone and lipid), while maintaining an acceptable safety profile. Pharmacodynamic responses were generally characterized by high variability precluding definitive conclusions regarding the magnitudes of these effects as a function of dose. Based on the observed trends for treatment effects across studies, it can be inferred that multiple dosing of lasofoxifene decreased LDL-C, LH, and FSH concentrations and NTX excretion.

The pharmacodynamic endpoints (LDL-C, HDL-C, LH, FSH, BSAP, and urinary NTX) measured in the multiple-dose Phase 1 trials in healthy menopausal women (218-001, 218-002, 218-004, and A2181011) were evaluated as biomarkers to assess the pharmacologic activity of lasofoxifene during short-duration therapy (14 days) in early development. These data should be considered preliminary and were not used for selection of doses for the Phase 3 trials.

Doses ranging from 0.017 mg to 10 mg were studied in Phase 2 osteoporosis prevention trials. The Month 6 lumbar spine BMD, Month 12 total hip BMD and Month 6 LDL-C results in these studies were analyzed to determine the lasofoxifene dose response curves.

The surrogate endpoints for assessing phamacodynamics and thus dose-response relationships were well chosen and acknowledged. The results obtained from phase II studies have been applied for an Emax model commonly employed for describing dose-response relationships. The resulting model fits the clinical observations. Thus a sigmoidal relationship between dose and response has been demonstrated.

Data for bone markers as osteocalcin and free deoxypyridinoline are not provided. This is an omission, but more data are obtained from the PEARL study. Data on coagulation factors (fibrinogen, protein S, thrombin and antithrombin complex, prothrombin time, prothrombin fragments 1 and 2, plasminogen, D-dimer quantitative and activated partial thromboplastin time) are also missing. This is an important point as coagulation factors might play an important role in DVT, a safety issue. Finally in pharmacodynamics the influence of lasofoxifene on hot flushes, the breast and on the endometrium should have been considered in detail. The effect of lasofoxifene on cardiac repolarisation was not assessed.

The majority of the remaining deficiencies are solved in the Phase 3 clinical trials described below.

Clinical efficacy

- Dose response study(ies)

The applicant provided arguments for a minimal effective dose based on the pharmacodynamic parameters. These data were not considered sufficient by the CHMP to conclude a minimally effective dose. However, clinical arguments for a minimal effective dose based on dose-response studies were provided. Doses from 0.017 mg to 10 mg were studied in Phase 2 trials in the osteoporosis prevention population; 2 dose levels were chosen for the pivotal osteoporosis treatment study A2181002 (0.25 mg and 0.5 mg), and 3 dose levels were chosen for the pivotal Phase 3 osteoporosis prevention trials A2181003 (0.025 mg, 0.25 mg and 0.5 mg) and A2181004 (0.025 mg, 0.25 mg and 0.5 mg). The basis was dose response modelling of percent change from baseline in lumbar spine BMD at month 6, total hip BMD at month 12, and LDL-C at month 6. Month 12 rather than month 6 hip BMD data were used because the hip responds more slowly than the spine to anti-resorptive therapy.

During the assessment the applicant was requested to conduct analyses of the principal fracture endpoints that included only PEARL subjects who were deemed to be at high risk for fracture, based upon FRAX probabilities. These new analyses showed comparable results in subjects with a 10 year probability of > 10 % in the full data set, in the 5-year data set as well as in the 3-year data set.

- Main study

The main study of this application is study A2181002 (PEARL). This was a prospective, randomized, double-blind, placebo-controlled, multinational study in postmenopausal women with osteoporosis (defined by low bone mineral density of the femoral neck or lumbar spine). The study was initially designed as a 3-year study, but in a subsequent protocol amendment, it was extended to 5 years with a prospectively defined 3-year interim analysis.

METHODS

Study Participants
Women had to be within 60-80 years of age, at least 5 years postmenopausal, with osteoporosis based on screening BMD T-score of ≥ -4.5 and ≤ -2.5 in the lumbar spine or femoral neck. Women with >3 vertebral fractures on X-ray by site read or new vertebral fracture within the past year, medical disease that might be associated with metabolic bone diseases, venous thromboembolic disease (deep vein thrombosis [DVT], pulmonary embolism [PE] or retinal vein thrombosis [RVT]), or breast cancer (except lobular carcinoma in situ treated by local excision) were excluded from participation. It is noted that subjects below the age of 60 were not included despite they were more than 5 year postmenopausal.

Treatments
Following a 6- to 8-week single-blind placebo and calcium/vitamin D screening/run-in period, eligible subjects were randomized to receive lasofoxifene 0.25 mg, 0.50 mg or placebo. All subjects were to take a daily supplement of calcium 1000 mg and vitamin D 400-800 IU.

Objectives
The primary objective was to compare the risk of new/worsening radiographic vertebral fractures between each dose of lasofoxifene and placebo. The principle secondary objectives were to compare the incidence of multiple radiographic vertebral fractures at 3 years and to compare the risk of clinical vertebral fractures between each dose of lasofoxifene and placebo. According to the current EU guideline (CPMP/EWP/552/95 rev. 2), the primary endpoint should be the incidence of new vertebral fractures, and not worsening of previous radiographic vertebral fractures. Therefore, the applicant has also analysed time to first new radiographic vertebral fracture.

Outcomes/endpoints
The primary endpoint was the occurrence of a new/worsening vertebral fracture over the first 3 years of the study regardless of trauma. Vertebral fractures were determined from X-rays of the lateral thoracic and lumbar spine (T4-L4) obtained at screening and at 1, 2, and 3 years in asymptomatic subjects. Additionally, in subjects whose symptoms were suggestive of fracture, spine X-rays were taken at the time they presented with symptoms to aid in diagnosis.

The definition of the primary endpoint included both new and worsening fractures. A worsening fracture was defined as significant additional compression in a vertebra with a prevalent baseline fracture. A new fracture was defined as significant compression in a vertebra with no evidence of a fracture at baseline. The primary endpoint, which includes worsening fractures, is referred to as new/worsening fractures. To comply with current European guidelines, a second analysis defining the endpoint as only new fractures was conducted and referred to as the analysis of new fractures.

Secondary endpoints included the incidence of multiple (0, 1, more than 1) radiographic vertebral fractures at 3 years and time to the first clinical vertebral fracture through 3 years where the censoring time was the date of last study visit. Furthermore, BMD of the hip and lumbar spine (L1-L4) were measured in all subjects pre-treatment and at baseline and at 1, 2, and 3 years by dual energy X-ray absorptiometry (DXA) using a Hologic or Lunar densitometer. Additional BMD measurements at 3 months and measurements of whole body bone mineral content (BMC) and forearm BMD at baseline and at 1, 2 and 3 years were undertaken in a subset of subjects. Also the risk for breast cancer (confirmed by histology) was included as a secondary endpoint.

Sample size

A sample size of 5000 subjects on lasofoxifene and 2500 subjects on placebo had approximately 90% power to detect a 40% reduction in the risk of subjects for a new/worsening vertebral fracture after 3 years by means of a two-sided $\alpha = 0.05$ log rank test. In addition, the study had approximately 87% power to detect a 40% reduction in the risk for an individual active dose versus placebo (2500 subjects on lasofoxifene, 2500 subjects on placebo). The sample size calculation was based on a baseline annual vertebral fracture incidence of 1.5%, a cumulative lost to follow-up rate of 10% at 1 year, 20% at 2 years, and 30% at 3 years, and a drop-in and dropout rate of 1% per year.

Randomisation

Subjects were allocated to treatment groups in a 1:1:1 ratio of lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo.

Blinding (masking)

Subject eligibility for participation in the active treatment phase of the study was determined after the 6- to 8-week single-blind placebo and calcium/vitamin D run-in period. The active treatment part of the study is double-blind.

Statistical methods

The analyses of primary and secondary endpoints were performed on the Full Analysis Set (FAS). The FAS includes all randomized subjects (if applicable) with at least one non-missing post-baseline observation for the measurement of interest.

For the primary endpoint, radiographic vertebral fractures, each lasofoxifene treatment group was tested against placebo using a log-rank test stratified for geographic region and vertebral fracture at baseline in the FAS. Censoring time was defined as the date of the last X-ray. The Hochberg procedure was used to control Type I error in the comparison of each lasofoxifene treatment group to placebo. The hazard ratio and 95% confidence interval (CI) for each lasofoxifene dose versus placebo were calculated using a Cox proportional hazards regression model with treatment group as a covariate and stratified by vertebral fracture at baseline and geographic region. Cumulative and annual incidences were calculated using Kaplan-Meier methods.

RESULTS

Participant flow

The patient flow at the 5 year time period of the study is presented in table 5.

Table 5 Patient flow in study A2181002 (5-year)

	Lasofoxifene 0.25 mg	Lasofoxifene 0.5 mg	Placebo
Number (%) of Subjects			
Randomized	2852	2852	2852
Treated	2849	2852	2851
Discontinued	657 (23.0)	639 (22.4)	646 (22.7)
Completed Month 60	2195 (77.0)	2213 (77.6)	2206 (77.3)
On treatment	1753 (61.5)	1777 (62.3)	1820 (63.8)
Off treatment	442 (15.5)	436 (15.3)	386 (13.5)
Analyzed for Primary Efficacy:			
Radiographic vertebral fracture	2734 (95.9)	2748 (96.4)	2744 (96.2)
Non-Vertebral Fracture	2852 (100.0)	2852 (100.0)	2852 (100.0)
Breast Cancer	2730 (95.7)	2746 (96.3)	2741 (96.1)
Analyzed for Safety:			
Adverse events	2852 (100.0)	2852 (100.0)	2852 (100.0)
Laboratory	2670 (93.6)	2660 (93.3)	2673 (93.7)

Discontinuation rates were low to moderate (around 8%) and similar over treatment arms. The number of major protocol violations (violations assumed to affect the outcomes) was low.

Conduct of the study
There were three global protocol amendments with one introducing the option for patients to continue in the study for an additional 2 years beyond month 36.

Baseline data
Baseline demographics and characteristics are shown in table 6 and table 7, respectively.

Table 6 Baseline demographics, study A2181002 (PEARL)

Treatment (mg)	Mean Age (Range) (yrs)	Race W/B/A/H/O (# Subject)	Mean Weight (Range) (Kg)	Mean Height (Range) (cm)	Mean BMI (Range)
Laso 0.25	67.5 (60-80)	2111/26/530/138/47	61.0 (27-120)	155.5 (131-177)	25.2 (13.3-47.0)
Laso 0.5	67.3 (60-80)	2108/29/519/144/52	61.2 (30-111)	155.3 (134-182)	25.4 (12.2-42.4)
Placebo	67.5 (59-80)	2118/27/521/141/45	61.6 (25-132)	155.6 (132-178)	25.4 (13.7-55.4)

Table 7 Baseline characteristics, study A2181002 (PEARL)

Treatment (mg/day)	Years post menopause Mean (Range)	Hysterectomy N (%)	LS-BMD T-Score Mean (SD)	FN BMD T-Score Mean (SD)	Pre-existing Vertebral Fx Number (%)
Laso 0.25	19.5 (2.0-52.0)	554 (19.4)	-3.024 (0.735)	-2.289 (0.698)	804 (28.2)
Laso 0.5	19.4 (2.0-57.0)	550 (19.3)	-3.020 (0.715)	-2.229 (0.693)	808 (28.4)
Placebo	19.5 (5.0-55.0)	543 (19.0)	-3.007 (0.736)	-2.248(0.714)	804 (28.2)

Baseline demographics were similar across treatment groups. According to the current CHMP guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 rev. 2), risk for fracture should be expressed as the ten-year probability of fracture. It is recommended that 10 years probabilities of 15-20% for spine fracture, 5-7.5% for hip fracture and 10-15% for major non-vertebral fractures should be reflected in the inclusion criteria. Based on the Fracture Risk algorithm (FRAX) model the applicant has analysed baseline data in the PEARL study and found mean probability of a major osteoporotic fracture of 43.5% and of 34.7% for a hip fracture at baseline. Excluding BMD, these probabilities were markedly decreased. The proportions of patients with probabilities that equalled or exceeded the lower thresholds proposed by

the CHMP were 91% in the case of a major osteoporotic fracture and 93% for hip fracture. Hence, the PEARL study enrolled high risk patients.

Numbers analysed
A total of 8556 female subjects was randomized with 2852 subjects in each treatment group. All of the randomized and treated subjects were analyzed for adverse events and ~ 94% of subjects had clinical laboratory data.

Outcomes and estimation
Bone fracture results are presented in the following tables. 5-year data were provided during the assessment in a preliminary report in addition to the 3-year data, and the data from this report are presented in the below tables.

Time to new/worsening radiographic vertebral fracture, the primary outcome of the study, is shown in table 8. A statistically significant reduction was reached in risk of new/worsening radiographic vertebral fractures through 3 years and through 5 years in postmenopausal women with osteoporosis. The risk for a new/worsening radiographic vertebral fracture was reduced by 31% and 42% in the lasofoxifene 0.25 mg and 0.5 mg groups, respectively, compared with placebo through 36 months and through 5 years. This effect was observed from 1 year onwards for both the doses of lasofoxifene. Similar results are reported in women with or without prevalent fracture at baseline. Lasofoxifene 0.5 mg, but not lasofoxifene 0.25 mg, significantly reduced the risk in subjects (N=1,316) with baseline lumbar spine BMD T-score > -2.5, who were eligible for the study on the basis of their baseline femoral neck BMD T-score < -2.5.

Data from the analysis of the time to first new radiographic vertebral fracture (table 9) are consistent with those of time to new/worsening radiographic vertebral fracture (table 8). Lasofoxifene 0.5 mg and 0.25 mg were associated with statistically significantly reduced risks of 42% and 32%, respectively, and 41% and 32% through 5 years, respectively, pointing to 0.5 mg as the most effective dose.

Analysis of the time to first nonvertebral fracture (hip, pelvis, femur, knee, lower leg, ankle, calcaneus, foot, shoulder, humerus, elbow, forearm, wrist, scapula, clavicle, rib, sternum, nonthoracic/nonlumbar spine) revealed a significant effect compared to placebo for the 0.5 mg dose, but not for the 0.25 mg dose both through 3 years and through 5 years (table 10). Regarding hip fractures: at 3 years there were 20 (HR=0.87: 95% CI: 0.48, 158) and 18 (HR=0.78: 95% CI: 0.42, 1.44) in the 0.25 and 0.5 mg groups respectively, and 23 in the placebo group. Through 5 years, there were 31 (HR=0.88: 95% CI: 0.54, 1.42) and 27 (HR=0.77: 95% CI: 0.46, 1.27) in the 0.25 and 0.5 mg groups respectively, and 35 in the placebo group. Therefore, the effect on hip fractures is considered modest at best and the SPC contains a statement in the indication section that an effect on hip fractures has not been demonstrated.

Table 8 Analysis of Time to First New/Worsening Radiographic Vertebral – Study A2181002 – Full Analysis Set through 5 Years

	Lasofoxifene		Placebo
	0.25 mg	**0.5 mg**	
1 Year			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	29 (1.1)	28 (1.0)	61 (2.2)
Hazard ratio vs. placebo (95% CI)	0.47 (0.30, 0.73)	0.45 (0.29, 0.70)	
P-value	0.0007*	0.0003*	
2 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	73 (2.7)	60 (2.2)	128 (4.7)
Hazard ratio vs. placebo (95% CI)	0.56 (0.42, 0.74)	0.46 (0.34, 0.62)	
P-value	0.0001*	<0.0001*	
3 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	129 (4.7)	106 (3.9)	180 (6.6)
Hazard ratio vs. placebo (95% CI)	0.69 (0.55, 0.87)	0.57 (0.45, 0.73)	
P-value	0.0014*	<0.0001*	
4 Years			
Number of subjects at risk	2734	2748	2744
Number (%) with fracture	135 (4.9)	114 (4.1)	191 (7.0)
Hazard ratio vs. placebo (95% CI)	0.68 (0.55, 0.85)	0.58 (0.46, 0.73)	
P-value	0.0007*	<0.0001*	
Overall (through 5 years)			
Number of subjects at risk	2734	2748	2744
Number (%) with fracture	189 (6.9)	156 (5.7)	262 (9.5)
Hazard ratio vs. placebo (95% CI)	0.69	0.58	
P-value	0.0001*	<0.0001*	
With prevalent vertebral fracture at baseline – 5 years			
Number of subjects at risk	775	778	774
Number (%) with fracture	90 (11.6)	69 (8.9)	117 (15.1)
Hazard ratio vs. placebo (95% CI)	0.70 (0.53, 0.92)	0.56 (0.41, 0.75)	
P-value	0.0132*	0.0001*	
Without prevalent vertebral fracture at baseline – 5 years			
Number of subjects at risk	1,959	1,970	1,970
Number (%) with fracture	99 (5.1)	87 (4.4)	145 (7.4)
Hazard ratio vs. placebo (95% CI)	0.67 (0.52, 0.87)	0.59 (0.45, 0.77)	
P-value	0.0027*	0.0002*	

*P-value significant versus placebo

Table 9 Analysis of Time to First New Radiographic Vertebral Fracture – Study A2181002 – Full Analysis Set through 5 Years

	Lasofoxifene		
	0.25 mg	0.5 mg	Placebo
1 Year			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	29 (1.1)	27 (1.0)	58 (2.1)
Hazard ratio vs. placebo (95% CI)	0.50 (0.32, 0.78)	0.45 (0.29, 0.72)	
P-value	0.0018*	0.0005*	
2 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	72 (2.6)	59 (2.1)	124 (4.5)
Hazard ratio vs. placebo (95% CI)	0.57 (0.42, 0.76)	0.46 (0.34, 0.63)	
P-value	0.0002*	<0.0001*	
3 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	124 (4.5)	105 (3.8)	176 (6.4)
Hazard ratio vs. placebo (95% CI)	0.68 (0.54, 0.86)	0.58 (0.46, 0.74)	
P-value	0.0011*	<0.0001*	
4 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	130 (4.8)	113 (4.1)	187 (6.8)
Hazard ratio vs. placebo (95% CI)	0.67 (0.54, 0.84)	0.59 (0.47, 0.74)	
P-value	0.0005*	<0.0001*	
5 Years			
Number of subjects at risk	2,734	2,748	2,744
Number (%) with fracture	183 (6.7)	155 (5.6)	255 (9.3)
Hazard ratio vs. placebo (95% CI)	0.68 (0.56, 0.83)	0.59 (0.48, 0.72)	
P-value	0.0002*	<0.0001*	

*P-value significant versus placebo

Table 10 Analysis of Time to First Nonvertebral Fracture – Study A2181002 – Full Analysis Set through 3 Years and through 5 Years

	Lasofoxifene		
	0.25 mg	0.5 mg	Placebo
3-Years			
Number of subjects at risk	2,852	2,852	2,852
Number (%) with fracture	189 (6.6)	169 (5.9)	212 (7.4)
Hazard ratio (95% CI)	0.88 (0.73, 1.07)	0.79 (0.64, 0.96)	
P-value	0.2122	0.0195*	
5-Years			
Number of subjects at risk	2,852	2,852	2,852
Number (%) with fracture	269 (9.4)	230 (8.1)	296 (10.4)
Hazard ratio (95% CI)	0.90 (0.76, 1.06)	0.76 (0.64, 0.91)	
P-value	0.1885	0.0020*	

CI=confidence interval
*P-value significant versus placebo, Hochberg procedure with overall alpha = 0.05

Measurements of BMD were performed in a 3-year substudy of PEARL, including 1,126 subjects. Time points of measurement were baseline, 3 months and 1, 2, and 3 years. BMD at the lumbar spine, hip and hip components, and forearm was significantly increased (evident at 3 months, sustained through 3 years) in osteoporotic women treated with lasofoxifene 0.25 mg or 0.5 mg compared to placebo (Table 11). Greater increases at all sites were observed with 0.5 mg as compared to 0.25 mg. Whole Body BMC was increased at 3 years as compared to placebo.

Table 11 Analysis of BMD by Site and Whole Body BMC: Percent Change from Baseline at Month 36 – Study A2181002 – BMD Subgroup Non-Japanese Subjects

	Lasofoxifene 0.25 mg	Lasofoxifene 0.5 mg	Placebo
Lumbar spine BMD	**N= 254**	**N=253**	**N=253**
LS Mean	4.623	4.677	1.331
LS mean diff vs placebo (95% CI)	3.293 (2.489, 4.096)	3.346 (2.542, 4.151)	
P-value	<0.001*	<0.001*	
Total hip BMD	**N= 254**	**N=252**	**N=253**
LS Mean	1.742	2.527	-0.516
LS mean diff vs placebo (95% CI)	2.258 (1.620, 2.896)	3.043 (2.403, 3.683)	
P-value	<0.001*	<0.001*	
Femoral neck BMD	**N= 254**	**N=252**	**N=253**
LS Mean	1.871	2.465	-0.826
LS mean diff vs placebo (95% CI)	2.696 (1.900, 3.492)	3.291 (2.493, 4.089)	
P-value	<0.001*	<0.001*	
Greater trochanter BMD	**N= 254**	**N=252**	**N=253**
LS Mean	2.184	3.469	-0.122
LS mean diff vs placebo (95% CI)	2.306 (1.473, 3.139)	3.591 (2.756, 4.426)	
P-value	<0.001*	<0.001*	
Intertrochanteric area BMD	**N= 254**	**N= 252**	**N= 253**
LS Mean	1.439	2.059	-0.578
LS mean diff vs placebo (95% CI)	2.016 (1.326, 2.707)	2.637, (1.943, 3.330)	
P-value	0.001*	<0.001*	
Ward's triangle BMD	**N= 254**	**N= 252**	**N= 253**
LS Mean	1.416	2.894	-2.957
LS mean diff vs placebo (95% CI)	4.374 (2.665, 6.082)	5.851 (4.138, 7.565)	
P-value	0.001*	<0.001*	
Forearm BMD	**N=215**	**N=210**	**N=216**
LS Mean	-0.445	0.085	-1.713
LS mean diff vs placebo (95% CI)	1.268 (0.647, 1.888)	1.798 (1.173, 2.423)	
P-value	0.001*	0.001*	
Whole Body BMC	**239**	**233**	**242**
LS Mean	1.877	2.054	-0.729
LS mean diff vs placebo (95% CI)	2.606 (1.839, 3.373)	2.783 (2.010, 3.555)	
P-value	<0.001*	<0.001*	

LS = least squares; diff = difference; vs = versus; CI = confidence interval
P-values and LS means are based on an analysis of covariance on percent change from baseline with treatment, geographical region and baseline values as covariates
BMD was measured in g/cm2; BMD was measured in grams
*P-value significant, Hochberg procedure with overall alpha = 0.05

Markers of bone turnover were assessed in the same subjects as BMD measurements were done. Samples were collected at baseline, 1, 3, and 6 months and at 1, 2, and 3 years. Lasofoxifene-treated subjects had significantly decreased levels of markers of bone turnover compared to placebo from Month 1 through 3 years (with the exception of P1NP at Month 1).

Bone quality was assessed by evaluating tetracycline-labelled transiliac biopsies in a subset of subjects (N=71) who participated in Studies A2181003/A2181004 (OPAL). Lasofoxifene 0.5 mg treated subjects had significantly reduced bone formation rate as compared with placebo at 24 months. Bone quality in lasofoxifene treated subjects was normal and no pathologic or woven bone was noted.

Ancillary analyses

In A2181002 (PEARL) mammograms were performed annually. At 36 months as compared with placebo, lasofoxifene 0.5 mg reduced the risk of all breast cancers by 65%, the risk of ER+ breast cancer by 67%, invasive, and ER+ invasive breast cancer by 75%. Through 5 years, lasofoxifene 0.5 mg reduced the risk of all breast cancers by 79%, the risk of ER+ breast cancer by 81%, invasive breast cancer by 85%, and ER+ invasive breast cancer by 83%.

There were 3 Phase 2/3 Studies with lasofoxifene for the treatment of vulvar and vaginal atrophy. Lasofoxifene 0.5 mg decreased vaginal pH and improved vaginal cell maturation index.

- Analysis performed across trials (pooled analyses and meta-analysis)

Due to differences in demographic and baseline characteristics the CHMP considered that pooling of the data from the PEARL study and from the JADE study was not appropriate.

- Clinical studies in special populations

Studies in special populations have not been conducted.

- Supportive study(ies)

Supportive studies were the osteoporosis prevention trials (see table 3), and the osteoporosis treatment trial performed in 497 Asian women (JADE). In the JADE study, subjects were randomized to receive lasofoxifene 0.025 mg, 0.25 mg, 0.5 mg daily or placebo. All three lasofoxifene doses were significantly superior to placebo in increasing lumbar spine BMD at month 12. Percentages changes from baseline were 2.3, 2.8, 3.0 and -0.9 for lasofoxifene 0.025 mg, 0.25 mg, 0.5 mg daily and placebo respectively. Also changes at total hip were in favour of lasofoxifene compared to placebo.

Study 218-102 and Study A2181030 (CORAL) were 2-year studies versus raloxifene and placebo. In both studies, subjects were randomized to receive lasofoxifene 0.25 mg, raloxifene 60 mg, or placebo. In addition, study 218-102 included a lasofoxifene 1 mg dose. At month 24, lasofoxifene 0.25 and 1 mg, significantly increased lumbar spine BMD (about 3.3 and 3.9%) compared to placebo. For lumbar spine BMD lasofoxifene effects were superior to those of raloxifene. For other BMD parameters, performance of lasofoxifene and raloxifene were approximately equal.

Clinical safety

A routine GCP inspection at two sites (Romania and Argentina), which recruited approximately 10% of the study population, has detected major GCP non-compliance with regard to safety assessment. Two major issues were of particular importance for the assessment of the marketing authorisation application: (1) assessment of baseline medical history and (2) assessment of causality of reported AE's and SAE's by the investigators. The procedures may have resulted in an underreporting of new or suspected (serious) adverse drug reactions. The applicant was asked to discuss the impact of these procedures on the overall safety assessment and to address concerns about its reliability.

With regard to retrospective revision and update of medical histories the applicant provided reassuring data that this have no or very limited impact on the overall assessment of safety. Geographical differences in the frequencies for update of baseline medical history are explained by the organisation of the health care system in the countries involved in the study and, for example lack of nationwide update personal medical files – especially for middle-aged women without healthcare insurance. Although the frequency of updates of medical history was high at the Argentinean site only 7-8% of these updates were linked to report of AE's and there was no indication of a disproportionate number of updates among the different treatment groups including placebo. All in all it is the CHMP's view that these retrospective updates have not seriously affected the safety assessment for FABLYN.

Moreover, the applicant has provided a comprehensive review of the actual methods used for causality assessment at the two sites and supporting examples further indicating that a trustworthy assessment of causality has been carried out by the investigators.

Looking at these two concerns – update of medical history and causality assessment of AE's – there is no clear sign that these procedures have been carried out routinely at the two sites inspected. Update of medical history was far more frequently undertaken in Argentina as compared to Romania whereas causality assessment resulting in ascribing causality to the event itself was more frequently seen at the Romanian site as compared to Argentina. Therefore, these observations seem to be a random phenomenon with limited if any impact on the overall (safety) data of the PEARL trial.

- Patient exposure

The clinical safety database consisted of 15,404 subjects representing 42,143 subject-years of exposure, of who 10,257 received lasofoxifene (representing 27,910 subject-years of exposure). The 5-year PEARL study has been completed (database locked April 2008) and there are presently no ongoing studies in the lasofoxifene clinical program. Subsequent to 22/5/2007, the Phase 2 LACE study (A2181042) also completed. Updated analyses including 5-year Phase 2/3 Clinical Program data (that includes final 5-year data from the PEARL study and the LACE study), and final 5-year PEARL data alone, are presented below.

- Adverse events

The most common all causality AEs associated with lasofoxifene based on a cross-program analysis through 3 years were hot flush, muscle spasms, and vaginal discharge, most events mild or moderate in severity (Table 12).

Table 12 All Causality Adverse Events Reported in ≥ 5% of Subjects in Any Treatment Group: Phase 2/3 Clinical Program

		Number (%) of Subjects			
		Lasofoxifene			
SOC*	Preferred Term	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	Placebo N=4,676
Gastrointestinal Disorders					
	Constipation	299 (6.6)	309 (7.2)	704 (6.9)	291 (6.2)
General Disorders and Administration Site Conditions					
	Therapeutic response unexpected	367 (8.1)	356 (8.3)	832 (8.1)	302 (6.5)
Infections and Infestations					
	Influenza	288 (6.4)	292 (6.8)	653 (6.4)	312 (6.7)
	Nasopharyngitis	388 (8.6)	372 (8.6)	858 (8.4)	358 (7.7)
	Upper respiratory tract infection	386 (8.5)	353 (8.2)	865 (8.5)	423 (9.0)
	Urinary tract infection	334 (7.4)	315 (7.3)	737 (7.2)	337 (7.2)
Musculoskeletal and Connective Tissue Disorders					
	Arthralgia	599 (13.2)	570 (13.2)	1305 (12.8)	687 (14.7)
	Back pain	657 (14.5)	670 (15.6)	1431 (14.0)	745 (15.9)
	Muscle spasms	630 (13.9)	633 (14.7)	1411 (13.8)	322 (6.9)
	Osteoarthritis	234 (5.2)	233 (5.4)	490 (4.8)	264 (5.6)
	Pain in extremity	348 (7.7)	377 (8.8)	811 (7.9)	391 (8.4)
Nervous System Disorders					
	Dizziness	233 (5.2)	208 (4.8)	489 (4.8)	245 (5.2)
	Headache	240 (5.3)	234 (5.4)	565 (5.5)	338 (7.2)
Reproductive System and Breast Disorders					
	Vaginal discharge	286 (6.3)	250 (5.8)	648 (6.3)	124 (2.7)
Vascular Disorders					
	Hot flush	680 (15.0)	627 (14.6)	1601 (15.6)	297 (6.4)
	Hypertension	398 (8.8)	401 (9.3)	836 (8.2)	479 (10.2)

*SOC=System Organ Class.
†Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups.

Among less common (<5% incidence) AEs, are reproductive tract disorders: endometrial disorder, endometrial hypertrophy (sonographic endometrial thickness findings) and uterine polyp (Table 13).

Other important disorders are vascular, inter alia deep vein thrombosis. After 3 years lasofoxifene was associated with a 2-fold greater incidence of venous thromboembolic events compared with placebo. In this respect the new 5-year data are comparable to the 3 year data and importantly, the incidences are not further increased after 5 years.

Table 13 Selected All Causality Adverse Events with <5% Incidence in All Treatment Groups: Phase 2/3 Clinical Program

		Number (%) of Subjects			
		Lasofoxifene			
SOC[†]	Preferred Term	0.25 mg N=4,523	0.5 mg N=4,308	Pooled[‡] N=10,233	Placebo N=4,676
Infections and Infestations					
	Vaginal candidiasis	142 (3.1)	146 (3.4)	306 (3.0)	19 (0.4)
	Vulvovaginal mycotic infection	62 (1.4)	65 (1.5)	164 (1.6)	18 (0.4)
	Vulvovaginitis	36 (0.8)	35 (0.8)	80 (0.8)	18 (0.4)
Investigations					
	Blood alkaline phosphatase increased	6 (0.1)	6 (0.1)	13 (0.1)	31 (0.7)
	Blood cholesterol increased	5 (0.1)	6 (0.1)	15 (0.1)	22 (0.5)
	Blood calcium increased	7 (0.2)	5 (0.1)	15 (0.1)	23 (0.5)
Musculoskeletal and Connective Tissue Disorders					
	Resorption bone increased	31 (0.7)	27 (0.6)	58 (0.6)	83 (1.8)
Metabolism and Nutritional Disorders					
	Hypercholesterolaemia	21 (0.5)	23 (0.5)	52 (0.5)	66 (1.4)
Neoplasms Benign, Malignant and Unspecified					
	Uterine leiomyoma	45 (1.0)	70 (1.6)	142 (1.4)	38 (0.8)
Nervous System Disorders					
	Paraesthesia	57 (1.3)	34 (0.8)	116 (1.1)	74 (1.6)
	Sinus headache	10 (0.2)	1 (< 0.1)	22 (0.2)	17 (0.4)
Reproductive System and Breast Disorders					
	Endometrial disorder	39 (0.9)	44 (1.0)	94 (0.9)	11 (0.2)
	Endometrial hypertrophy[§]	186 (4.1)	148 (3.4)	375 (3.7)	38 (0.8)
	Genital discharge	83 (1.8)	61 (1.4)	176 (1.7)	22 (0.5)
	Uterine polyp	69 (1.5)	77 (1.8)	185 (1.8)	26 (0.6)
	Vaginal disorder	48 (1.1)	44 (1.0)	106 (1.0)	23 (0.5)
Vascular Disorders					
	Deep vein thrombosis	26 (0.6)	18 (0.4)	47 (0.5)	6 (0.1)
	Thrombophlebitis superficial	7 (0.2)	24 (0.6)	31 (0.3)	7 (0.1)

*Events occurring at apparently different incidence between the lasofoxifene 0.5 mg and placebo groups
[†]SOC=System Organ Class.
[‡]Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups.
[§]Endometrial hypertrophy events based on investigator reporting of endometrial thickness findings.

- Serious adverse event/deaths/other significant events

The incidence of serious adverse events was similar for lasofoxifene-treated subjects (14.7%) and placebo-treated subjects (14.1%) in Phase 2/3 studies through 3 years. The most common all causality serious adverse events among lasofoxifene- and placebo-treated subjects were cholelithiasis, fall, cataract and osteoarthritis. These events occurred at comparable incidence rates between the lasofoxifene and placebo treatment group and at a rate of less than 1 event per 100 subjects.

All causality serious adverse events that appeared to be associated with lasofoxifene generally were gynaecological in nature, including uterine polyps and endometrial hypertrophy (sonographic endometrial thickness findings), and uterine prolapse.

Death
Initially, there were 138 deaths reported across the lasofoxifene clinical development program through 3 years (i.e., including 3-year interim data from the PEARL study) in the initial file. The incidence of deaths was 48/4,523 (1.1%) for lasofoxifene 0.25 mg, 50/4,308 (1.2%) for lasofoxifene 0.5 mg, and 38/4,676 (0.8%) for placebo, i.e. risk of death did not significantly differ between lasofoxifene and placebo treated subjects. However one death due to leiomyosarcoma uteri was reported during lasofoxifene. After 3 years there were 3 deaths related to pulmonary embolism among lasofoxifene-

treated subjects, and none in the placebo-treated group. Two of the 3 deaths occurred in the setting of recent surgery. Accordingly in the SPC it is stated that FABLYN should be discontinued at least 3 weeks prior to and during prolonged immobilization (e.g. post-surgical recovery, prolonged bed rest), and FABLYN therapy should be resumed only after the patient is fully ambulatory.

PEARL, the study with the largest population, highest mean age of participants, and longest duration, accounted for the majority of deaths in the lasofoxifene clinical development program. An analysis of mortality through 5 years in PEARL is shown in table 14.

Table 14 Analysis of Time to All Cause Mortality – Full analysis Set

	Lasofoxifene			
	0.25 mg N=2,852	**0.5 mg N=2,852**	**Pooled N=5,704**	**Placebo N=2,852**
Subject-years at risk	12883.4	12849.7	25733	12817.8
Number (%)with an event	90 (3.2)	73 (2.6)	163 (2.9)	65 (2.3)
IR (95% CI)	0.70 (0.56, 0.86)	0.57 (0.45, 0.71)	0.63 (0.54, 0.74)	0.51 (0.39, 0.65)
HR (95% CI)	1.38 (1.00, 1.89)	1.12 (0.80, 1.56)	1.25 (0.94, 1.66)	
P-value	0.0489	0.5109	0.1311	

Source: Appendix 1, Table 5.13.
N=number of subjects, IR=incidence rate/100 subject-years, CI=confidence interval, and HR=hazard ratio (versus placebo).

Borderline significance is noted for the lower dose of 0.25 mg lasofoxifene in comparison to placebo, while this is not the case for the 0.5 mg to be marketed. The difference is explained by more fatal cases of cancer and stroke. Further analysis showed the following:

- No specific pattern in causes of death can be found, i.e. causes do not appear to focus on any one organ system;
- There is no dose-effect relationship;
- There is no signal that hormone-related tumours are involved;
- There is a higher number of lasofoxifene-treated subjects who died from stroke, but a lower number of subjects with non-fatal stroke in comparison to placebo, i.e. an inverse effect to what would be expected.

In view of these observations, it is concluded that a causal relationship with the use of lasoxifene is unlikely and that the findings do not reflect a true increase in mortality in lasofoxifene-treated subjects.

Table 15 Death Causality as Determined by External Endpoint Adjudication Committee

	Number (%) of Subjects		
	Lasofoxifene 0.25 mg N=2,852	Lasofoxifene 0.5 mg N=2,852	Placebo N=2,852
All Deaths	90 (3.2)	73 (2.6)	65 (2.3)
Coronary death	18 (0.6)	18 (0.6)	21 (0.7)
Sudden death	13 (0.5)	12 (0.4)	15 (0.5)
Fatal myocardial infarction	3 (0.1)	3 (0.1)	3 (0.1)
Fatal ischemic heart disease	2 (0.1)	3 (0.1)	1 (0.0)
Death from revascularization procedure	0	0	2 (0.1)
Noncoronary death	72 (2.5)	55 (1.9)	44 (1.5)
Vascular	18 (0.6)	9 (0.3)	7 (0.2)
Stroke	12 (0.4)	7 (0.2)	5 (0.2)
Other vascular	6 (0.2)	2 (0.1)	2 (0.1)
Nonvascular	54 (1.9)	46 (1.6)	37 (1.3)
Cancer	34 (1.2)	25 (0.9)	20 (0.7)
Suicide	0 (0.0)	1 (0.0)	0 (0.0)
Homicide	0 (0.0)	0 (0.0)	0 (0.0)
Other traumatic death	2 (0.1)	3 (0.1)	4 (0.1)
Other cause of death	18 (0.6)	17 (0.6)	13 (0.5)

N=number of subjects

Including the 5-year data of the Pearl study, 7 PE-associated deaths have been reported across the Phase 2/3 Clinical Program; 3 occurred in the lasofoxifene 0.25 mg group, 3 occurred in the lasofoxifene 0.5 mg group and one occurred in a placebo-treated subject. All deaths occurred in PEARL, the study with the largest population, highest mean age and longest duration of treatment. Three of these events were reported in the initial submission; the subsequent 4 cases were reported after the 22/5/2007 cut-off date. Incidence rates were low: 0.02, 0.02 and 0.01 events per 100 subject years at risk for lasofoxifene 0.25 mg, lasofoxifene 0.5 mg and placebo, respectively (NS). Further, all but two cases were associated with coexistent risk factors for VTE and one had discontinued study drug for >60 days at the time. In four cases, the PE event was not confirmed by imaging or autopsy. Thus lasofoxifene treatment does not seem to increase the risk of death from PE.

Gynaecological adverse events

The results for gynaecological safety are presented for the Full Analysis Set, excluding women with a pre-treatment hysterectomy. Gynaecological safety surveillance was extensive and driven by the possible association with uterine cancer. Central review of endometrial biopsies was done as a key to obtain accurate assessment of endometrial histology. Further in a number of studies transvaginal ultrasounds (TVUs) were done.

In addition in Study A2181002 (PEARL) [N=8,556] an independent committee of external experts was involved in the assessment of endometrial cancer, endometrial hyperplasia, endometrial polyps, endometrial thickness and cystic changes, vaginal bleeding, ovarian cancer, cervical cancer and surgery for prolapse or urinary incontinence. In PEARL patients had TVUs because of participation in a substudy or if required by a local authority. In other subjects with a uterus [N=4,054], TVUs were performed as required for follow-up of e.g. vaginal bleeding.

Endometrial thickness

The change in sonographic endometrial thickness was assessed in a sub-study of 326 subjects with an intact uterus at baseline. Mean thickness increased with 0.5 mg lasofoxifene, ranged from 0.61-1.44 mm and was significantly different from placebo. Lasofoxifene is also associated with an increased incidence of subjects with an endometrial thickness >= 8 mm (endometrial thickness outliers), as shown in Table 16.

Table 16 Incidence of Endometrial Thickness Outliers- Lasofoxifene Phase 2/3 Osteoporosis Prevention/Treatment Studies

	Lasofoxifene			
	0.25 mg	0.5 mg	Pooled*	Placebo
A2181002 (PEARL) - TVU-I – Month 36				
Number of subjects with measurement	100	95	195	107
Number (%) of subjects ≥8 mm	19 (19.0)	17 (17.9)	36 (18.5)	0
95% CI	(11.8, 28.0)	(10.7, 27.1)	(13.2, 24.6)	(0.0, 2.7)
P-value vs placebo	0.001*†	0.001†	0.001†	-
A2181037 (JADE) – FAS excluding pre-treatment hysterectomy – 12 months				
Number of subjects with measurement	103	101	307	99
Number (%) of subjects ≥8 mm	3 (2.9)	3 (3.0)	11 (3.6)	1 (1.0)
95% CI	(0.6, 8.2)	(0.6, 8.4)	(1.8, 6.3)	(0.0, 5.5)
P-value vs placebo	0.622	0.622	0.308	-
A2181030 (CORAL) - FAS excluding pre-treatment hysterectomy – 24 months				
Number of subjects with measurement	128	-	-	63
Number (%) of subjects ≥8 mm	13 (10.2)	-	-	0 (0.0)
95% CI	(5.5, 16.7)	-	-	(0.0, 4.6)
P-value vs placebo	0.006†	-	-	-
A2181003, A2181004 (OPAL) - FAS excluding pre-treatment hysterectomy – 24 months				
Number of subjects with measurement	305	295	891	305
Number (%) of subjects ≥8 mm	36 (11.8)	28 (9.5)	95 (10.7)	10 (3.3)
95% CI	(8.4, 15.9)	(6.4, 13.4)	(8.7, 12.8)	(1.5, 5.9)
P-value vs placebo	0.001†	0.003†	0.001†	
Phase 2 Prevention Studies - FAS excluding pre-treatment hysterectomy – 3 months to 24 months				
Number of subjects with measurement	56	55	485	155
Number (%) of subjects ≥8 mm	61 (10.7)	6 (10.9)	55 (11.3)	3 (1.9)
95% CI	(4.0, 21.8)	(4.1, 22.2)	(8.6, 14.5)	(0.4, 5.5)
P-value vs placebo	0.012†	0.012†	0.001†	

FAS = full analysis set
*Pooled includes all lasofoxifene doses in each study: A2181002 (0.25 mg, 0.5 mg), A2181037 (0.025 mg, 0.25 mg, 0.5 mg), A2181030 (0.25 mg only), A2181003/A2181004 (0.025 mg, 0.25 mg, 0.5 mg), Osteoporosis Prevention Phase 2 Studies (0.017 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, 10 mg)
†P-value significant versus placebo ≤0.05

Endometrial histology
Endometrial histology data indicated the endometrial pattern to change into "benign cystic atrophy" in a number of women. The pattern of "benign cystic atrophy" is said to be due to accumulation of fluid in both the stroma and glands of the endometrium and has been confirmed by external experts as benign in nature.

Interpretation of endometrial safety data is further complicated by the noted increase in endometrial thickness, with outliers up to >8 mm, although reversible in some patients under treatment (table 16).

This endometrial pattern is not noted during use of raloxifene and other SERMs. This endometrial pattern led to discrepancy in locally-read and centrally-read biopsy findings: through 5 years of follow-up in the PEARL study, in 41 cases local pathologists diagnosed endometrial hyperplasia (without atypia) of which after central reading the number was reduced to only 5 confirmed cases, i.e. in 36 women endometrial hyperplasia was not confirmed. The discrepancy is said to be due to the unfamiliarity of local pathologists with "benign cystic atrophy", a pattern that can be confused with simple endometrial hyperplasia. However, extensive follow-up information on these 36 subjects sufficiently demonstrated that these cases should be considered benign and as such, will not be taken into account in the assessment of the risk of endometrial cancer or hyperplasia.

Based on 3- and 5-year treatment data, the incidence of endometrial hyperplasia/endometrial cancer during treatment with lasofoxifene was not higher than noted for placebo. Four cases of endometrial cancers were observed in the lasofoxifene-treated patients versus 3 in the placebo-treated patients [incidence rate/100 treatment years is 0.019 vs 0.029, HR 0.67). For endometrial hyperplasia these numbers were 5 versus 0 cases, respectively (incidence rate/100 treatment years is 0.024 versus 0.0).

But it appears that only a limited number of women had scheduled end-of-study endometrial biopsies taken in the PEARL study. Therefore the diagnosis of endometrial hyperplasia and endometrial cancer relies very much on reporting of symptoms, which may be indicative of the presence of endometrial hyperplasia/cancer. The most important symptom for evaluation of the endometrium is unexpected vaginal bleeding.

The incidence of endometrial hyperplasia or cancer in lasofoxifene-treated subjects had not been evaluated systematically by comparing biopsies taken at baseline and after 12 months of treatment in at least 300 women, a design that is recommended for combined HRT in the CHMP guideline on HRT. Therefore, the conclusion of the applicant that the reported incidence rate of 0.02 (95% CI: 0.01, 0.05) per 100 subject-years does not suggest an increased risk for endometrial cancer as it falls within the upper limit of the 95% CI of 2% as defined by this guidance (the upper limit of a two-sided 95% confidence interval of the observed frequency of endometrial events should not exceed 2%), cannot be supported.

Reliable conclusions on endometrial safety can only be drawn when a sufficient number of women had at least 1 year of exposure to FABLYN before a biopsy was taken.

Therefore, additional endometrial biopsy data were submitted for 321 women who have been treated for more than one year.

Table 17 Incidence of Endometrial Hyperplasia or Cancer among Subjects with Adequate Histology and ≥ 1 Year of Confirmed Study Drug Treatment

	Lasofoxifene			
	0.025 mg	**0.25 mg**	**0.5 mg**	**Pooled**
Number with on-study biopsy	213	366	321	1127
Study drug exposure (years) prior to biopsy*	421.1	798.7	645.6	2124.8
Number (%) with event	1 (0.5)	5 (1.4)	4 (1.2)	10 (0.9)
Incidence rate/100 subject-years	0.237	0.626	0.620	0.471
95% CI	(0.006,1.323)	(0.203,1.461)	(0.169,1.586)	(0.226,0.865)

*Total years of study drug exposure is the elapsed time from first dose of randomized study medication to first endometrial cancer/hyperplasia or in the absence of endometrial cancer/hyperplasia, the last centrally-read biopsy.
Pooled=all lasofoxifene doses
Includes Studies 218-101E, 218-102, 218-103, A2181002, A2181003, A2181004, A2181014, A2181015, A2181016, A2181021, A2181030, A2181037.

Based on total exposure in these women, the applicant presents incidence rate per 100 treatment years of 0.6% with an upper limit of 95% CI of 1.59%. However, as it is likely that the risk of hyperplasia is not constant over time, calculation of the incidence rate expressed per proportion of subjects is considered less unbiased and therefore preferable. This is also the primary calculation requested for HRT, as the risk of HRT is definitely not constant over time, but increasing with longer duration of use.

The incidence rate expressed per proportion of subjects is 1.2% (4/321) with an upper limit of 3.2%, (95% CI). It is noted that the incidence rate of 1.2% with an upper limit of 3.2% expressed in terms of proportion of subjects with hyperplasia differs substantially from the incidence rate of 0.6 / 100 treatment years with an upper limit of 1.59%.

The upper limit of 95% CI of 3.2% is higher than the maximum of 2% considered acceptable in the HRT guideline. However, the recommendations in the HRT guideline refer to an incidence rate in all users i.e. in an unselected population with non-abnormal endometrium, verified by endometrial biopsy

at baseline. The FABLYN population evaluated is a selected population i.e. only subjects with an indication for an endometrium biopsy (vaginal bleeding or increased endometrial thickness) have been included. Additionally, no baseline biopsies were taken to rule out any endometrial malignancy prior to study entry. Hence, the incidence figures given are the incidences of hyperplasia in women with complaints/signs. Therefore, the incidence rate of 1.2 with an upper limit of the 95% CI of 3.2% is considered acceptable.

In conclusion, additional analyses of endometrial biopsies were taken "for cause" in women who had used FABLYN for at least 1 year did not demonstrate an increase in the risk of pre-malignant or malignant changes in the endometrium.

Nevertheless, there remain concerns about the benign endometrial changes induced by lasofoxifene and the resulting invasive 'minor' uterine procedures. Lasofoxifene is associated with endometrial changes that apparently prompt gynaecologists to carry out invasive "minor" uterine diagnostic procedures, especially endometrial biopsy-taking and hysteroscopy. Despite the educational programme it is most likely going to be very difficult to avoid all such "unnecessary" procedures, because the endometrial thickening and cystic changes induced by lasofoxifene in many women have a "dramatic" appearance on ultrasonographic examination. Ultrasound examination is widely performed in connection with a gynaecological examination, and it is not easy to see how the use of this informative, fast and safe modality should be avoided in lasofoxifene treated women.

Two cases of uterine sarcoma were reported in all lasofoxifene studies. No new cases have been detected in the 5-year PEARL study. In both cases the sarcoma was detected within 6 months after randomization. A causal relationship with lasofoxifene is therefore considered unlikely. It is planned to monitor the occurrence of uterine sarcomas post-marketing because there is a known small association between such sarcomas and tamoxifene treatment.

In conclusion on gynaecological adverse events, gynaecological safety is still a cause of concern. Based on the available data the risk of endometrial cancer was not increased by lasofoxifene use. However, it remains a cause of concern that lasofoxifene use was associated with a significant increase in minor uterine procedures. Also there was a trend towards an increase in risk of undergoing surgery for Pelvic Organ Prolapse and Urinary Incontinence in lasofoxifene treated women. All in all, the CHMP considers that the implications of these observations for daily practice are difficult to assess and based on assumptions. On the one hand incidence of minor uterine procedures may increase as trans-vaginal ultrasound will be used less discriminative than current guidelines which recommend screening transvaginal ultrasound only in patients with vaginal bleeding; on the other hand the company has proposed a very extensive educational plan to bring this histological pattern to the attention of the health professionals which would be expected to have some effect. In the absence of an increased risk of endometrial malignancy, the demonstrated absolute difference of 4.2% in uterine procedures is considered adequately addressed with the measures in the risk management plan.

- Laboratory findings

The incidences of laboratory test abnormalities were comparable between the lasofoxifene and placebo treatment groups. Apparent exceptions included platelet count, alkaline phosphatase, total cholesterol and LDL-C, which decreased on lasofoxifene compared with placebo, and triglyceride levels, which increased on lasofoxifene compared with placebo. There was a lower incidence of elevated total cholesterol and elevated LDL-C and a greater incidence of elevated triglycerides in the lasofoxifene 0.5 mg group than in the placebo group. Lipids were not collected after 3 years for the Phase 2/3 Clinical program for lipids (including triglycerides). Although a decrease in median triglycerides from baseline was observed with lasofoxifene treatment the decrease seen in the placebo treated groups for the same studies was greater. However, in the total phase 2/3 Clinical Program, 5-year data do not indicate an increased risk of pancreatitis or stroke or coronary events.

Fibrinogen was reduced as well as platelet count. In view of established DVT the question arises what the data are of other coagulation factors: protein S, thrombin and antithrombin complex, prothrombin time, prothrombin fragments 1 and 2, plasminogen, D-dimer quantitative and activated partial

thromboplastin time. This is an important issue as coagulation factors might play an important role in DVT, a safety issue. Laboratory assessments were not conducted beyond 3 years in PEARL. Lasofoxifene was associated with a median decrease in the platelet count compared to placebo. This change was not associated with an excess of very low platelet counts and not associated with bleeding episodes and the incidence of low (less than 50x103/mm3) platelet counts was similar across treatment groups in the 3-year Phase 2/3 Clinical Program. There were three subjects with a platelet count of <20x103/mm3, two on placebo and one on lasofoxifene 0.25 mg. It seems that this sign is consistent with what has been observed with other SERMs, including raloxifene.

In all lasofoxifene treatment groups, high sensitivity C-Reactive Protein decreased from baseline by a median of 0.10- 0.20 mg/L within one month of treatment initiation and remained stable through 36 months of treatment. Data indicate that there is a rapid and sustained decrease of this inflammatory marker upon lasofoxifene treatment.

The effect of lasofoxifene on cardiac repolarisation was assessed. In the studies presented there was no evidence of an effect on QTc.

- Discontinuation due to adverse events

In the Phase 2/3 Clinical Program that includes 3-year interim data from the PEARL study, there was no difference in percentage of discontinuations in lasofoxifene treated patients or placebo treated patients. In all groups the percentage was 20%. Among all causality adverse events resulting in discontinuation from treatment, there was an apparent imbalance within the following SOCs: Musculoskeletal and Connective Tissue Disorders, with discontinuations occurring in 1.3%, 1.3%, 1.3%, and 0.9% of subjects and Vascular Disorders, with discontinuations occurring in 2.5%, 2.7%, 2.7%, and 1.1% of subjects in the lasofoxifene 0.25 mg, 0.5 mg, pooled, and placebo groups, respectively. The incidence of discontinuation due to events in the Reproductive System and Breast Disorders SOC was comparable among treatment groups.

Hot flush was the all causality adverse event most commonly resulting in lasofoxifene discontinuation, and discontinuation due to this event was more common among lasofoxifene- than placebo-treated subjects. Discontinuations due to all causality muscle spasms (≤ 0.8% of subjects) and deep vein thrombosis (≤ 0.5% of subjects) were less common though occurred at greater incidence among subjects receiving lasofoxifene compared with placebo.

- Post marketing experience

There is no post-marketing experience as the product is not licensed yet.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 18 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Increase in VTEs	Multi-tiered pharmacovigilance system Prospective cohort study to determine the incidence of gynecological and non-gynecological outcomes in women treated with lasofoxifene, raloxifene, or no SERM in a community setting	SPC: 4.3 Contraindications: Patients with an active or past history of VTEs should not take FABLYN. 4.4 Special Warnings and Precautions: Patients should discontinue FABLYN three weeks prior to and during prolonged immobilization. 4.8, Venous Thromboembolic Events PL: Section 2, Before you take FABLYN: Do not take FABLYN if you currently have or previously had blood clots, for example in your veins, lungs or eyes (deep vein thrombosis, pulmonary embolism or retinal vein thrombosis). Take special care with FABLYN: **…**Your doctor may recommend that you stop treatment at least 3 weeks prior to this time. …if you are taking FABLYN, you should walk around or exercise your legs and feet at regular intervals when traveling long distances. Educational programme
Increase in diagnostic uterine procedures	Multi-tiered pharmacovigilance system Prospective cohort study to determine the incidence of gynecological and non-gynecological outcomes in women treated with lasofoxifene, raloxifene, or no SERM in a community setting	SPC 4.3 Contraindications: - Unexplained uterine bleeding. SPC; 4.4 Special Warnings and Precautions: Lasofoxifene has been associated with benign endometrial effects. These included, in some subjects, a small excess in the incidence of vaginal bleeding as well as endometrial cystic change viewed on ultrasound and histological benign cystic atrophy (a variant of atrophic endometrium). These cystic findings contributed to an approximate 1.5 mm increase in mean endometrial thickness. As a consequence of these benign effects, more FABLYN-treated patients had a diagnostic uterine procedure compared to placebo-treated patients in the PEARL trial (see section 5.1). However, in clinical practice, these benign findings do not warrant further evaluation in women with no vaginal bleeding (in accordance with guidelines for postmenopausal women), as the risks of diagnostic uterine procedures in asymptomatic women outweigh any benefits. Pathologists should be made aware of a history of lasofoxifene use when assessing endometrial histology, to ensure an accurate diagnosis of benign cystic atrophy when present SPC 5.1 Pharmacodynamic Properties, Effects on the endometrium: diagnositic uterine procedures were performed in greater number of FABLYN-treated women … PL: Section 2, Before you take FABLYN, Do not take FABLYN… if you have any

		vaginal bleeding. This must be investigated by your doctor before starting treatment. Take special care with FABLYN… any vaginal bleeding while you take FABLYN is unexpected. You should have this investigated by your doctor … Educational programme Peer-review publication on the morphologic changes in the uterus of postmenopausal women
Important potential risks		
Safety events associated with other SERMs and Hormone Therapy, including: endometrial cancer, pelvic organ prolapse/urinary incontinence and gallbladder events.	Multi-tiered pharmacovigilance system Prospective cohort study to determine the incidence of gynecological and non-gynecological outcomes in women treated with lasofoxifene, raloxifene, or no SERM in a community setting	No additional risk minimization activities are planned for potential risks.
Important missing information		
Effect of long term treatment (>5 years) in the normal practice setting	Prospective cohort study to determine the incidence of gynecological and non-gynecological outcomes in women treated with lasofoxifene, raloxifene, or no SERM in a community setting	None planned

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in the Annex "Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product to be implemented by the Member States".

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this 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. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe

Non-clinical pharmacology and toxicology

The pharmacological effects of lasofoxifene were investigated in up to 12-months in OVX rats and 24-month in OVX monkeys. In general, lasofoxifene partially inhibited the OVX-induced changes in bone parameters but not always with obvious dose-response relationship. The toxicity study programme is considered sufficient for safety assessment except for the assessment of carcinogenicity. The applicant has agreed to provide further information regarding the relevance of the tumours observed in animal carcinogenicity studies for humans. The applicant has committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

Efficacy

The main study for the establishment of efficacy of lasofoxifene for the treatment of osteoporosis in postmenopausal women was a single randomised, double-blind, placebo-controlled clinical trial (study A2181002, PEARL) with an overall duration of 5 years and a pre-planned interim analysis at 3 years. Two doses of lasofoxifene (0.25 mg and 0.5 mg) were compared against placebo. 8556 patients were randomised. Participants were between 60 and 80 years of age, and had at screening a BMD T-score of ≥ -4.5 and ≤ -2.5 in the lumbar spine or femoral neck. The risk for a new/worsening radiographic vertebral fracture was reduced by 31% and 42% in the lasofoxifene 0.25 mg and 0.5 mg groups, respectively, compared with placebo through 36 months. Preliminary data through 5 years were consistent with these findings. Regarding the time to first new radiographic vertebral fracture, which is the appropriate endpoint in accordance with European guidelines, lasofoxifene 0.5 mg and 0.25 mg were associated with statistically significantly reduced risks of 42% and 32%, respectively. These data were confirmed with preliminary data through 5 years (41% and 32%, respectively).

The effects were observed from 1 year onwards for both the doses of lasofoxifene. Similar results are reported in women with or without prevalent fracture at baseline. Lasofoxifene 0.5 mg, but not lasofoxifene 0.25 mg, significantly reduced the risk in subjects with baseline LS BMD T-score > -2.5, who were eligible for the study on the basis of their baseline femoral neck BMD T-score < -2.5.

A significant effect on the time to first nonvertebral fracture compared to placebo was observed only for the 0.5 mg dose and not for the 0.25 mg dose. A clinically relevant effect on hip fractures has not been demonstrated (at 5 years: 31, 27 and 35 in the 0.25 mg, 0.5 mg, and placebo groups, respectively).

BMD measurements over 3 years demonstrated a greater increase at all sites with the 0.5 mg dose compared to the 0.25 mg dose; this effect was not found in those with a lumbar spine BMD T-score > -2.5. A decrease of the level of markers of bone turnover was observed for lasofoxifene-treated patients compared to placebo-treated patients. In a separate study in Asian women, an effect of lasofoxifene on lumbar spine was also demonstrated at month 12.

The available data demonstrate the efficacy of lasofoxifene for the treatment of postmenopausal osteoporosis in terms of significant reduction of both vertebral and non-vertebral fractures but not hip fractures in osteoporotic patients (BMD T-score [lumbar spine or femoral neck] < 2.5). Furthermore, it supports the selection of 0.5 mg daily as the most effective dose.

Safety

The most common all causality AEs associated with lasofoxifene were hot flush, muscle spasms, and vaginal discharge. Most adverse events were mild or moderate in severity. The incidence of serious adverse events was similar for lasofoxifene-treated subjects (14.7%) and placebo-treated subjects (14.1%) in Phase 2/3 studies. The most common all causality serious adverse events among lasofoxifene- and placebo-treated subjects were cholelithiasis, fall, cataract and osteoarthritis. Risk of death did not significantly differ between lasofoxifene and placebo treated subjects. After three years there appeared to be three deaths related to pulmonary embolism among lasofoxifene treated subjects and none in the placebo treated group. However two of the three deaths occurred in the setting of recent surgery. After five years, seven PE associated deaths were reported across the Phase 2/3 clinical programme: three in the lasofoxifene 0.25 mg group, 3 in the lasofoxifene 0.5 mg and one in a placebo- treated subject.

An increased risk for gynaecological AEs has been demonstrated. The observed significant increase in minor uterine procedures remains a cause of concern. Based on the available data however, the risk of endometrial cancer was not increased with the use of lasofoxifene.

Two cases of uterine carcinosarcoma tumor are reported with lasofoxifene (0.025 mg and 0.25 mg). Additionally, 1 woman died of leiomyosarcoma.

The use of lasofoxifene was associated with a considerably and clinical significant higher incidence of VTE (hazard ratio of 2.13 (95% CI 1.34, 3.39; p=0.0010). This association mostly was driven by a higher incidence of DVT in the lasofoxifene group compared with placebo. Also a higher incidence of pulmonary embolism was noted among lasofoxifene treated subjects. There were 6 deaths related to pulmonary embolism among lasofoxifene-treated subjects and 1 in the placebo-treated group. All but 2 cases were associated with coexistent risk factors for VTE. This thrombogenic potential has also been observed with other SERMs.

Elevations of ALT and AST were more common among lasofoxifene- than placebo-treated subjects and the incidence of hepatic steatosis was higher among lasofoxifene treated subjects. Also cholelithiasis as a treatment-related SAE was more common among lasofoxifene- than placebo-treated subjects. Although these events were rare and no indication of severe liver injury associated with the use of lasofoxifene were observed, an impact of lasofoxifene cannot be excluded.

A decrease in platelet count associated with lasofoxifene treatment was observed and the rationale for this remains to be elucidated.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation for the proposed package leaflet has been performed. Overall, the test was considered acceptable.

Risk-benefit assessment

Benefits

Lasofoxifene 0.5 mg was associated with a significant reduction in the risks of new vertebral fractures– an effect that was evident after 12 months and in subgroups of subjects, including women with or without prevalent fractures at baseline. In terms of non-vertebral fractures, including hip fractures, treatment with 0.5 mg lasofoxifene results in a significant reduction in the fracture rate compared to placebo. Stratified on baseline BMD, lasofoxifene 0.5 mg as well as 0.25 mg reduced the risk of these fractures in subjects with baseline BMD T-score ≤-2.5, whereas no effect was demonstrated in subjects with LS BMD T-score > -2.5. Treatment with lasofoxifene 0.5 mg was associated with significant risk reductions in multiple vertebral fractures and clinical fractures. Overall, significant and clinically relevant increases in BMD were demonstrated for the spine, hip and components of hip (femoral neck, greater trochanter, intertrochanteric area, and Ward's triangle), for the lasofoxifene 0.25mg and 0.5 mg treatment groups compared to placebo and it appeared from the pivotal study that this effect was sustained from month 3 throughout the study.

Significant decreases in levels of bone markers indicating a reduction in bone turnover were demonstrated with all active treatments at all time points. Significant benefits in the risks of breast cancer events were demonstrated through 3 years and through 5 years. After 36 month the risks of ER+ breast cancer as well as ER+ invasive breast cancer were significantly reduced in the active treatment groups compared to placebo and a composite endpoint consisting of adjudicated ER+, ER-, invasive, and DCIS breast cancer, as well as invasive breast cancer showed a risk reduction with the 0.5 mg treatment group. Through 5 years, lasofoxifene 0.5 mg significantly reduced the risk of all breast cancer, invasive breast cancer, and ER+ invasive breast cancer lasofoxifene 0.25 mg did not significantly reduce these three endpoints. No treatment differences were observed for DCIS through 5 years. Lasofoxifene has favourable effects on endpoints associated with vaginal atrophy in postmenopausal women with osteoporosis. Lasofoxifene significantly reduced vaginal pH and demonstrated favourable effects on vaginal maturation index. Lasofoxifene decreases total and LDL cholesterol and increases serum triglycerides whereas no effect on HDL-cholesterol was obtained.

Risks

Lasofoxifene treatment was associated with an increased risk for gynecological AEs which is considered a potential serious health concern. The main concerns relate to endometrial changes with increased thickness, to a significant increase in minor invasive procedures and to a tendency towards increased incidence of pelvic organ prolapse associated with lasofoxifene treatment. However, this is satisfactorily addressed in the risk management plan.

The unfamiliar endometrial pattern observed, the increased endometrial thickness, in addition to increased vaginal bleeding incidences, all increase the number of unnecessary uterine diagnostic procedures and cause unnecessary emotional stress in the patients involved. It has not been specified how this increased number of minor uterine procedures could be avoided, and an insufficient amount of data is available regarding uterine and vaginal prolapse. It is however unlikely that the significant increase in uterine procedures associated with lasofoxifene can be fully avoided. Endometrial thickening, cystic appearance, polyps, bleeding etc. remain important issues associated with lasofoxifene to a significantly higher degree than with for example raloxifene. In the absence of an increased risk of endometrial malignancy, the demonstrated absolute difference of 4.2 % in uterine procedures is considered adequately addressed with the measures in the risk management plan.

No increase in endometrial carcinoma was seen: 7/7,247 cases of endometrial carcinoma were reported during lasofoxifene versus 4/3,399 in the placebo group. However, as no routine biopsies were taken, the diagnosis of endometrial hyperplasia and endometrial cancer relies very much on reporting of symptoms which may be indicative of the presence of endometrial hyperplasia/cancer. According to protocol, biopsies were taken for 'cause' i.e. in case of vaginal bleeding or increased endometrial thickness. Upon request from the CHMP additional data on endometrial biopsies taken for 'cause' were provided for 321 women treated for more than one year. The data fulfils the demands specified in the EMEA guideline for investigation of medicinal products for HRT. As it is likely that the risk of endometrial hyperplasia is not constant over time, an incidence expressed per proportion of women is the preferred analysis, as is also recommended in the HRT guideline. Based on the proportion of women, the incidence rate is 1.2% with an upper limit of 95% CI of 3.2%. The upper limit of 95% CI of 3.2% is higher than the maximum of 2% considered acceptable in the HRT guideline. However, as this is an analysis in a selected population, i.e. only subjects with an indication for an endometrium biopsy (vaginal bleeding or increased endometrial thickness) were included, the 3.2% is considered an overestimation. Additionally, no baseline biopsies were taken to rule out any endometrial malignancy prior to study entry. Hence, the incidence figures given are the incidences of hyperplasia in women with complaints/signs. Therefore, an upper limit of 95% CI of 3.2% is acceptable. In conclusion, additional analyses of endometrial biopsies taken "for cause" in women who had used FABLYN for at least 1 year did not demonstrate an increase in the risk of pre-malignant or malignant changes in the endometrium.

The noted increased risk of venous thromboembolism has been translated into a contraindication in subjects with a history of thromboembolic events and a special warning in the SPC, and is addressed in the risk management plan.

Balance

The present efficacy data support the osteoporosis treatment indication in high risk postmenopausal subjects in the age-group 60 -80 years, with the 0.5 mg dose, i.e. lasofoxifene treatment of this dose was associated with a reduction in the incidence of new vertebral fractures and non-vertebral fractures but not hip fractures as well as increases in BMD at all important sites and reduction in the risk of breast cancer. Lasofoxifene 0.5 mg treated subjects had a reduced risk of all breast cancer (a composite endpoint consisting of ER+, ER-, invasive, and DCIS). Further analyses were performed for breast cancer categories ER+, ER+ invasive, invasive and DCIS.

Concern has been raised regarding the clinically significant higher incidence of VTE associated with lasofoxifene treatment as well as the impact of lasofoxifene on liver function including the risk of

steatosis, cholecystolitiasis and serum triglycerides. All these issues have been adequately addressed in the SPC and/or RMP. An increased risk of endometrial cancer has been sufficiently excluded based on calculations in accordance with current guidance for HRT-products based on biopsies taken for 'cause' in women treated with lasofoxifene for at least 1 year. There is a noted increase in endometrial thickness, with outliers up to >8mm. Endometrial histology data indicated the endometrial pattern to change into "benign cystic atrophy" in a number of women. Locally-read and centrally-read biopsy findings show a discrepancy in simple endometrial hyperplasia that might be confused with "benign cystic atrophy". This endometrial pattern is not noted during use of raloxifene and other SERMs. Consequently, the number of unnecessary uterine procedures is increased. This is still a concern, but in the view of the CHMP this issue could be handled through the risk management plan. The applicant has provided a detailed description of a web-based educational material targeted at the prescribing physicians using CME. The system has not yet been developed or tested. The applicant has selected appropriate organizations and websites to reach the target population and provided a detailed plan. The conditions of the Marketing Authorisation will ensure that these activities are developed and in place before marketing. CME accreditation is important to ensure that the activities will reach the target population. Therefore, the applicant has committed to obtain CME accreditation for the web-based educational materials before marketing.

Taking all this into consideration the benefit-risk balance is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activities were required: see as detailed in the Annex "Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product to be implemented by the Member States".

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of FABLYN in the therapeutic indication:

> "FABLYN is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated (see section 5.1).
>
> When determining the choice of FABLYN or other therapies, including estrogens, for a postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits (see section 5.1)."

was favourable and therefore recommended the granting of the marketing authorisation.