European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

CONBRIZA

International Non-proprietary Name:
bazedoxifene

Procedure No. EMEA/H/C/913

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Wyeth Europa Ltd submitted on 4 September 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for CONBRIZA, 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 21 September 2006.

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

The application submitted is 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

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 30 March 2001. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status:
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: Harald Enzmann Co-Rapporteur: Steffen Thirstrup

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 05 September 2007.
- The procedure started on 27 September 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 December 2007.
- During the meeting on 21-24 January 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 24 January 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2008.
- The GCP inspection, requested by the CHMP, was carried out at one investigator site in Denmark (inspected 18-21 Feb 2008), one investigator site in Brazil (inspected 25-29 Feb 2008) and at the sponsor site in the USA (inspected 25-28 Mar 2008). The final Integrated Inspection report was issued on 20 June 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 October 2008.
- During the CHMP meeting on 20-23 October 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 December 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the CHMP List of Outstanding Issues on 27 January 2009.
- During the meeting on 16-19 February 2009, 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 CONBRIZA on 19 February 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 February 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Osteoporosis is characterized by a decrease in bone mass and architectural deterioration of bone tissue. Subtle modifications of bone remodelling, related to abnormalities of bone turnover, can induce a substantial loss of bone over a prolonged period of time. A period of asymptomatic bone loss results in reduced bone strength. When bone loss is sufficient to cause mechanical weakness, fractures may occur spontaneously or as a result of minimal trauma. 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. Hip, vertebral, forearm and humerus fractures also reduce, to various extents, health-related quality of life with deleterious effects lasting up to several years after the fracture event. 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.

Antiresorptive agents, such as bisphosphonates and selective oestrogen receptor modulators (SERMs), are currently one of the treatment options for the prevention of osteoporotic fractures. The efficacy results of the Women's Health Initiative (WHI) studies showed that standard dose oestrogen-progestin combination therapy or oestrogen alone (in women who have undergone hysterectomy) was effective in reducing the risk of fractures in postmenopausal osteoporosis as well as successfully treated the symptoms of menopause. However, an increased risk of stroke, deep vein thrombosis (DVT), pulmonary embolus (PE), and when combined with a progestin, breast cancer were reported. Bisphosphonates are non-hormone compounds that bind to the bone surface and are then taken up by osteoclasts. These widely used drugs have a profound effect on bone remodelling, and their efficacy in the prevention and treatment of osteoporosis is well established. SERMs have oestrogen agonist effects on bone tissue and oestrogen antagonist or neutral effects on endometrial and breast tissue. The efficacy of the first approved SERM, raloxifene, to reduce the incidence of vertebral fractures has been demonstrated in women at high risk for fractures through a large randomized placebo-controlled trial involving more than 7000 postmenopausal women (Multiple Outcomes of Raloxifene Evaluation (MORE) trial). AE associated with raloxifene included an increase in the absolute risk of VTEs similar to that seen with oestrogen therapy.

Bazedoxifene is a third-generation selective oestrogen receptor modulator (SERM) that exhibits oestrogen-agonistic tissue-selective activity on the skeletal system and lipid metabolism while also acting as an oestrogen antagonist on breast and uterine tissue. Bazedoxifene is formulated as an immediate-release, film-coated tablet and has been developed for the prevention and treatment of osteoporosis in postmenopausal women. Apart from the present program, bazedoxifene is also being studied in combination with conjugated oestrogens (CE) in an ongoing phase 3 program for the prevention of postmenopausal osteoporosis and the treatment of menopausal symptoms.

The indication as proposed by the applicant was:
"CONBRIZA is indicated for the treatment and prevention of postmenopausal osteoporosis in women at increased risk of fracture."

Approved indication:
"CONBRIZA is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip fractures has not been established.

When determining the choice of CONBRIZA or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits (see SPC section 5.1)."

The recommended dose is one tablet of 20 mg once daily, at any time of day, with or without food. Supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.
The present assessment reports concerns the complete marketing authorisation application for the new active substance bazedoxifene acetate applied via the centralised procedure.

2.2 Quality aspects

Introduction
CONBRIZA contains bazedoxifene acetate as active substance. Bazedoxifene is a third-generation selective estrogen receptor modulator (SERM). CONBRIZA is an immediate release, film-coated capsule shaped tablet. Tablets contain 20 mg of bazedoxifene expressed as free base. The tablets are supplied in blister packaging.

Active Substance
Bazedoxifene is the INN name of the active substance which is present in the product in the form of the acetate salt. Its chemical name is 1H-Indol-5-ol, 1-[[4-[2-(hexahydro-1H-azepin-1-yl) ethoxy] phenyl] methyl]-2-(4-hydroxyphenyl)-3-methyl-,monoacetate corresponding to the molecular formula $C_{30}H_{34}N_2O_3 \bullet C_2H_4O_2$ and molecular mass of 530.65.
It is a white to tan non-hygroscopic crystalline powder. It exists in at least three crystalline polymorphic forms. The route of synthesis described for the active substance is reported to yield only form I. Bazedoxifene solubility in water is largely pH dependent showing plateau of approx. 0.5 mg/ml below pH 5. Its pKa is approximately 11 and distribution coefficients show pH dependency in consistency with pH solubility profiles. It doesn't show any optical activity.

- Manufacture

The active substance is supplied by another company and is supported by an ASMF. Two alternate routes have been adequately described, differing only in one step. The remaining steps for both processes are identical. The synthesis process consistently yields form I. Data are provided for 29 batches of active substance, showing that the level of form II in active substance material is typically very low complying with the specifications in force of release. Some of the clinical trial batches contained low levels of Form II but always within proposed specifications.

- Specification

The drug substance specification includes tests for appearance (visual), identification (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water (Ph.Eur), residue on ignition (Ph.Eur), acetic acid content (HPLC), palladium content (ICP-OES), Heavy Metals (Ph.Eur) and Particle Size (Laser Diffraction) and polymorphic forms (DSC and XRD).
Batch analysis data are provided for 12 batches in various batch sizes produced using both processes. The results show compliance with the proposed specification and no significant differences in purity or impurity contents across the batch size range.

- Stability

Stability data, as described in the ASMF, were provided for the same 12 batches of micronised bazedoxifene acetate for which batch analyses have been provided. These batches were manufactured using both processes and nine of them were pilot scale and the remaining three were industrial scale. Stability data up to 24 months at 5°C and at 25°C/60%RH, and up to 6 months at 40°C/75%RH were obtained.
Additional supportive data are provided for three micronised batches made at industrial scale stored for up to 36 months at 5°C and at 25°C/60%RH and for up to 6 months at 40°C/75%RH.

The maximum holding time and storage/transport conditions for the bulk drug substance prior to micronisation has been also adequately defined.
All tests results were satisfactory and within acceptance criteria with minimal to no changes observed over time at any storage condition.
Stress study was performed on one of the three primary stability batches. The results showed extensive degradation under light and oxidative conditions, less but noticeable degradation under alkaline conditions and heat and no change in acidic conditions. Stress study was performed on one of the three primary stability batches. The ASMF holder provided photostability results obtained under ICH option 2 conditions demonstrating that micronised material was photostable.

In conclusion, the data collected to date under all studied conditions support the proposed retest period and packaging material.

Medicinal Product

- Pharmaceutical Development

A capsule formulation was initially developed for Phase I clinical studies. Later on, a tablet formulation was developed for subsequent commercialization which was very similar to the capsule formulation. The acetate form was chosen over other forms because it is less hygroscopic and more soluble than the other forms tested preclinically.
As bazedoxifene acetate is a poorly water-soluble drug substance, reduction of particle size by micronisation was employed. The intrinsic dissolution of the micronised particles is faster compared to that of the unmicronised substance. Extensive information was provided regarding polymorphic forms. The synthesis process for the active substance has been optimised to ensure production of the desired polymorph.
Capsules were initially developed and because bazedoxifene acetate is susceptible to oxidation especially in alkaline environment and increased temperature, ascorbic acid was added as an antioxidant to improve stability. Later on a tablet formulation was developed based on capsule formulation and excipient levels were adjusted to improve compressibility and a tablet coating was added.
The absolute bioavailability of 2 oral formulations (tablet and capsule containing micronised drug substance) with respect to an IV formulation and also the relative oral bioavailability and safety of bazedoxifene acetate administered in tablet form compared with a capsule formulation, were the primary objective of clinical study (3068A1-111). The dissolution profiles were comparable and the absolute bioavailability of both orals formulations was the same. Both formulations were bioequivalent as far as the exposure (AUC) is concerned.
All excipients used are widely used for immediate release tablet formulations and compatibility with the active substance has been demonstrated by appropriate studies examining binary mixtures of active substance and excipients.
Extensive information was provided regarding polymorphic forms. Results from a BE study (3068A1-129-US) performed with tablets formulated with a significant level of polymorphic form II in the drug product is not bioequivalent to tablets containing only form I. The polymorphic content in the finished product is controlled at release and during shelf life by appropriate tests and limits and a suitable analytical method.
Data were also provided on possible inter-conversion of the polymorphic forms of the drug substance. Through appropriate control and manufacturing conditions, the content of polymorphic forms in the finished product can be minimised.

- Adventitious Agents

Magnesium stearate is of vegetable origin. Only Lactose Monohydrate, used in the manufacture of CONBRIZA, is derived from animal sources i.e. bovine milk. A statement confirming compliance with the requirements of EMEA/410/01-Rev.2, October 2003 is provided by the lactose supplier.

- Manufacture of the Product

Manufacture consists of standard wet granulation techniques which include dry mixing, wet granulation, drying, the screen milling, blending, tablet compression, and film coating.
All of the results obtained from the evaluation performed on the blending, compression and coating processes of manufacturing 20 mg Bazedoxifene Film Coated Tablets were satisfactory. The overall validation data generated demonstrate that the process is well controlled, reproducible, and produces drug product that is in compliance with approved specifications and acceptance criteria.

- Product Specification

The specifications of the drug product at release and shelf-life include tests for appearance (visual), identity (HPLC-PDA), assay (HPLC), content uniformity (Ph.Eur.), degradation products (HPLC), microbial limits (Ph.Eur.), dissolution (Ph.Eur.), ascorbic acid content (HPLC) and polymorphic forms (XRD) Analysis results are presented for 7 different formulations covering 55 batches used in clinical testing phases I, II and III, and in stability testing. Batch results for three batches used in clinical and bioequivalence studies and in stability studies have been enclosed and the results are all within the specifications.

- Stability of the Product

Three production scale batches of 20 mg were stored for up to 24 months at 25°C/60%RH, 24 months at 30°C/65%RH, and up to 6 months at 40°C/75%RH.
Bazedoxifene tablets were initially packed in two blister systems but after the review of the 18 month data, it was proven that only one of the two blister configurations provides adequate protection for the product and this was chosen as the market packaging.
For the primary stability batches, data to 24 months at 25°C/60%RH, 24 months at
30°C/65%RH, and 6 months at 40°C/75%RH for all package show data remaining well within acceptance criteria with no significant increase in degradation, decrease in strength, or change in dissolution.
Photostability
Blister packed products were exposed to ICH option 2 light conditions. Total degradant content rises slightly though results are satisfactory and well within specification. Dissolution is unchanged.

Overall the stability results indicate that the product is stable in the proposed packaging material and during the proposed self-life when used in accordance with the SPC

Discussion on chemical, pharmaceutical and biological aspects

The quality of CONBRIZA film-coated tablet is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. 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.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction

With the exception of explorative studies nearly all non-clinical pharmacological, toxicological and kinetics studies have been performed in compliance with GLP regulations. It is accepted that the cardiovascular safety pharmacology studies in rats and monkeys were performed not in compliance with GLP regulations as these studies were performed prior to release of ICH S7A guidance.

Centralised scientific advice has been provided by the CHMP in which non-clinical issues (reproductive toxicity and carcinogenicity studies) were dealt with.

Pharmacology

Bazedoxifene is a selective oestrogen receptor modulator (SERM), which binds to both intracellular oestrogen receptor subtypes (α and β) and acts oestrogen like on the skeletal system in the species investigated and, at least in the rat on lipid metabolism, while exhibiting only minimal to negligible action on breast and uterine tissues. Oestrogen deficiency-dependent postmenopausal osteoporosis in women is characterized by major changes in the bone system with increased bone turnover rates and reduction in bone mineral density. In animal systems bazedoxifene was shown to counteract partially oestrogen deficiency-dependent changes in the bone system.

- Primary pharmacodynamics

The primary pharmacodynamic (PD) programme encompassed explorative studies to search for a compound with the desired properties in suitable in-vitro tests and to characterise basic properties on the molecular level, e.g. binding and activation (or inhibition) of certain oestrogen-responsive gene promoters. Hormone effects were also investigated in vivo or in selected cultured cells to mimic bazedoxifene's action on certain tissues (e.g. breast cancer). Regular in-vivo PD studies were also performed to test the desired effect of bazedoxifene on bone mass, turnover and stability in experimental animals.

In vitro studies
The explorative studies are in most cases difficult to assess since the methods used are very special and not formally validated. All relevant properties of bazedoxifene were investigated in standard PD, Pharmacokinetic (PK) and toxicology studies so that the explorative studies are mainly regarded as background information. According to the explorative studies, bazedoxifene has an around 4-fold higher affinity for the human oestrogen receptor (ER) type α (IC_{50}=26 nM) than for type β (IC_{50}=99 nM). From this rather small difference in affinity no meaningful selectivity is expected in vivo. Bazedoxifene also had lower *in-vitro* affinity for ER receptors than raloxifene (IC_{50}=2.4 nM) and showed lesser selectivity towards the ERα than raloxifene (18-fold for the latter). It should be noted that ERα selectivity is not an important criterion for SERMs since it is not yet known which type of ER is required for the desired effects of SERMs on the bone. In functional studies on various gene promoters and different cell types (including neuronal cells) bazedoxifene mainly acted oestrogen-antagonistic. Oestrogen-like activity was observed on the TGF-β3 promoter, a gene thought to be important in bone maintenance. In immature or ovariectomized (OVX) animals (where endogenous oestrogen is lacking) bazedoxifene, like raloxifene, displayed a minor oestrogen-agonistic activity whereas it behaved antagonistic towards estradiol if present. Therefore it has to be regarded as a partial agonist.

Bazedoxifene's action on the proliferation of a human breast cancer cell line (MCF-7) in vitro was also investigated. In this study bazedoxifene inhibited oestrogen-induced MCF-7 proliferation virtually completely, markedly more than two other SERMs also tested in the study (one of them was the established SERM raloxifene). Gene expression profiling in MCF-7 cells after stimulation with oestrogen, bazedoxifene and other SERMs alone or in combination were also provided, but the results do not allow meaningful conclusions since too few is known about the relation between gene expression and clinically relevant physiological events. Off-target effects included antagonistic action on the glucocorticoid receptor at higher concentrations (IC50, 282 nM; for the oestrogen receptor IC50 was around 4 nM, i.e. factor 70). In response to the request by the CHMP, the Applicant made clear, that due to the low affinity of bazedoxifene to the glucocorticoid receptor as demonstrated in vitro and supported by in vivo data it is expected that the glucocorticoid receptor mediated effects are minimal and therefore of no clinical relevance to humans.
Furthermore, some binding activity at the so-called sigma receptor was detected in the Nova Screen. The significance of this finding is unknown, but it is not considered as a hint for an addictive potential of bazedoxifene. The sigma receptor was originally described pharmacologically as an opiate binding site, was then recognised to bind several further compounds, e.g. haloperidol, and was – after cloning

– identified as being unrelated to other opioid receptors. Newer publications on opiate addiction indicate a prominent role of the mu opiate receptor. Sigma receptors seem to have other functions although (as for many other receptors) some indirect function in craving or relapse was suggested, e.g. Martin-Fardon et al. 2007, Neuropsychopharmacology 32: 1967-1973. Thus, since the affinity of bazedoxifene to the sigma receptor is low and since no direct link between sigma receptors and addictive behaviour exists, there is no specific concern for an addictive potential of bazedoxifene.

In vivo studies

BONE

Currently, there are no completely satisfactory animal models of human osteoporosis, but many useful models do exist. In line with the recommendations made in the "Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis" (CPMP/EWP/552/95), evaluations of the effect of bazedoxifene on bone quality (bone mass, strength and architecture) were performed in OVX rats and in OVX monkeys. The study duration in the submitted pivotal non-clinical studies were more than 6 remodelling cycles as requested in CPMP/EWP/552/95.

Six week prevention studies in OVX rats
The effect of bazedoxifene and the reference compound raloxifene on bone were evaluated in the OVX rat model of bone loss. The oral dose were 1, 3 and 5mg/kg/day administered for 6 weeks.
Significant prevention of decreases in bone mineral density (BMD) of the proximal tibia and improvement of compressive strength at a lumbar vertebra due to bazedoxifene-administration was observed, whereas uterine stimulation was very limited. Of all non-clinical pharmacodynamic studies on bone, only in this short term rat study, raloxifene was used as a comparator. For the most part the comparator raloxifene was used in a dosage of 3 mg/kg bodyweight per os, a dose which had been established in the publicly accessible literature as an optimal dose rate for a comparable experimental setting.

12 month prevention study in OVX rats
In a 12-month prevention GLP study in OVX Sprague-Dawley rats, bazedoxifene was administered PO by gavage at dosages of 0.15, 0.3, or 1.5 mg/kg/day. DEXA (dual-energy x-ray absorptiometry)-scans revealed, due to bazedoxifene treatment, increases of BMD at lumbar vertebrae 1 to 4 and femur. Trabecular BMD of the femur and tibia (determined using peripheral quantitative computed tomography [pQCT]) and cortical BMD of the diaphyseal femur increased as well. Biomechanical investigations revealed an increase in resistance to stress at a lumbar vertebra. Histomorphometric evaluations of trabecular bone volume (trabecular thickness, trabecular separation, etc.) showed variability with regard to the effect of bazedoxifene on preventing the ovariectomy-induced effects, with showing protective effect in some sites, and no significant change under the various conditions for other sites and parameteres.
Transient increases in markers of bone turnover were reduced, and bazedoxifene showed a dose-related reduction in oestrogen-deficiency dependent increase in total serum cholesterol. Uterine weights were increased and pituitary weights decreased in bazedoxifene treated animals in comparison to vehicle controls.

Fracture repair in the rat
In a fracture repair study in OVX Sprague-Dawley rats of approximately 6 months of age, effects of bazedoxifene treatment on outcome of femoral osteotomy were investigated. Bazedoxifene was administered orally by gavage to rats at a dosage of 1 mg/kg/day for 140 days and osteotomy was performed 4 weeks after start of bazedoxifene treatment. No significant effect of bazedoxifene treatment was demonstrated in BMD scans, biomechanical tests or histopathological evaluations indicating that bazedoxifene had neither beneficial nor deleterious effects on bone-healing in OVX rats.

18 month prevention study in OVX aged Cynomolgus monkeys
In a 18 month prevention GLP study in OVX cynomolgus monkeys, beneficial effect on in-vivo determined trabecular bone mineral density (DEXA: lumbar vertebrae 1 – 4; pQCT: metaphyseal

tibia) and on cortical bone mineral density (pQCT: diaphyseal tibia, diaphyseal radius) is documented. Beneficial (reducing) effects of bazedoxifene (0.2, 0.5, 1, 5, or 25 mg/kg/day administered by oral gavage) on biochemical markers of bone turnover underline the positive effects of bazedoxifene on BMD. Static histomorphometrical parameters on trabecular bone were unchanged in the groups, whereas a variable effect was seen with regard to dynamic histomorphometrical parameters on trabecular bone (bone formation rate, mineralizing surface, etc.) in preventing the ovariectomy-induced changes. In cortical bone evaluated histomorphometrically at the tibia and femur, treatment with bazedoxifene partially prevented the ovariectomy-induced changes.
Uterine weights were not increased significantly due to bazedoxifene treatment. Unfortunately, no SERM (e.g. raloxifene) was administered as a comparator in this main non-clinical pharmacodynamics study. Therefore, a comparative assessment of the magnitude of bazedoxifene effects on the bone system on one hand side and on the female reproductive tract on the other hand side is precluded.
Three bazedoxifene-treated monkeys were diagnosed with renal carcinomas, whereas none of the animals of the control groups were. These carcinomas are considered to be of questionable relevance for humans mainly for the following reasons:

1. The incidence of renal carcinoma is roughly in line with few data found in the literature.
2. Even with highly genotoxic rodent carcinogens, renal carcinoma can hardly be induced in monkeys.
3. Due to the slow growth characteristics of renal carcinoma in humans, the carcinomas observed at study end in the monkeys have very likely been present prior to the start of the study.
4. The age of the monkeys (13.5 to 14.2 years out of a lifespan of 20 to 25 years) is comparable to the higher age in humans, the age at which renal cell carcinoma occurs most commonly in humans.

In order to confirm that the renal carcinomas observed in the monkey study are unrelated to treatment with bazedoxifene, the applicant performed several preclinical studies using tissue samples of the monkey study:

1. Histochemical staining did not show evidence of possible bazedoxifene-related renal injury such as basement membrane thickening or fibrosis.
2. (2) Preliminary results do not indicate bazedoxifene-induced DNA-adduct formation.
3. Preliminary results from immunohistochemical studies investigating proliferative markers Ki-67 and PCNA show no relevant increase in renal cell proliferation.

It is concluded that the renal cell tumours in monkeys should not be regarded as bazedoxifene-related. Nevertheless, the renal tumour findings in the rat and monkey are mentioned in SmPC section 5.3.

UTERUS
Studies aimed to investigate uteral effects of bazedoxifene showed that it has no significant effects on the uterus in immature rats and that it antagonises the 17-α Ethinyl oestradiol- and raloxifene-induced effects on the uterus. Thus, bazedoxifene seems to act as an antagonist at the uterus.

OVARIES
The effects of bazedoxifene (0.1-10 mg/kg/day) and raloxifene on ovarian cyst generation were investigated in cycling female rats, hypophysectomised rats, and lupron-treated rats
The treatment period was relatively short (<3 cycles) since this model has high morbidity.
The results of this study indicated that gonadotropins are necessary for the generation of the ovarian cysts and that bazedoxifene alone does not stimulate cysts' formation in rodents.

PLASMA/HDL Cholesterol
OVX female, 60 day-old SD rats were treated PO with doses ranging from 0.01 to 3.0 mg/kg/day bazedoxifene for 4 consecutive days. At high doses (1.0 to 3.0 mg/kg) bazedoxifene reduced total plasma cholesterol levels.

- Secondary pharmacodynamics

In order to investigate bazedoxifene's potential to cross-react with non-target receptors, a binding assay was performed on 43 targets with bazedoxifene at 3 concentrations (1 nM, 100 nM, and 10 µM) The target receptor types represented were neurotransmitter related, opioids, ion channels, uptake/transporter, second messengers, steroids (oestrogen and testosterone), brain/gut peptides,

prostaglandins, growth peptides, and hormones. No relevant off-target activity was detected in these studies.

- Safety pharmacology programme

Studies on CNS and respiratory safety did not reveal relevant effects on the parameters investigated. From the available preclinical in-vitro and in-vivo data bazedoxifene is highly unlikely to have a torsadogenic potential or to exhibit relevant effects on heart rate and blood pressure**.** The Applicant demonstrated that exposure to the metabolites was significantly higher in the cardiovascular safety studies conducted in monkeys as compared to humans (> 4.9 times). Therefore, bazedoxifene and its metabolites are not likely to affect the cardiac function at the therapeutic concentrations.

- Pharmacodynamic drug interactions

With the exception of *in-vitro* and *in-vivo* studies with combined use of oestrogen agonists and bazedoxifene, the Applicant has not performed pharmacodynamic interaction studies. As drugs, which are likely to be taken by patients concomitantly with bazedoxifene, and which might show pharmacodynamic interactions with bazedoxifene (i.e. calcium, vitamin D), were co-administered in clinical studies, no further preclinical pharmacodynamic interaction studies are considered necessary.

Pharmacokinetics

Analytical methods were developed and validated for the quantification of bazedoxifene in the plasma of mice, rats, rabbits, dogs, and monkeys.

Absorption

Bazedoxifene is extensively absorbed after oral administration; the steady-state volume of distribution (Vd_{ss}) values are large in rats (16.8 L/kg), dogs (7 L/kg), and monkeys (11 L/kg), and plasma clearance are high in rats (3.9 L/h/kg), monkeys (6.7 L/h/kg) and in dogs (5 L/h/kg), respectively. The mean bioavailability is low (7 – 16%), suggesting effective first – pass effect. The pharmacokinetic profile of bazedoxifene suggests enterohepatic recirculation in rats, dogs and monkeys.

Distribution

The distribution of ^{14}C -bazedoxifene has been studied after single and repeated-dose administration both in Sprague-Dawley rats and Long-Evans rats. The mean peak radioactivity was found at 8 hours with the highest values in pancreas, liver and lung. The uveal tract in Long-Evans rats contained also high concentrations of radioactivity.

After repeat-dose oral administration of ^{14}C-bazedoxifene in Sprague-Dawley rats for 8 days, radioactivity was well distributed to most tissues but did not readily cross the blood-brain barrier.

The radioactivity AUC_{0-168} values in plasma and several tissues after repeat-dose administration were higher than those after single-dose administration, indicating that radioactivity accumulated in plasma and tissues after repeat dosing. The highest repeat-dose to single-dose radioactivity AUC_{0-168} ratios were observed in the thyroid gland and bone, respectively. In Long–Evans rats ^{14}C-bazedoxifene-derived radioactivity accumulated in the uveal tract with repeat dosing, indicating that bazedoxifene binds with high affinity to melanin–containing tissues.

Bazedoxifene is highly (>95%) bound to plasma proteins of animals and humans, and does not readily cross the placenta of rats.

Metabolism

Bazedoxifene is rapidly and extensively metabolized with glucuronidation being the main metabolic pathway in mice, rats, monkeys and humans, respectively. Although two main metabolites were identified, the predominant metabolite was bazedoxifene-5-glucuronide in all species examined, which constitutes 40% to 95% of the radioactivity in plasma in humans at all time points.

The 4'-glucuronide of bazedoxifene was found in variable but significant amounts (0-20%) in humans but has only been detected in small amounts (<3%) in rats and monkeys. Initial concerns with regards to the cardiac safety of this metabolite were raised but no signal for cardiovascular concern has emerged from any of the clinical trials with bazedoxifene at doses up to 120mg (i.e. at dosage more than 6 times higher than the anticipated therapeutic dose). Also, the CHMP considered that bazedoxifene and its metabolites were not likely to affect the cardiac function at therapeutic

concentration. Toxicity of this metabolite has been evaluated during the carcinogenicity studies in mice, in which this metabolite constitutes 25 – 45 % of the radioactivity in plasma.

Excretion
The main route of excretion in mice, rats, monkeys, and post-menopausal women were via bile with the faeces. The majority of the radioactive dose (>80%) was excreted within the first 48 hours post-dosing.

Pharmacokinetic drug interaction
Pharmacokinetic drug-drug interactions due to alterations of protein binding between bazedoxifene and warfarin, digoxin, or diazepam are unlikely at therapeutic concentrations

Other pharmacokinetic studies

The investigation of the intestinal permeability of bazedoxifene showed that Bazedoxifene is a highly permeable compound. It belongs to the Class 2 compound (high permeability, low solubility) according to the Biopharmaceutical Classification system.

Toxicology

- Single dose toxicity

Single-dose studies were performed in Sprague-Dawley (S-D) rats, CD-1 mice and cynomolgus monkeys, following PO, IP and/or IV administration. They revealed low acute toxicity as expected for hormonal compounds.
In mice and rats, bazedoxifene was well-tolerated and did not cause mortality up to 4000 mg/kg following a single PO administration.

- Repeat dose toxicity (with toxicokinetics)

The main repeated-dose studies were performed in two species, rat (SD) and monkey (cynomolgus) for up to six and nine months, respectively. Reversibility of the observed changes was assessed in a 1-month rat study with 1 month recovery and in a 1-month monkey study with three months recovery. Bazedoxifene was administered via oral gavage.
Reduced body weight gain and food consumption was observed in the bazedoxifene-treated animals of virtually all studies.

The most prominent changes that were observed in all studies of sufficient duration were clearly related to the desired pharmacological effect of bazedoxifene.
They consisted of vaginal, cervical and uterine atrophy (due to a direct anti-oestrogenic effect on these organs) and increased ovary weight accompanied by ovarian cysts (most likely follicles that proliferated but did not ovulate, leading to partly haemorrhagic-ovarian cysts) in female rats and monkeys.
The latter reflected a clomiphene-like action of bazedoxifene on the pituitary, i.e. increase of basal FSH / LH secretion and absence of mid-cycle LH surge as demonstrated in a special hormone study in monkeys. In males, increased testis weight was observed accordingly.

In one rat study, hypertrophy of mammary gland (severity slight) and lobuloalveolar change in the mammary gland were observed in female rats at dosage of 3 mg/kg/day PO and above. This may correspond to a markedly elevated oestrogen level due to ovarian follicle hyperplasia.
The NOAEL for these findings corresponded to the therapeutic exposure in human following treatment with bazedoxifene.

There were, however, some additional endocrine findings in most repeated-dose (and also carcinogenesis) studies which do not clearly fit the pharmacodynamic profile of bazedoxifene but suggest suppression of the pituitary. Most prominent was a decreased pituitary weight (relative to body weight and brain weight) observed in most rat studies and in one monkey study. Accordingly, in the 2-year rat carcinogenesis study, the incidence of pituitary neoplasms was markedly reduced. Data obtained suggest that at least part of the avoided neoplasms were prolactinomas.

Relative organ weight reduction was observed not only for the pituitary but also for the adrenals (in rats) and – in one study –for the thyroid (rats). Vice versa, markedly increased thyroid and adrenal weight was observed after recovery in monkeys. This further argues for suppressive action of bazedoxifene on several hormone axes.

Another salient finding was pronounced nephrotoxicity (progressive chronic nephropathy with calcification and, later on, tumours) in rats.
In male rats, renal tubular corticomedullary mineralization occurred at all dosages. Furthermore, haematuria was observed clinically at all dosages in some treated male rats and generally correlated with the severity and incidence of mineralization. Additionally, increased incidence and severity of hyaline droplets occurred in the renal tubular epithelium of male rats given 100 mg/kg/day. At the end of the 1-month recovery period, mineralization was still present microscopically at 5 and 100 mg/kg/day PO but not 25 mg/kg/day PO.

Some small haematological changes were observed occasionally for which are considered secondary to the other changes, are not considered toxicologically meaningful and give no hints for a specific organ toxicity of bazedoxifene.

Toxicokinetic data were obtained in most repeated-dose toxicology studies.
Exposure margins are calculated based on exposures in healthy postmenopausal woman volunteers at steady state (after 14 days of once daily administration) for the maximum recommended dosage in humans (20 mg/day). The steady-state bazedoxifene C_{max} and AUC_{0-24} values for human at 20 mg/day were 6.2 ng/mL and 82 ng·h/mL.
In general, exposure was approximately proportional to dose at lower doses and less than dose-proportional at higher doses, which is a usual finding. Accumulation after repeated dosing was not observed in animals, in contrast to humans. No consistent gender differences became obvious.

- Genotoxicity

Genotoxicity of bazedoxifene was evaluated in vitro in an Ames test, a mouse lymphoma assay and a chromosomal aberration test with Chinese hamster CHO cells. Potential clastogenic or aneugenic effects in vivo were assessed using the micronucleus bone marrow test performed after oral administration in mice. All studies were negative indicating the bazedoxifene is devoid of genotoxic properties.

- Carcinogenicity

Two long-term carcinogenicity studies were performed, one in transgenic Tg.rasH2 mice for 6 months and one in the rat (Sprague-Dawley) for 2 years. Bazedoxifene was administered orally via diet.
In the transgenic mouse study, mice were given bazedoxifene 150 or 500 mg/kg/day. Urethane as a positive control and raloxifene as a comparator were also included. The neoplastic findings consisted of benign granulosa cell tumours which are considered secondary to the established effect of bazedoxifene on ovarian follicle growth.
Non-neoplastic observations for bazedoxifene and raloxifene included (apart from the expected uterine and vaginal and ovarian changes) lymphoid atrophy in the thymus and (in males only) extramedullar haematopoiesis in the spleen at all doses. Lymphoid atrophy was also observed in rats at high doses in the dose-ranging studies.
In the rat study the most salient findings consisted of benign granulosa cell tumours (like in the mouse study), a reduced incidence of mammary (females) and pituitary tumours and, mainly in males, a pronounced nephrotoxicity as already observed in the repeated-dose studies, this times with renal tumours.
It is suspected that the decreased mammary tumour incidence is secondary to the decreased pituitary tumour (most likely prolactinoma) incidence. The rat strain used displayed a rather high incidence of spontaneous pituitary tumours. It is plausible that these pituitary tumours are oestrogen-dependent and hence reduced in incidence by bazedoxifene.

Concerning nephrotoxicity, the Applicant claimed a gender- and species specific (male rats) mechanism. However, it should be noted that it was observed in females, too (albeit with a much lower incidence). In the Applicant's opinion the established mechanism for renal toxicity (binding of

the drug to a small protein formed sex-hormone-dependently in the liver and accumulated in the kidney) is not plausible in the case of bazedoxifene. Instead, the Applicant proposed that two initially independent rat-specific nephropathies were responsible for the findings in male rats, which, acting together, eventually cause exaggerated regeneration/proliferation of tubular epithelial cells and tumours. First, so-called progressive nephropathy (CPN) was involved, which also spontaneously occurred in control males but did not lead to tumours in controls. Second, corticomedullary nephrocalcinosis (CN) obviously formed in males, identified by typical histological changes. Usually CN is only found in females, and it is thought to be oestrogen-dependent according to published literature. However, it is plausible to assume that bazedoxifene, via an oestrogen-like action also caused this disease in males; it is known that oestrogen receptors (type alpha) are expressed in kidneys of male rats. It is also reasonable to assume that a combination of both nephropathies, CPN and CN, could induce tumours because both set proliferative stimuli and both target the same cell population (proximal tubular epithelial cells). Similar observations were made with raloxifene albeit to a quantitatively lesser extent at comparable exposures, but this is easily explained by the markedly lower potency of raloxifene as observed in preclinical PD studies. The Applicant compiled clinical data on raloxifene to demonstrate that this SERM could not be attributed to kidney damage to date. Furthermore, preclinical data show that the renal damage is a clearly staged process with early signs detectable in urine chemistry. This is also reassuring for clinical users of bazedoxifene. Nevertheless, renal damage in humans cannot be completely ruled out to date. Therefore the preclinical kidney findings are mentioned in the SPC to make the prescriber aware of a possible link between bazedoxifene and kidney disease and take a closer look if a patient receiving bazedoxifene develops kidney disease.

- Reproduction Toxicity

Reproductive and developmental toxicity were evaluated in rats and embryotoxicity studies in rats and rabbits. Toxicokinetic parameters were obtained within each study. No study on pre- and postnatal development was performed.

Fertility and early embryonic development
Male and female fertility was investigated in two separate studies.
Male fertility was studied in Sprague-Dawley rats. No effects were seen on reproductive performance of the males and sperm analysis was not conducted.
In females, adverse effects on reproductive parameters included cessation of oestrous cycles, reductions in ovulation, implantations and live foetus's, and increases in pre- and post-implantation embryonic mortality at all dosages. Accordingly, a NOAEL for reproductive parameters in females was not identified. These effects were consistent with the pharmacologic activity of these compounds. They were only marginally reversible after cessation of treatment for 4 weeks and only at the lowest dose tested.

Embryo-foetal development
Embryo-foetal development was studied in Sprague-Dawley rats and New-Zealand white rabbits.
In the embryotoxicity studies performed in rats, decreased embryo-foetal survival, decreased foetal body weights, delayed ossification and an increase in vascular variations were observed already at the lowest dose of 0.3 mg/kg/day.
In rabbits, administration of bazedoxifene resulted in foetal ventricular septum defects, anomalies in skeletal development and foetuses with hydropericardium starting at a dose of 0.05 mg/kg/day. Since signs of compromised health of the dams were observed in this rabbit study, a second study was performed. In the second study, bazedoxifene treatment resulted in abortions at doses of 0.5 mg/kg/day, but no foetal effects were seen. Effects on reproductive and developmental toxicity were in general already observed below human therapeutic exposure levels.

As bazedoxifene showed adverse effects on fertility and early embryonic development at low doses (0.03 mg/kg/day) in female rats, bazedoxifene is only for use in post-menopausal women.
Due to lack of prenatal and postnatal developmental studies, including maternal function, toxicity observed in embryo-foetus and lack of knowledge concerning excretion into milk, bazedoxifene is not intended for use in breast-feeding women.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
As the target population for the claimed indication is an adult population, i.e. postmenopausal women, no study in juvenile animals was performed.

- Toxicokinetic data

Toxicokinetic data were obtained during the repeat-dose and reproduction toxicity studies.

- Local tolerance

In toxicity studies, bazedoxifene was administered orally by gavage and is administered orally in patients. Therefore, local tolerance studies were not conducted. In single-dose toxicity studies in rats and monkeys where bazedoxifene was administered IV, no macroscopic lesions at the injection site were noted at necropsy. Because of a lack of macroscopic observations, injection sites were not examined microscopically.

- Other toxicity studies

Antigenicity
Bazedoxifene was not antigenic in the active systemic anaphylaxis assay in guinea pigs or in the passive cutaneous anaphylaxis assay in mice, rats and guinea pigs.

Immunotoxicity
Immunotoxicity studies were not performed. This is acceptable in respect to immunosuppression since general toxicology and secondary PD data yielded no special concern in this regard. The clinical data did not indicate any significant immunotoxic effects of bazedoxifene-treatment as compared to placebo and raloxifene.

Phototoxicity
Also, phototoxicity studies were not performed. According to the pharmaceutical documentation there is a small light absorption peak of bazedoxifene at 298 nm (larger peaks are at 226 nm and below 200 nm). The European Note for Guidance on Photosafety Testing (CPMP/SWP/398/01) would require such testing if a compound will absorb light with a wavelength of 290 nm upwards and will be distributed to the skin (which is the case for bazedoxifene). However, based on the combination of low exposure and absence of toxicity to the skin and eyes, literature indicating that binding to melanin containing tissues does not lead to ocular toxicity, and bazedoxifene being absorbed at a peak wavelength outside the visible range, phototoxicity testing was not conducted as it would not provide additional data that would alter the safety assessment of the compound.

Ecotoxicity/environmental risk assessment
The Applicant provided a detailed environmental risk assessment on bazedoxifene including a PBT assessment, an assessment for the aquatic and terrestrial compartment as well as the sediment. No final conclusion could be reached on the persistent and bioaccumulative character of the active substance. The applicant has committed to cover this issue as a follow-up measure.

2.4 Clinical aspects

Introduction

As monotherapy bazedoxifene has been studied since 1998 in humans. The submission is based on 20 phase 1 studies (18 monotherapy, 2 bazedoxifene / CE), 3 phase 2 studies, and 2 phase 3 studies.
The efficacy and safety conclusions are based on a 2-year, multicentre, double-blind, randomized, placebo- and raloxifene-controlled, phase 3 study (300-GL) conducted in postmenopausal women for the prevention of osteoporosis and on a 3-year, multicentre, double-blind, randomized, placebo- and raloxifene-controlled, phase 3 study (301-WW) conducted in older, osteoporotic postmenopausal women for the treatment of osteoporosis. For the evaluation of safety parameters the databases of these studies were pooled for the 20 mg and 40 mg doses. The Applicant included an active control

arm in both phase 3 studies that would allow linking to existing data for raloxifene 60 mg, another SERM, approved and marketed in the EU for prevention and treatment of osteoporosis.

The CHMP Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis was revised in 2007 (CPMP/EWP/552/95 Rev. 2, effective since 31 May 2007). The regulatory guidance in place at the time the development of bazedoxifene was initiated and subsequently executed was Rev. 1 of this guideline, effective since July 2001. Revision 1 was the basis for national and centralised scientific advice received in 2001 for the development of bazedoxifene.
However revision 2 no longer recognises prevention of osteoporosis as a separate indication per se and recommends including women at increased risk for fractures (10-year probability of 15% to 20% for vertebral fractures and 10% to 15% for major non-vertebral fractures) in clinical trials in support of the treatment of osteoporosis indication. As outlined in the revised guideline an indication for prevention of osteoporosis or postmenopausal bone loss will not be specifically granted to new products. However, the prevention indication did not disappear but merged into the treatment indication, since the goal of therapy is not prevent osteoporosis per se but to prevent fractures. During the procedure, the applicant addressed this issue by rewording the indication to be in line with the current version of the guideline.

GCP

According to the applicant all studies have been performed according to GCP standards effective at time of conduct of the studies. The CHMP had requested a GCP inspection of the clinical study 3068A1-301-WW. The inspection included investigator sites, as well as the sponsor and central lab. The investigator sites recruited nearly 18% of the subjects randomly assigned to the 4 study groups, respectively. The scope of this inspection was to verify compliance with GCP and applicable regulations, in particular where it has an impact on the validity of the data or the ethical conduct of the study. The inspection revealed major, as well as critical deviations, the main problems relating to the larger site. Among them, the monitoring was considered as inadequate, since many AEs at the bigger site had not been discovered until subjects had finished the core trial. Deviations identified also related to the assessment and processing of DXA and X-ray.
No signs of fraud at the sites have been detected and source data (hospital files, informed consents, diaries etc.) were generally available. For one large study site the data were deemed acceptable based on the re-monitoring conducted at that site. Concerns existed, that the lack of focus in monitoring could have led also to under-reporting of AEs at sites, and whether therefore the safety of the use of bazedoxifene could sufficiently be established based on the data from study 301-WW. However, the trial was both placebo and active comparator-controlled and it can be assumed that the critical findings identified are independent from treatment since fraud has been excluded and there are no concerns about early unblinding.
Therefore, based on the fact that overall efficacy and safety of bazedoxifene 20 mg appears to be comparable to that of raloxifene, and the actions taken by the applicant, it was considered by the CHMP that the findings did not jeopardize the use of data from study 301-WW for the evaluation of efficacy and safety of bazedoxifene in the treatment of osteoporosis in postmenopausal women.

To further reassure the validity of the provided data and the robustness of the findings the applicant has provided evaluations of the fracture data, as well as SAE with and without inclusion of data from the large study site. These evaluations do not indicate changes in the efficacy in fracture reduction or in the AE profile when data from this site are excluded from the analysis. Results were consistent with overall analyses of the entire population and it was therefore considered by the CHMP that the findings do not impact the reliability or interpretation of the data. In addition the results of the adjudication/re-adjudication process of potential cerebrovascular event cases have been provided. The results are overall consistent with the non-adjudicated cerebrovascular safety analysis as reported by study investigators and in agreement with the safety assessment based on the initial adjudication of cerebrovascular events.

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.

Pharmacokinetics

Pharmacokinetics of bazedoxifene were solely examined in postmenopausal women. The mean pharmacokinetic parameters of bazedoxifene after multiple doses in healthy postmenopausal ambulatory women who were naturally postmenopausal or who had undergone bilateral oophorectomy are summarized in Table 1

Table 1. Mean ± SD pharmacokinetic parameters of bazedoxifene (n=23)

	C_{max} (ng/ml)	t_{max} (h)	$t_{½}$ (h)	AUC (ng•h/ml)	Cl/F (l/h/kg)
Multiple dose 20 mg/day	6.2 ± 2.2	1.7 ± 1.8	28 ± 11	82 ± 37	4.1 ± 1.7

- Absorption

Bazedoxifene is rapidly absorbed with a time to peak plasma concentration of approximately 2 hours (1 to 4 hours) after oral dosing and has a mean oral absolute oral bioavailability of 6%. Bazedoxifene appears to undergo enterohepatic recirculation as shown by a second peak following oral administration occasionally with a higher concentration than seen in the initial peak, resulting in some individual t_{max} values of up to 8 hours. Steady-state concentrations are achieved at the second week of daily dose administration with an approximate 2-fold accumulation, however, data are only given for day 1, day 7 and day 14, and, thus, it is not possible to determine when a plateau is reached. Pooled from phase I studies normalised to a 20 mg dose mean maximum plasma concentration (C_{max}) was 3.9 ± 1.7 ng/ml after a single dose and 5.8 ± 2.3 ng/ml at steady-state, respectively. The overall data is shown in table 1.

Bazedoxifene revealed a more or less pronounced food effect. Across food effect studies, increase in bazedoxifene exposure ranged from 20 to 70% when bazedoxifene was administered with both a medium-fat and a high-fat meal. When single doses of 20 mg bazedoxifene were administered with a high-fat meal, C_{max} and AUC increased by 28% and 22%, respectively. An additional study evaluating the effects of a standardized medium-fat meal on the pharmacokinetics of bazedoxifene at steady-state showed a 42% and 35% increase in C_{max} and AUC, respectively, when 20 mg bazedoxifene was administered with food. These changes were not considered clinically relevant by the CHMP, neither compromising safety nor efficacy, and therefore bazedoxifene can be administered independently from meals.

- Distribution

Following intravenous administration of a 3 mg dose of bazedoxifene the mean volume of distribution is approximately 15 L/kg (14.7 ± 3.9 L/kg). Bazedoxifene is highly bound (95.8% - 99.3%) to plasma proteins *in vitro*. Binding to the proteins in plasma from postmenopausal women was similar to the protein binding in plasma from women of childbearing age.

- Metabolism

Bazedoxifene is extensively metabolised. Glucuronidation is the major metabolic pathway. The major radioactive component in plasma was the bazedoxifene-5-glucuronide constituting 40% to 95% of the radioactivity in plasma at all time points. Unchanged bazedoxifene and the bazedoxifene-4'-glucuronide were observed in small amounts (about 0% to 20%). The major route of excretion of radiolabelled bazedoxifene was the faeces, where 85% of the dose was recovered after 10 days. Excretion in urine represented a minor route of elimination of radioactivity. Less then 1% of the dose was eliminated in urine.

- Elimination

Bazedoxifene is eliminated with a mean half-life ($t_{½}$) of approximately 30 hours. Following intravenous administration, plasma clearance is 0.4 ± 0.1 L/h/kg. Mean apparent oral dose clearance (Cl/F) pooled from phase I studies normalised to a 20 mg dose was 6.2 ± 3.2 L/h/kg after a single dose and 5.2 ± 2.5 L/h/kg at steady-state, respectively.

- Dose proportionality and time dependencies

Dose proportionality for single doses has been established over the dose range of 5 to 120 mg. Accumulation of bazedoxifene after repeated doses is deemed time-invariant.

- Special populations

Since bazedoxifene is primarily metabolised by glucuronidation with less than 1% excreted unchanged or as a metabolite in the urine, a decline in renal function was not expected to affect the pharmacokinetics of bazedoxifene. In moderate renal impairment, negligible amounts of bazedoxifene were eliminated in urine, and the impaired renal function showed little or no influence on bazedoxifene pharmacokinetics, thus not requiring a dosing adjustment. However, information on patients with severe renal impairment is too limited for definite conclusions, and this is reflected in the SPC.

The disposition of a single 20 mg dose of bazedoxifene was compared in patients with hepatic impairment [Child-Pugh Class A (n=6), B (n=6), and C (n=6)] and subjects with normal hepatic function (n=18). On average, patients with hepatic impairment showed a 4.3-fold increase in AUC compared with controls. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency. Therefore, as stated in the SPC, the use of bazedoxifene in subjects with hepatic impairment is not recommended.

Compared to women 51 to 64 years of age, women 65 to 74 years of age showed a 1.5-fold and women >75 years of age showed a 2.3-fold increase in bazedoxifene exposure. It was concluded, that this age dependence most likely reflects the observation, that bazedoxifene metabolism is reduced in subjects with impaired hepatic function and that hepatic function decreases with age.

Race and body weight had no apparent meaningful influence on bazedoxifene exposure.

The pharmacokinetics of bazedoxifene have not been studied in the paediatric population.

- Pharmacokinetic interaction studies

Potential interactions between bazedoxifene and an aluminium hydroxide and magnesium hydroxide containing antacid (Maalox®)), ibuprofen, azithromycin, atorvastatin, and conjugated oestrogens (CE) were investigated in healthy postmenopausal women.

Pharmacokinetics of bazedoxifene were not affected by an aluminium hydroxide and magnesium hydroxide containing antacid (Maalox®) in relevant extent. Ibuprofen had a slight effect on both bazedoxifene C_{max} and AUC. Azithromycin slightly affected bazedoxifene AUC and CL/F. Atorvastatin had no meaningful effect on bazedoxifene pharmacokinetics when both drug were administered concomitantly. Otherwise, bazedoxifene slightly affected the pharmacokinetics of atorvastatin and possibly the efficacy of atorvastatin.

Bazedoxifene C_{max} and AUC were increased when bazedoxifene and CE were administered together in a combination tablet compared to bazedoxifene alone tablet. These changes were considered possibly due to a metabolic interaction between bazedoxifene and CE or due to formulations differences between the combination and monotherapy tablets.

Bazedoxifene does not inhibit CYP enzymes in human liver microsomes. Therefore, it is concluded that the drug has a rather low probability to interact with co-administered drugs that are metabolized by CYP enzymes. Additionally, it has been shown that the potential for a drug-drug interaction between bazedoxifene and co-administered warfarin, diazepam, or digoxin, due to alterations of protein binding with bazedoxifene, is low.

Pharmacodynamics

- Mechanism of action

Bazedoxifene is a third-generation selective oestrogen receptor modulator (SERM) which is thought to exhibit tissue-selective agonist activity on the skeleton and lipid metabolism while acting as an antagonist on breast and uterine tissue.

- Primary and Secondary pharmacology

Bone mineral density was not investigated in the phase 2 trials; bone turnover markers have been investigated in all phase II studies.

In an ascending multiple dose study (30 consecutive daily doses) the pharmacokinetics of bazedoxifene was examined, and it was also attempted to establish some information on the pharmacodynamics of the compound by examining lipids (LDL cholesterol, HDL cholesterol, and triglycerides), coagulation parameters, and various bone markers. Regarding the urinary bone marker N-telopeptide, there was a distinctive concentration-effect relationship in which the maximum effect is approximately a 20% reduction from baseline and the concentration required to produce a 50% maximum effect is approximately 500 pg/mL. Based on these data, it appeared that a dose between 5 and 10 mg of bazedoxifene (achieving approximately 1 ng/mL bazedoxifene) has a pharmacologic effect after 30 days of administration to postmenopausal women.

Bazedoxifene revealed no effect on lipoprotein(a) and coagulation parameters, with the exception of fibrinogen levels, which appeared to decrease. Bazedoxifene has no obvious effect on the incidence of hot flushes, on endometrial thickening and on the incidence of ovarian cyst.

Bazedoxifene showed no clinically relevant effects on cardiac repolarisation after a therapeutic dose of 20 mg as well as after a high dose of 120 mg.

Clinical efficacy

Clinical efficacy are based on 3 phase 2 studies (200-BR, 204-US/CA, and 205-CN), a large, multicenter, double-blind, randomized, placebo- and raloxifene-controlled, phase 3 study (300-GL), and the results of a pre-specified analysis of 36-month data from a large, on-going, multicenter, randomized, double-blind, placebo- and raloxifene-controlled, 5-year phase 3 study (301-WW).

Completed Clinical Studies of Efficacy With Bazedoxifene

Study Title	Objectives	Subjects Enrolled	Subjects Enrolled/Completed
200-BR A double-blind, randomized, controlled study of the effects of TSE-424 on biochemical markers of bone metabolism in healthy postmenopausal women	Primary: To evaluate the effects of bazedoxifene on urinary N-telopeptide (NTx) in postmenopausal women. Secondary: To evaluate the effects of bazedoxifene on other urinary and serum biochemical bone markers, lipids, coagulation factors, vaginal maturation index, the incidences of vasomotor symptoms, mastalgia, and vaginal bleeding and to evaluate the safety and tolerability of bazedoxifene given once daily for 168 consecutive days.	595	Part 1: BZA 2.5 mg 60/59 BZA 5 mg 60/55 BZA 10 mg 58/56 BZA 20 mg 60/51 Premarin 0.625 mg/ MPA 2.5 mg 59/57 Placebo 59/58 Part 2: BZA 20 mg 60/55 BZA 30 mg 60/55 BZA 40 mg 60/58 Placebo 59/55
204-US/CA A multicenter, double-blind, randomized, active-and-placebo-controlled pilot trial of the vasomotor effect of TSE-424 in non-flushing postmenopausal women	Primary: To evaluate and compare the effect of bazedoxifene with placebo on the incidence of subjects experiencing hot flushes in a non-flushing postmenopausal population. Secondary: To evaluate the effects of bazedoxifene on the mean number and severity of hot flushes, the serum lipids, and the biochemical indices of bone metabolism, and to evaluate and compare the effect of 60 mg of raloxifene and placebo on the incidence of subjects experiencing hot flushes.	487	BZA 5 mg 96/89 BZA 10 mg 101/90 BZA 20 mg 98/89 RLX 60 mg 98/89 Placebo 94/86

Study Title	Objectives	Subjects Enrolled	Enrolled/Completed	
205-CN A double-blind, randomized, placebo-controlled study of the effects of bazedoxifene acetate on biochemical markers of bone metabolism in healthy postmenopausal women	Primary: To evaluate the effects of bazedoxifene on biochemical markers of bone metabolism in postmenopausal women. Secondary: To evaluate the safety and tolerability of bazedoxifene given once daily for 3 months.	227	BZA 20 mg BZA 40 mg Placebo	59/57 63/62 105/96
300-GL A double-blind, randomized, controlled study of the effects of TSE-424 on biochemical markers of bone metabolism in healthy postmenopausal women	Primary: To evaluate the safety and efficacy of bazedoxifene in comparison with those of placebo and raloxifene in preventing osteoporosis in postmenopausal women. Secondary: To evaluate the effect of bazedoxifene in comparison with that of placebo and raloxifene on endometrium, metabolic parameters, vasomotor symptoms, adverse events, and quality of life. Samples were collected for population pharmacokinetic analysis.	1583	BZA 10 mg BZA 20 mg BZA 40 mg RLX 60 mg Placebo	321/218 322/224 319/222 311/224 310/225
301-WW A multicenter, double-blind, randomized, placebo-controlled, calcium and vitamin D supplemented, phase 3 study for reduction of fracture risk in postmenopausal women with osteoporosis	Primary: To evaluate the safety and efficacy of bazedoxifene compared with placebo in the reduction of risk for radiographically confirmed new vertebral fractures in postmenopausal osteoporotic women after 36 and 60 months of therapy. Secondary: To evaluate the effect of bazedoxifene compared with raloxifene 60 mg and placebo on breast cancer incidence, clinical vertebral fractures, worsening vertebral fractures, non-vertebral fractures, height changes, bone mineral density (BMD) of the lumbar spine and hip, serum bone markers, lipid parameters, QoL, and effects on endometrium and bone histomorphometry after 36 months of therapy. In addition, the efficacy of raloxifene 60 mg to placebo in reducing the incidence of new vertebral and other (non-vertebral) fractures after 36 months of treatment was to be compared. A 2-year double-blind study extension will provide additional safety and efficacy data.	7492	BZA 20 mg BZA 40 mg RLX 60 mg Placebo	1886/1254[b] 1872/1229[b] 1849/1252[b] 1885/1256[b]

BZA = bazedoxifene; CE = conjugated oestrogens; MPA = medroxyprogesterone acetate; RLX = raloxifene; QoL = quality of life.

a. Subjects who took at least 1 dose of study drug.

b. Completed the 3-year core study.

The two pivotal efficacy studies were also intended to determine the final therapeutic dose.

- Dose response studies

The dose finding studies comprised 3 phase 2 studies.

Study 200-BR (CSR-36893)
The primary objective was to evaluate the effects of 6 doses of bazedoxifene (2.5, 5, 10, 20, 30, and 40 mg) on the surrogate marker urinary N-telopeptide (NTx) in postmenopausal women. Part 1 (200-BR) examined 2.5, 5, 10, and 20 mg bazedoxifene, placebo, and conjugated oestrogens (CE) / MPA. Per protocol amendment, it was decided to also study higher doses of bazedoxifene; therefore part 2 (200-BR-Ext) examined 20, 30, and 40 mg bazedoxifene, and placebo.
Healthy postmenopausal women were eligible. Premarin 0.625 mg / MPA 2.5 mg was included as an active control group. The primary efficacy parameter was urinary NTx after 88 days of treatment in the ITT population.

In part 1 of the study, after 84 days of treatment, no significant differences in urinary NTx levels were found for any of the primary comparisons between the bazedoxifene and placebo groups, however, a significantly ($p < 0.001$) greater decrease in urinary NTx levels was seen with CE 0.625 mg / MPA 2.5 mg than with placebo and all bazedoxifene doses. By 6 months of treatment, bazedoxifene induced a greater decrease from baseline than placebo in urinary NTx that approached statistical significance at 10 mg (median decrease -25.0%; $p = 0.057$ vs -14.4% for placebo) and that was statistically significant for 20 mg bazedoxifene (-33.2%; $p < 0.001$). Overall, CTx displayed the same dose response as NTx. In part 2 of the study bazedoxifene 40 mg demonstrated the greatest inhibition of resorption; median decreases in urinary NTx at month 3 were -35.0% compared with -25.9% in the placebo group ($p = 0.028$); decreases at month 6 were -37.9% compared with -29.7% in the placebo group ($p = 0.012$). These results were supported by a more rapid effect on bone resorption as indicated by serum CTx (median decrease 3 months -33.1%; $p < 0.001$), and by significant ($p < 0.05$) decreases of at least 41% in urinary CTx.

In both parts a dose response was observed, with higher reductions in markers of bone turnover seen in the highest bazedoxifene dose groups. The data indicate that dosages below 10 mg of bazedoxifene may not provide sufficient inhibition of bone resorption.

Regarding the secondary endpoints, an influence on reduction in TC and LDL-C was only seen in part 2 with the 40 mg dose. No significant change from baseline in TG was seen.
There was no consistent effect of bazedoxifene on the Vaginal Maturation Index (VMI) at 2.5 mg through 20 mg bazedoxifene, while there was a reduction in the VMI at month 6 for the bazedoxifene 30 and 40 mg treatment groups.
Bazedoxifene 2.5 to 20 mg did not increase the incidence of flushing compared to placebo; however among subjects experiencing hot flushes, the number per week was significantly greater than placebo, The severity was significantly ($p < 0.05$) greater than placebo only for the 20 mg bazedoxifene dose at month 3 and 6. There were no significant differences from placebo for incidence, the number per week, or the severity of hot flushes at doses of 20 or 30 mg from 3 through 6 months. In subjects treated for 3 months with 40 mg of bazedoxifene, the number of hot flushes per week and the severity of hot flushes were significantly ($p < 0.05$) greater than in subjects who received placebo; a significant difference was not observed at month 6.

Study 204-US/CA (CSR-35056)
The primary objective was to evaluate the effect of 5 mg, 10 mg, and 20 mg of bazedoxifene compared to placebo and raloxifene 60 mg on the incidence of subjects experiencing hot flushes in non-flushing postmenopausal women during 12 weeks of treatment.
The primary efficacy parameter was the incidence of subjects in the ITT population experiencing hot flushes as assessed by daily flush diary. Secondary parameters were additional parameters with regard to hot flushes, serum lipids, biochemical indices of bone metabolism, and QoL, the outcome of which did not deliver definitive conclusions.
There were no significant differences in the incidence of hot flushes between any of the treatment groups in the ITT and PP populations. No significant differences were observed between groups in total severity of hot flushes over each 4-week period in the ITT population; in the PP population, however, the bazedoxifene 20 mg treatment group showed a significant ($p = 0.030$) increase in total severity at weeks 9 to 12 compared to placebo.

Study 205-CN (CSR-45948)
The primary objective was to evaluate the effects of 2 doses of bazedoxifene, 20 mg and 40 mg, on biochemical markers of bone metabolism in postmenopausal women.

After 3 months of treatment, both bazedoxifene 20 mg and 40 mg demonstrated a statistically significant decrease in urinary CTx normalized by urinary creatinine compared to placebo.
Results of analysis of secondary efficacy variables of bone metabolism were similar; serum osteocalcin, serum CTx and urinary NTx were reduced statistically significant compared to placebo. No statistically significant changes were seen in serum bone-specific alkaline phosphatase values at 3 months in any of the treatment groups.

- Main studies

Based on the results of these studies, 2 dosages, 20 mg and 40 mg, of bazedoxifene were selected to be studied in the phase 3 clinical program. Since the dosages to prevent bone loss may be lower as compared with dosages needed to reduce the risk of fracture in established osteoporosis, the 10 mg dosage was added to the phase 3 prevention study 300-GL.
Based on national and centralised scientific advice the main clinical studies had been designed to be in line with the CHMP Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95 Rev. 1), which was effective from July 2001 until 31 May 2007. Both phase 3 studies were outpatient, multicentre, double-blind, randomised, placebo- and raloxifene-controlled trials.
The phase 3 study 300-GL, as well as the phase 2 studies, enrolled healthy, relatively young (mean age 52 to 58 years) postmenopausal women, at risk of rapid bone loss (> 1 to < 5 years postmenopausal) or osteopenic, with at least 1 risk factor for osteoporosis.
The phase 3 study 301-WW enrolled postmenopausal women (mean age 66 years) with osteoporosis, defined as either the presence of at least 1 prevalent vertebral fracture or a BMD value in the osteoporotic range. Similarly, the mean number of years since the last menstrual period was greater in study 301-WW (19.5 years) than in the other studies (5 to 11 years).

Study 300-GL

METHODS

Study 300-GL was a 5-arm, outpatient, multicentre, double-blind, randomised, placebo- and raloxifene controlled study in postmenopausal women. It examined the effect of bazedoxifene 10 mg, 20 mg, and 40 mg as well as raloxifene 60 mg and placebo on BMD over a period of up to 24 months. It was designed as an "osteoporosis prevention" trial, with inclusion criteria and primary endpoint considered to be in line with Revision 1 of the Guideline on Osteoporosis.

Study Participants
Included were healthy women > 45 years of age and either ≥ 1 year postmenopausal or ≥ 1 year since surgical menopause (bilateral oophorectomy), with women ≤ 5 years since the event fulfilling additional biochemical criteria.
In addition, patients had to qualify for 1 of the following osteoporosis risk-related categories:

- > 1 year and < 5 years postmenopausal with at least 1 of the following risk factors:
  - BMD T-score at lumbar spine or at femoral neck ≥ -1 and ≤ -2.5
  - Family history of fracture
  - Bilateral oophorectomy
  - Current history of smoking
  - Small-boned or thin frame (weight < 58 kg)
  - Inadequate intake of calcium
  - Little or no weight-bearing exercise
- > 5 years postmenopausal with BMD T-score at lumbar spine or at femoral neck between ≥ -1 and ≤ -2.5 with at least 1 of the following risk factors:
  - · Family history of fracture
  - · Bilateral oophorectomy

- · Menopause occurring at or before the age of 40 years
- · Current history of smoking
- · Small-boned and/or thin frame (weight < 58 kg)
- · Inadequate intake of calcium
- · Little or no weight-bearing exercise.

Treatments
Patients received bazedoxifene 10 mg, 20 mg, and 40 mg as well as raloxifene 60 mg and placebo over a period of up to 24 months. Patients received additional 600 mg of elemental calcium as calcium carbonate as a supplement.

Objectives
The primary objective of this study was to evaluate the safety and efficacy of 3 doses of bazedoxifene compared to placebo and to raloxifene in preventing osteoporosis (i.e. maintaining BMD) in postmenopausal women. Among secondary objectives were the effects of bazedoxifene in comparison with that of placebo and raloxifene on endometrium, metabolic parameters, vasomotor symptoms, AE.

Outcomes/endpoints
The primary endpoint was percentage change from baseline in BMD of the lumbar spine (L1 to L4) at the month 24 assessment. All BMD measurements were evaluated centrally and after screening all BMD data remained blinded throughout the study.
Secondary efficacy variables were: all other BMD evaluations including total hip, femoral neck, and femoral trochanter, as well as serum bone markers (CTx and osteocalcin); a lipid panel and the results of the WHQ.

Sample size
Sample size and study designs were considered adequate, specifically with regard to the chosen inclusion criteria and primary endpoint according to Revision 1 of the Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95).

Randomisation, Blinding, Statistical methods
These were considered to be adequate.

RESULTS

Participant flow

4767 patients were screened, 1735 patients were randomly assigned to the 5 study groups, and of these, a total of 1583 subjects were included in the efficacy and safety analyses

Recruitment
4767 patients were screened and of these 3032 did not meet the inclusion and exclusion criteria leaving 1735 patients to be randomly assigned to the 5 study groups

Conduct of the study
The study was conducted in Canada, Europe, and the United States. An amendment of the protocol resulted in slight changes of some of the inclusion criteria.
The study was terminated at 3 sites, which had randomly assigned 104 patients to treatment, for issues related to GCP and the data from these sites were not included in either the final study efficacy or safety analyses. It is not expected that the small number and nature of the protocol violations in this study might affect the integrity of the study.

Baseline data
The baseline data did not reveal any relevant differences between groups and multiplicity has adequately been controlled for. Approximately 93% of the subjects were white. Approximately 88% of the subjects had natural menopause and approximately 12% were surgically menopausal. Approximately one third of the study subjects had had a hysterectomy. The mean age for each

treatment group was approximately 57 years. The mean weight in each treatment group ranged from 67.0 to 68.7 kg, with a mean BMI of approximately 25 kg/m^2. The mean number of years since the last menstrual period was 10.9 years. The mean baseline T-scores at the lumbar spine ranged from -1.12 to -1.24; the corresponding mean baseline T-scores at the total hip ranged from -0.70 to -0.83

Numbers analysed

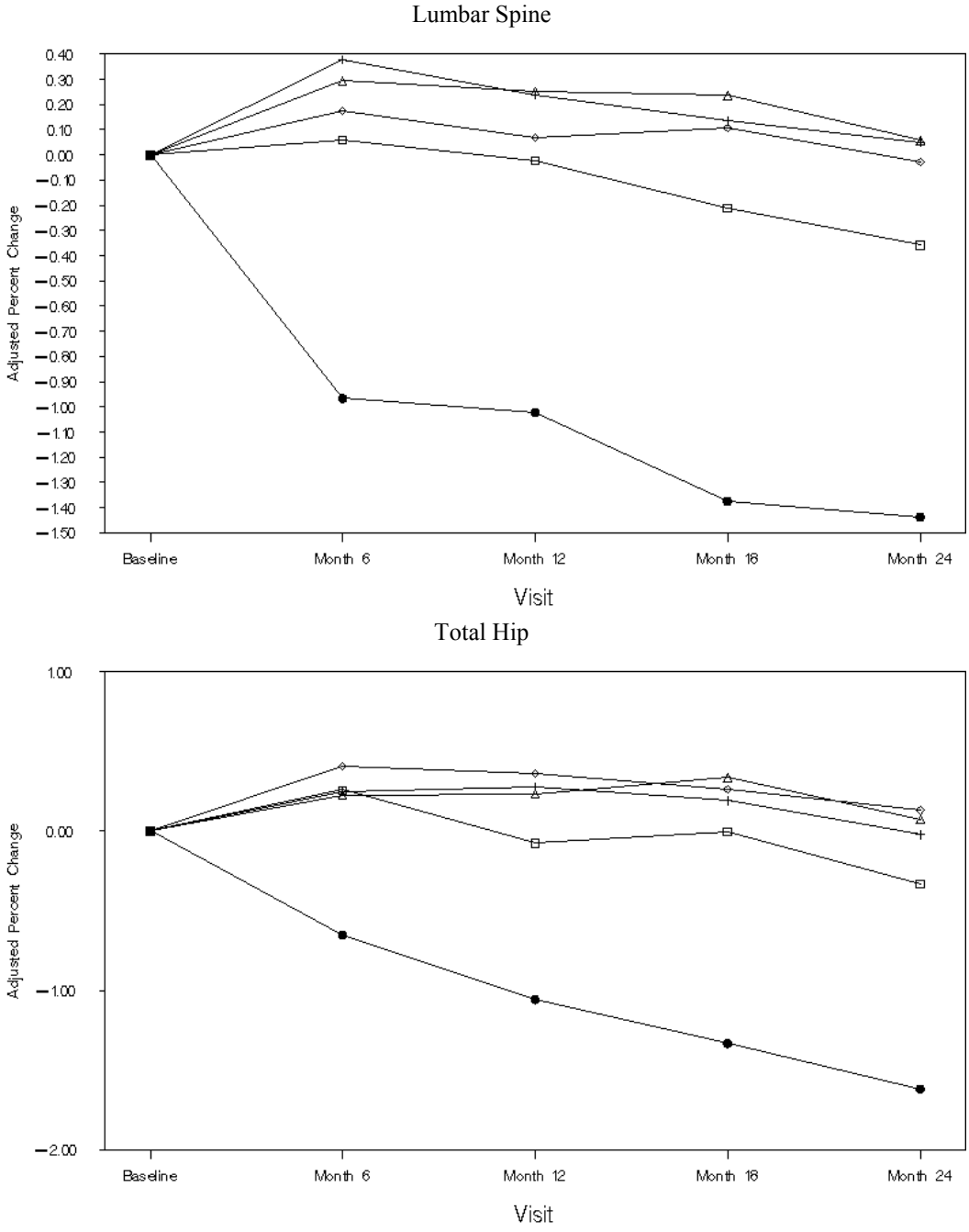
The discontinuation was slightly lower in the raloxifene arm (28.0%) compared to bazedoxifene arms (30.4-32.1%). Discontinuation due to AE demonstrated a positive trend over the bazedoxifene doses and was higher than in the raloxifene arm for all doses. However, discontinuation due to AE was also lower in the raloxifene arm compared to placebo.

A total of 1583 subjects were included in the efficacy and safety analyses. Of these, there were 1434 subjects in the ITT population, 1402 in the PP1 population, 1055 in the PP2 population, and 1226 in the MITT population for the primary endpoint. For the secondary assessments, these figures were 1430, 1398, 1047, and 1218 patients respectively

Outcomes and estimation

Bazedoxifene 20 mg and 40 mg prevented bone loss at both the lumbar spine and total hip while a significant ($p < 0.05$) bone loss was observed for the placebo group. Similar results were observed at the femoral neck and femoral trochanter. The effects were evident from 6 months onwards. At month 24, the BMD of the lumbar spine and total hip was statistically significant ($p < 0.001$) greater with all bazedoxifene treatment groups than with the placebo group. Significant treatment effects were evident with all bazedoxifene treatment groups within the first 6 months of therapy and were preserved through the study. The mean differences (± SE) between the placebo group and bazedoxifene treatment groups in the change in BMD from baseline to month 24 for the lumbar spine were 1.08% (± 0.28%), 1.41% (± 0.28%), and 1.49% (± 0.28%) for bazedoxifene 10 mg, 20 mg, and 40 mg, respectively, and 1.29% (± 0.21%), 1.75% (± 0.21%), and 1.60% (± 0.21%), respectively, for the total hip. All bazedoxifene dose groups met the prespecified criteria for non inferiority to the raloxifene 60 mg group for lumbar spine and total hip.

Figure 1: Percentage Change From Baseline in BMD of Lumbar Spine and Total Hip (ITT)



□ = Bazedoxifene 10 mg; ◊ = Bazedoxifene 20 mg; + = Bazedoxifene 40 mg; Δ = Raloxifene 60 mg; ● = Placebo.

This is supported by the responder analysis provided, clearly showing a lower percentage of responders on bazedoxifene 10 mg compared to bazedoxifene 20 mg and 40 mg and raloxifene 60 mg. The percentage of responders was comparable between the latter groups. Reductions in levels of bone markers were consistently greater in the bazedoxifene 10 mg, 20 mg, and 40 mg treatment groups than in the placebo group and sustained through month 24.

Table 2: Responder Analysis: Percentage Change from Baseline in BMD of Lumbar Spine at Month 24 (ITT)

Treatment	n	Responder n (%)	---------- p-Value[a] vs ---------- Placebo	Raloxifene
Bazedoxifene 10 mg	292	133 (44.5)	0.050	0.24
Bazedoxifene 20 mg	288	151 (52.4)	< 0.001	0.79
Bazedoxifene 40 mg	290	154 (53.1)	< 0.001	0.63
Raloxifene 60 mg	280	142 (50.7)	…	…
Placebo	284	109 (38.4)	…	…

a. Cochran-Haenszel-Mantel stratified by years since menopause.

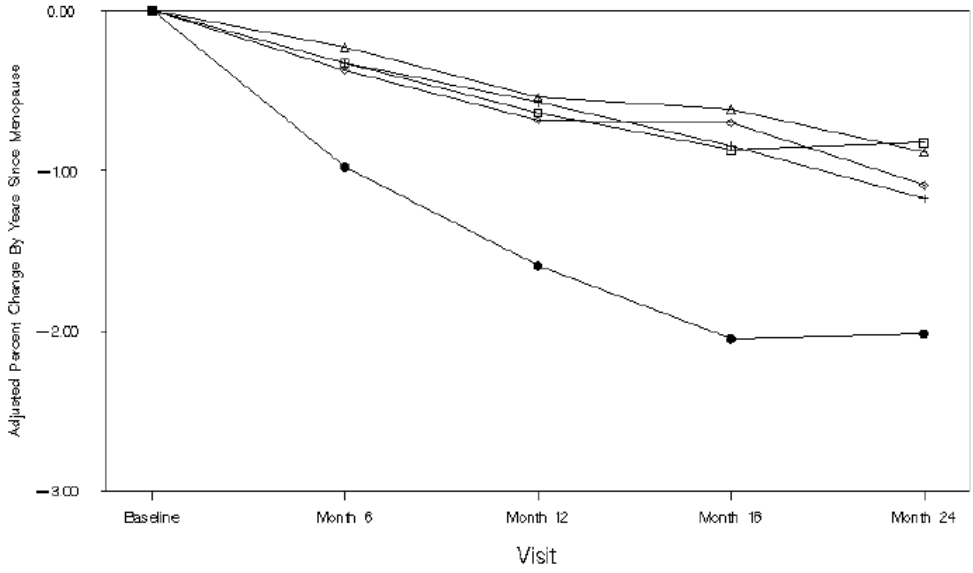
Despite comparable effects on BMD in this study between bazedoxifene and raloxifene treatment groups decrease in markers of bone turnover differed: At all time points evaluated, the decreases in serum CTx levels and serum osteocalcin were significantly greater with bazedoxifene 10 mg, 20 mg, and 40 mg compared to placebo. However decreases observed with raloxifene 60 mg were always greater than those seen with the bazedoxifene treatment groups.
Assessment of markers of lipid metabolism did not reveal any unexpected or critical finding.

Ancillary analyses

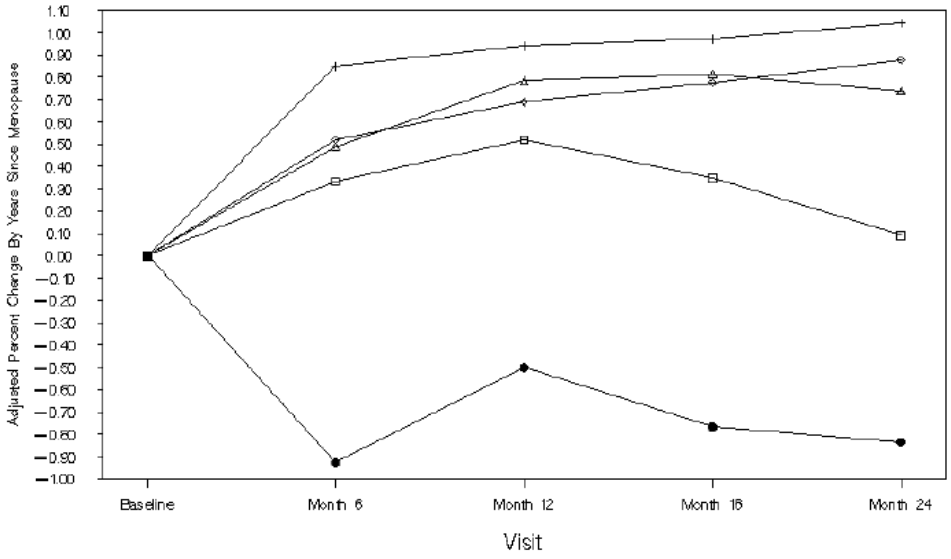
A prespecified subgroup analysis by year since menopause ≤ and > 5 years overall confirmed results obtained for the complete study population. However, effects of bazedoxifene 10 mg are clearly distinguished of those of the 20 mg and 40 mg doses in the higher risk group > 5 years since menopause, but not in those ≤ 5 years and in the group of subjects postmenopausal for at least 1 year and less than 5 years, non inferiority to raloxifene could be demonstrated for the bazedoxifene 10 and 20 mg but not for the 40 mg group after month 18.

Figure 2: Percentage Change From Baseline in BMD of the Lumbar Spine, Years Since Menopause (ITT)

Postmenopausal for > 1 and < 5 Years



Postmenopausal for ≥ 5 Years



□ = Bazedoxifene 10 mg, ◊ = Bazedoxifene 20 mg, + = Bazedoxifene 40 mg, Δ = Raloxifene 60 mg, ● = Placebo.

Study 301-WW

Study 301-WW is considered the main (pivotal) trial. Inclusion and exclusion criteria and primary endpoint were mainly in line with Revision 1 of the Guideline on Osteoporosis and scientific advice received by the applicant with the exception of exclusion of women with a very high risk of osteoporotic fractures. According to the applicant this is due to ethical considerations regarding the placebo-control included in this study, which was considered to be a valid argument. A 2-year double-blind study extension to provide cumulative long-term data is ongoing.

METHODS

Study 301-WW was a 4-arm, outpatient, multicentre, double-blind, randomised, placebo- and raloxifene controlled study over 3 years in postmenopausal osteoporotic women, conducted in Asia/Pacific countries, Canada, Europe, Latin America, South Africa, and the United States. Treatment groups included bazedoxifene 20 mg and 40 mg, raloxifene 60 mg, and placebo.

Study Participants

Inclusion Criteria in the Core Study were:

- Generally healthy postmenopausal women

- Age 55 to 85 years (non-US countries)
- Age 55 to 80 years (US only)

– At least 2 years postmenopausal defined by any of the following:
  - Last natural menstrual cycle ≥ 2 years before screening; or,
  - Over 60 years of age; or,
  - Surgical menopause (bilateral oophorectomy) ≥ 2 years before screening.
– Osteoporotic subjects without vertebral fracture:
  - In non-US countries: BMD T-score at the femoral neck or lumbar spine of –2.5 or worse without the presence of a vertebral fracture.
  - In US only BMD T-score at the femoral neck or lumbar spine between –2.5 and –4.0 (inclusive) without the presence of a vertebral fracture.

or

– Osteoporotic subjects with vertebral fracture:
  - In non-US countries: presence of 1 - 5 mild or moderate asymptomatic vertebral fracture(s) and lumbar spine and femoral neck BMD T-score not worse than –3.5.
  - In US only: presence of 1 mild asymptomatic vertebral fracture and a lumbar spine and femoral neck BMD T-score not worse than -4.0.

Treatments
Patients received bazedoxifene 20 mg and 40 mg, raloxifene 60 mg, and placebo over 3 years. All patients were supplemented with approximately 1200 mg of calcium and 400 IU of vitamin D, depending on local standards.

Objectives
The primary objectives of this study were to evaluate the safety and efficacy of bazedoxifene 20 mg and 40 mg in the reduction of new radiographically confirmed vertebral fractures in postmenopausal osteoporotic women compared to placebo. Among the secondary objectives were: to evaluate the effect of bazedoxifene 20 mg and 40 mg compared with raloxifene 60 mg and placebo on breast cancer incidence, clinical vertebral fractures, worsening vertebral fractures, non-vertebral fractures, height changes, BMD of the lumbar spine and hip, serum bone markers, lipid parameters, QoL, and effects on endometrium and bone histomorphometry.
An additional secondary objective of this study was to compare the efficacy of raloxifene 60 mg with placebo in reducing the incidence of new vertebral and other (non vertebral) fractures after 36 months of treatment.

Outcomes/endpoints
The primary endpoint was the cumulative incidence of new radiographically confirmed vertebral fractures of the thoracic and lumbar spine (T4-L4) from baseline to month 36 (Kaplan-Meier). Fracture incidence was also analyzed based on subject vertebral fracture status at baseline. All radiographs were evaluated centrally.
Secondary endpoints were incidence of breast cancer, of non-vertebral fractures (all osteoporosis-related, hip, or wrist fractures), and of clinical and worsening vertebral fractures. Further secondary endpoints were percentage changes from baseline in BMD of the lumbar spine, total hip, femoral neck, and femoral trochanter, serum bone marker measurements, qualitative assessment of changes in bone histomorphometry at month 24, comparison of raloxifene 60 mg to placebo in reducing the incidence of new vertebral fractures and other fractures after 36 months of treatment, and QoL questionnaire scores

Sample size
Sample size and study designs were considered adequate, specifically with regard to the chosen inclusion criteria and primary endpoint according to Revision 1 of the Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95).

Randomisation and Blinding
Randomization was stratified to ensure that the distribution of subjects with vertebral fracture was equal across treatment groups. Randomisation and blinding were considered to be adequate.

Statistical methods
Primary analysis was in the ITT population, defined as all subjects randomly assigned to a treatment group, had recorded at least 1 dose of test article, and had a baseline and an on-therapy vertebral radiographic assessment. New vertebral fracture data were assessed using Kaplan-Meier estimates of fracture incidence and unadjusted estimates of fracture incidence. Between-group comparisons were performed using log-rank test at 0.05 level, and hazard ratio estimates were based on Cox proportional hazard regression, adjusted for baseline vertebral status fracture and baseline BMD T-score.
The non-vertebral fractures were considered the secondary endpoint of greatest interest. Analyses were based on data from principal investigators and on adjudicated data from the Clinical Fracture Adjudication Board reviews. Kaplan-Meier estimates of the incidence of non-vertebral fractures were calculated for each treatment group and between-group comparisons were performed using the log-rank test at the 0.05 level.
The statistical methods were considered to be adequate.

RESULTS

Participant flow
7609 subjects were randomly assigned to a study group. 7492 of these were included in the efficacy and safety analyses.

These 7492 subjects are included in the safety population, while only 6847 met the criteria to be included in the ITT population for the primary efficacy analysis. The ITT population for assessments of the secondary study parameters, BMD of the lumbar spine, total hip, femoral neck, and femoral trochanter, comprised 6956, 6916, 6941, and 6941 subjects, respectively. 649, 137, and 403 subjects were included in the endometrial safety, bone histomorphometry, and ECG substudies, respectively. 4991 (67%) subjects completed the 3 years of the core study.
AE was the most common reason for discontinuation, followed by "subject request unrelated to study AE". With exception of the "unsatisfactory response – lack of efficacy" category ($p = 0.007$), no significant differences existed among the treatment groups for the total number of subjects who were withdrawn from the study or the reasons for withdrawal. Subjects who had a new vertebral fracture at any time during the study or a $\geq 7\%$ decrease in BMD of the lumbar spine or hip were to be withdrawn. 75 (4.0%) subjects in the placebo group were withdrawn for this reason compared with 52 (2.8%), 52 (2.8%), and 39 (2.1%) subjects in the bazedoxifene 20 mg, bazedoxifene 40 mg, and raloxifene 60 mg treatment groups, respectively, and the difference between the placebo and the active treatment groups was statistically significant ($p < 0.01$).

Recruitment
26,749 subjects were screened; of these 19,140 did not meet the inclusion and exclusion requirements. 7609 subjects were randomly assigned to a study group. 117 of these never received test article, mostly because they withdrew consent, and are not included in any analyses. The remaining 7492 participants were included in the efficacy and safety analyses.

Conduct of the study
During the conduct of the core study there were 5 amendments to the original study protocol. The amendments primarily reflected concerns of local IRBs and IECs as well as investigators about preventing the enrolment of subjects at high risk for vertebral fracture determined by baseline T-scores and the severity of prevalent vertebral fractures. Amendment 3 allowed enrolment of osteoporotic women without fractures, and increased the total number of subjects to be included in the study.
The data on discontinuation due to AE confirm findings from study 300-GL. There was a slight positive trend for discontinuation over the bazedoxifene 20 mg and 40 mg groups and the rate was lowest in the raloxifene 60 mg group, including placebo. Nature and number of protocol violations in this study do not indicate that the integrity of the study was systematically affected

Baseline data
The demographic and baseline characteristics did not reveal significant differences between treatment groups. Participants were healthy postmenopausal women with a mean age of 66.4 years; the mean number of years since the last menstrual period was approximately 19.5 years. Approximately 91%

had natural menopause and approximately 9% were surgically menopausal; approximately 21% had had a hysterectomy. The study included mostly Caucasian (87.3%) subjects. Mean weight across groups ranged from 64.5 kg to 65.4 kg. The mean BMI was 26.5 kg/m^2. The mean LS and FN T-scores at baseline were -2.4 and -1.7, respectively.
About 56% of participants had at least 1 prevalent fracture. Among participants with prevalent vertebral fracture, 73% had 1, 19% had 2, and about 8% had 3 or more prevalent fractures. The severity of prevalent fractures was classified as mild, moderate, or severe fracture using a semi quantitative methodology. The majority (65%) had 1 mild prevalent fracture.

Numbers analysed
See above

Outcomes and estimation

Primary Endpoint

Vertebral fractures

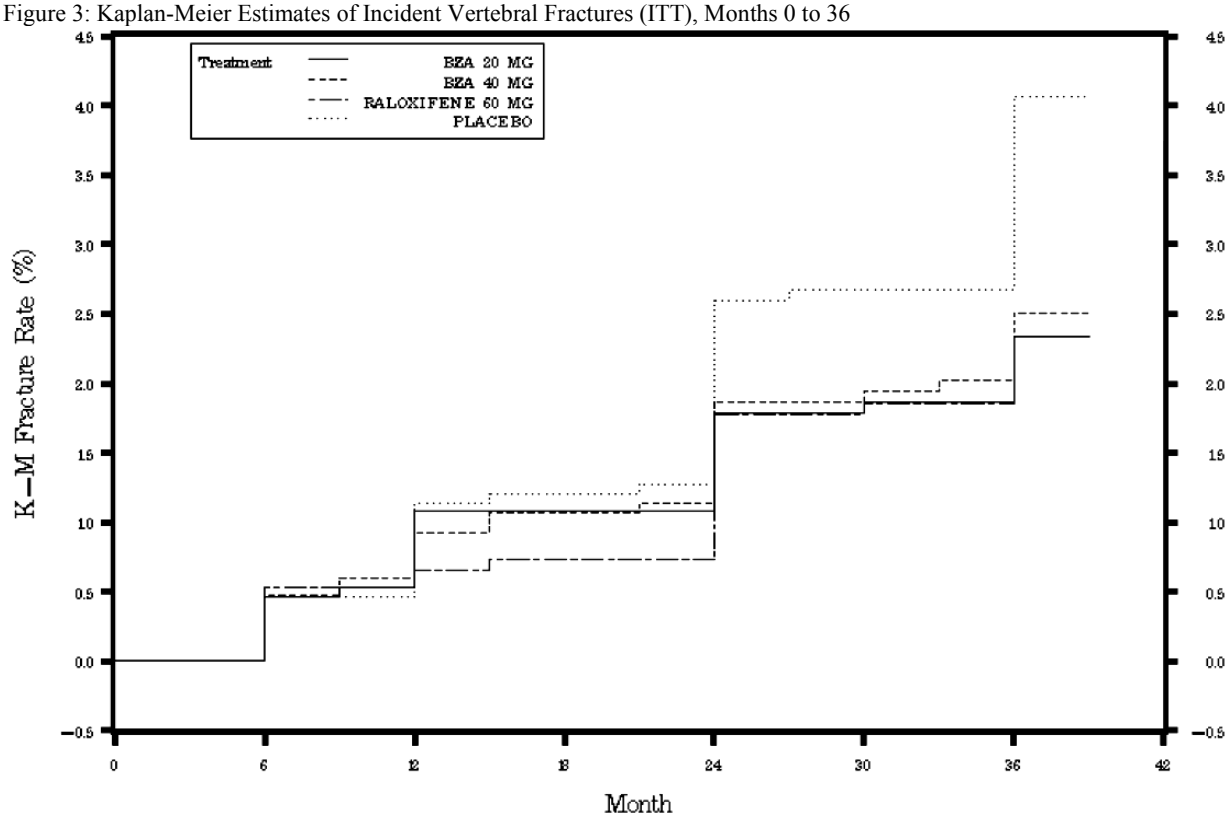
There was a clinically significant reduction in the incidence of new vertebral fractures compared to placebo for both bazedoxifene doses tested; the effects were independent of baseline status, apparent from 24 month of treatment onwards, statistically significant at 36 month of treatment and comparable to raloxifene treatment. After 36 months of treatment, the Kaplan-Meier rate estimates of cumulative fracture incidence for the bazedoxifene 20 mg and 40 mg, the raloxifene 60 mg and placebo were 2.34%, 2.51%, 2.34%, and 4.07%, respectively. For the months 0 to 24 interval, the Kaplan-Meier estimates of cumulative fracture incidence were 1.72%, 1.87%, 1.73%, and 2.54% respectively. Subgroup analysis by baseline vertebral fracture status endorses the assumption of a consistent effect across subgroups. However, this treatment effect was statistically significant only in the subgroup of subjects with ≥ 1 prevalent fracture at baseline, i.e. in the subjects with a higher risk. No statistically significant effect on the fracture incidence of neither bazedoxifene nor raloxifene was evident among subjects without a prevalent fracture at baseline. . In the analyses stratified on baseline fracture status, the PP analysis as a secondary analysis (with ITT considered as the primary one) showed statistically significant risk reductions only with raloxifene.

Table 3: Summary Tabulation New Vertebral Fracture Incidence (ITT), Months 0 to 36

Treatment Group	Comparator	Kaplan-Meier Rate Estimate (%)	Lower Limit 95% CI	Upper Limit 95% CI	Hazard Ratio	Lower 95% Limit	Upper 95% Limit
Overall							
Bazedoxifene 40 mg	Placebo	2.51	1.81	3.47	0.634	0.419	0.960
Bazedoxifene 20 mg	Placebo	2.34	1.68	3.25	0.584	0.383	0.891
Raloxifene 60 mg	Placebo	2.34	1.67	3.26	0.581	0.381	0.887
No Prevalent Fractures							
Bazedoxifene 40 mg	Placebo	2.14	1.25	3.67	0.647	0.322	1.301
Bazedoxifene 20 mg	Placebo	1.98	1.15	3.40	0.647	0.322	1.302
Raloxifene 60 mg	Placebo	1.84	1.04	3.22	0.592	0.289	1.212
≥ 1 Prevalent Fracture							
Bazedoxifene 40 mg	Placebo	2.80	1.86	4.20	0.624	0.373	1.045
Bazedoxifene 20 mg	Placebo	2.63	1.73	3.98	0.551	0.324	0.937
Raloxifene 60 mg	Placebo	2.74	1.81	4.14	0.574	0.340	0.968

Hazard ratio estimation based on Cox proportional hazard regression, adjusted for baseline BMD T-score

Figure 3: Kaplan-Meier Estimates of Incident Vertebral Fractures (ITT), Months 0 to 36



The relative risk reduction (RRR = 1.000 - hazard ratio) in cumulative vertebral fracture incidence for the bazedoxifene 20 mg treatment group compared with placebo was 42%, and for the bazedoxifene 40 mg treatment group compared with the placebo group it was 37%. The RRR for the raloxifene 60 mg treatment group versus the placebo group also was 42%. The hazard ratio estimates between the active treatment groups were similar.

For subjects with no prevalent vertebral fractures, Kaplan-Meier estimates of cumulative incidence of new vertebral fracture for the interval from 0 to 36 months for the bazedoxifene 20 and 40 mg treatment groups (1.98% and 2.14%, respectively) were similar to the rate estimate for the raloxifene 60 mg treatment group (1.84%), and all active treatment groups had lower rate estimates than the placebo group (3.13%).

For subjects with at least 1 prevalent vertebral fracture, the Kaplan-Meier rate estimates of cumulative incidence of new vertebral fracture from 0 to 36 months for the bazedoxifene 20 and 40 mg and the raloxifene 60 mg treatment groups were similar (2.63%, 2.80%, and 2.70%, respectively) and lower than that seen with the placebo group (4.80%).

Secondary Endpoints

Non-Vertebral fractures

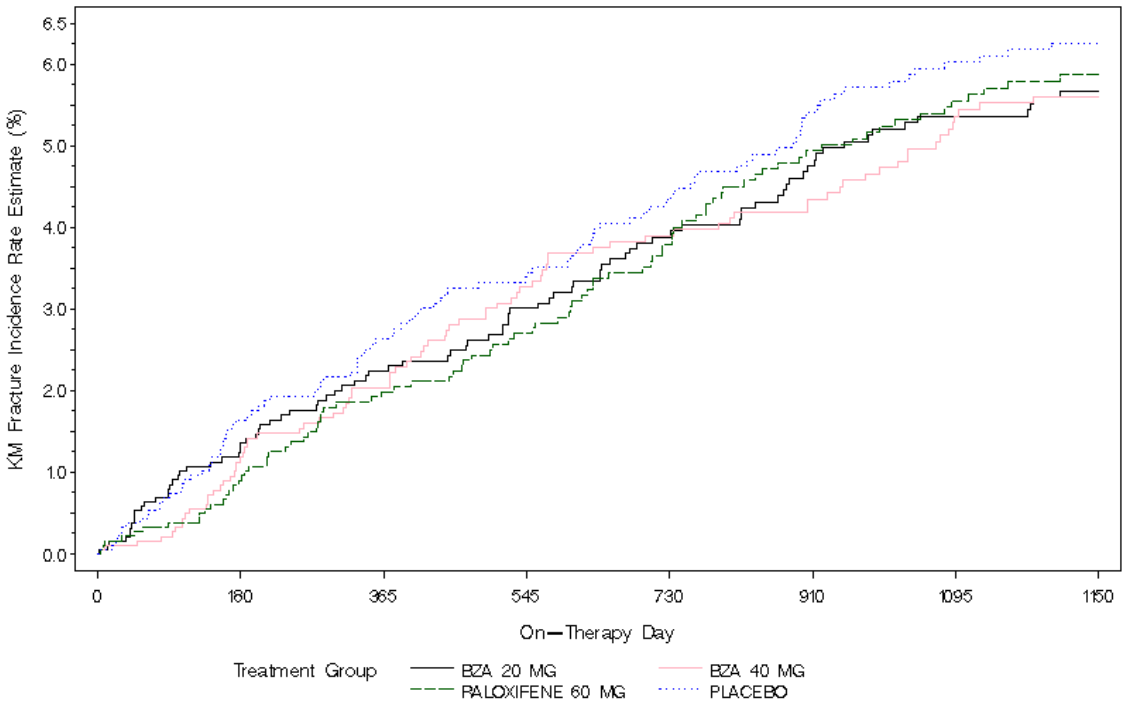
Regarding the incidence of non-vertebral fractures there was no statistically significant difference between active treatment and placebo. However the fracture rate was numerically lower in the active treatment groups compared to placebo. The overall incidence of non-vertebral fractures was low in this study compared to published data. Fractures of the toes, fingers, elbow, skull and face were excluded from analysis as these fractures were not considered osteoporosis related. In addition, traumatic and pathologic fractures were also excluded.

Table 4: Kaplan-Meier Estimates of Non-Vertebral Fracture Rate, Principal Investigator Data, Months 0 to 36

Treatment Group	Number of New Fractures	Number of Subjects	Fracture Rate (%)	Kaplan-Meier Rate Estimate (%)	Lower 95% Limit	Upper 95% Limit
Bazedoxifene 20 mg	89	1886	4.72	5.68	4.63	6.96
Bazedoxifene 40 mg	85	1872	4.54	5.61	4.55	6.90
Raloxifene 60 mg	89	1849	4.81	5.87	4.79	7.19
Placebo	99	1885	5.25	6.26	5.16	7.59

Pathologic non-vertebral fractures are excluded.

Figure 4: Kaplan-Meier Estimates of Non-Vertebral Fracture Rate, Principal Investigator Data, Months 0 to 36



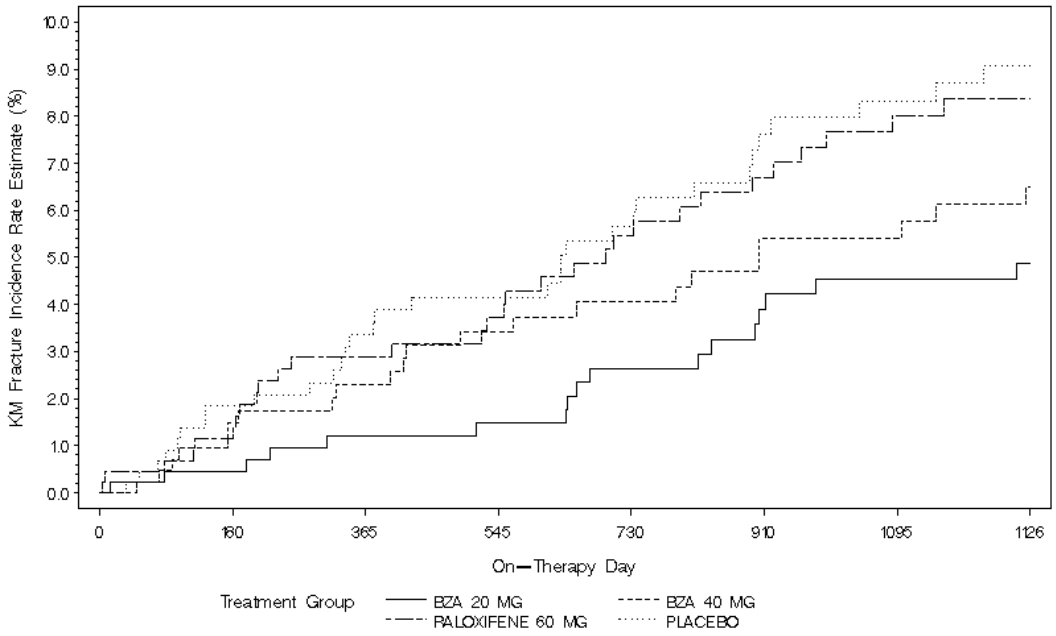
In a post-hoc analysis of a subgroup of women at high risk for non-vertebral fractures (femoral neck T-score < -3.0 or prevalent fracture excluding those with 1 mild fracture) there was a 50% reduction in non-vertebral fractures relative to placebo and a 44% reduction relative to raloxifene with bazedoxifene 20 mg. The effect was observed at month 12 and was sustained up to month 36. In this subgroup of subjects, the incidence of non-vertebral fractures in the placebo group was 9% at 3 years. The same exploratory analyses conducted on adjudicated data were consistent with the investigator-assessed data analysis. However, the data was not considered to be unequivocally supporting the notion of protection with regard to non-vertebral fractures by the CHMP, as the outcome was present only with the lowest bazedoxifene dose and was based on a non-prespecified post-hoc analysis.

Table 5: Non-Vertebral Fracture Incidence in Women at High Risk for Fracture, Kaplan-Meier Estimates, Months 0 to 36

Treatment Group	Number of New Fractures	Number of Subjects	Kaplan-Meier Rate Estimate (%)	-------- 95% CI -------- LL	UP
Bazedoxifene 20 mg	17	443	4.89	3.05	7.77
Bazedoxifene 40 mg	22	433	6.48	4.30	9.73
Raloxifene 60 mg	30	448	8.36	5.90	11.78
Placebo	32	448	9.06	6.46	12.64

CI = confidence interval; LL = lower limit; UP = upper limit.
The high risk group was defined as those subjects with a femoral neck T-score of -3 or lower, or the presence of at least 1 moderate vertebral fracture or multiple vertebral fractures at baseline.
Pathologic non-vertebral fractures are excluded, summary based on principal investigator's data.

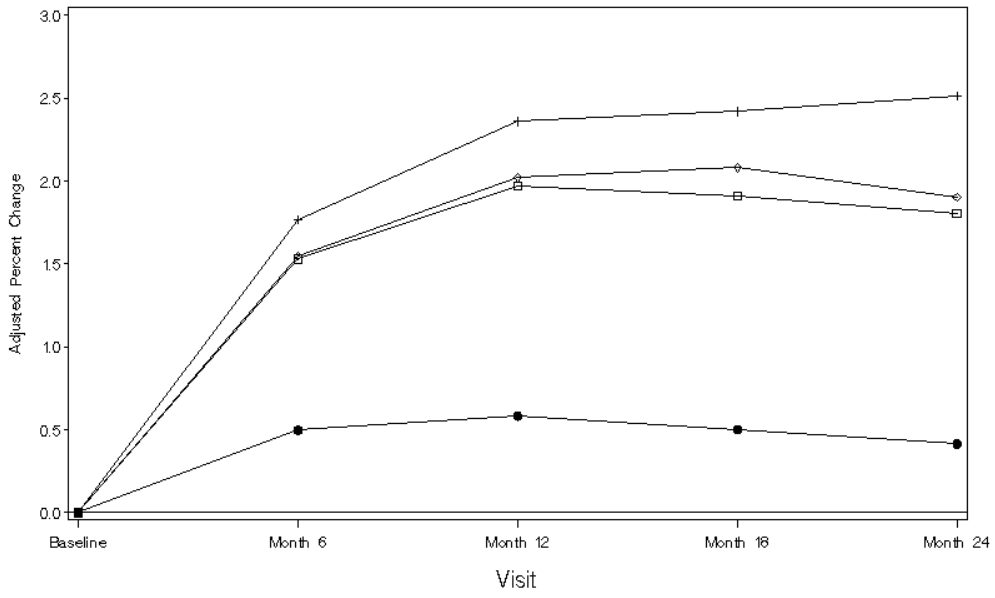
Figure 5: -Vertebral Fracture Incidence in Women at High Risk for Fracture, Kaplan-Meier Estimates, Months 0 to 36



Bone Mineral Density

The primary bone mineral density (BMD) analysis was percentage change from baseline in BMD at 24 months. Overall, at the lumbar spine as well as at the total hip, including femoral and trochanter a significant treatment effect was demonstrated for both bazedoxifene treatment groups at month 6 and maintained throughout month 36.

Figure 6: Percentage Change from Baseline in BMD of the Lumbar Spine, Months 0 to 24 (ITT)



□ = Bazedoxifene 20 mg; ◊ = Bazedoxifene 40 mg; + = Raloxifene 60 mg; • = Placebo

Changes in lipid metabolism were similar between bazedoxifene and raloxifene. Results do not raise a concern.

Incidence of new diagnosis of breast cancer was lower on bazedoxifene than on placebo or raloxifene. However absolute numbers are low and no conclusions can be drawn.

Results on bone histomorphometry in a small subset of subjects do not raise a concern.

Ancillary analyses

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

Results of the **analysis across studies** are mainly driven by those from study 301-WW since this study enrolled about 5 times the number of participants than study 300-GL. Regarding BMD and biochemical markers of bone metabolism results were not consistent in the two pivotal phase 3 studies. In study 300-GL, changes from baseline in BMD and biochemical markers were very similar between bazedoxifene and raloxifene treatment groups. In contrast in study 301-WW, the increases from baseline in BMD of the lumbar spine for the bazedoxifene treatment groups were statistically significant lower than for the raloxifene treatment group at all time points. This is supported by results from the responder analysis. Reduction of biochemical markers of bone metabolism were higher on raloxifene compared with bazedoxifene 20 mg and 40 mg. In both phase 3 studies, bazedoxifene treatment resulted in a favourable lipid profile, although the clinical relevance of these changes remains to be determined.

At the request of the CHMP the fracture risk of the population studied was investigated to be in concordance with the 2006 osteoporosis guideline. The applicant provided absolute risk of fractures based on the extrapolation of rates from the placebo arm, and additionally the estimated 10-year fracture probability, based on the FRAX™ model, a recently published algorithm by Prof. Kanis from the World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield. FRAX™ is a computer based algorithm (http://www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability. Probability of fracture is calculated from age, BMI computed from height and weight, and dichotomized risk variables.
The incidence of vertebral fractures was 4.1% in the placebo group after 3 years. If this rate is annualized, the incidence of new vertebral fractures would be about 1.3%, meaning that after 10 years the incidence would be about 13%. This estimate does not take into account the increase in age, it is reasonable to assume that based on the placebo rate the 10-year vertebral fracture probability would be at least 15%. The incidence of non-vertebral fractures in the placebo group was 6.3% after 3 years and accordingly, translating into an annualized rate of 2.1% and a 10-year fracture probability of at least 20%. However the incidence of hip fractures was low, 0.31% in the placebo group after 3 years, translating into an annualized rate of 0.1% and a 10-year fracture probability of 1%, lower than that specified in the new guideline (5% to 7.5%).
As these estimates do not adequately account for confounding factors like increasing age and death the FRAX™ algorithm that allows estimation of a 10-year fracture probability in men and women has also been applied. The 10-year fracture probability was estimated at 11%, overall in line with revision 2 of the CHMP guideline on osteoporosis. The following table shows the resulting 10-year fracture probability with and without BMD.

Table 6: Ten Year Fracture Probability (%) at Baseline Based on FRAX™

	Without BMD	With BMD
n	7479	6930
Mean	11.1	10.5
SD	8.5	8.3
Range	0.7-64.9	0.6-80.0

In summary estimations of the absolute fracture risk both based on data from the placebo arm of this study as well as on calculations using the FRAX™ algorithm suggest that the study overall is in line with the requests of revision 2 of the CHMP guideline on osteoporosis.

The fracture rate in this study was lower in comparison to the Multiple Outcomes of Raloxifene Evaluation (MORE) study probably based on the different enrolment criteria leading to enrolment of women with less severe osteoporosis. In study 301-WW, postmenopausal women were eligible for

inclusion if they had osteoporosis defined as lumbar spine or femoral neck BMD between ~2.5 and ~4.0 (inclusive) and no prevalent vertebral fracture, or at least 1 mild vertebral fracture and BMD not worse than ~4.0. The MORE study enrolled postmenopausal women with osteoporosis defined as BMD below ~2.5, or low BMD with 1 or more moderate or severe vertebral fractures, or who had at least 2 moderate fractures regardless of their BMD. The original protocol for study 301-WW included subjects with severe forms of osteoporosis. However, it was considered unethical to enrol severely affected subjects at a time when a large number of drugs were available for treatment. That resulted in enrolment of subjects with a milder disease, consistent with the recommendations of IRBs and ethics committees.

There was a significant increase in BMD in all active treatment groups. However, in contrast to results from study 300-GL, BMD was higher in the raloxifene treatment group compared to both bazedoxifene 20 mg and 40 mg groups. This difference is not reflected by the data on incidence of vertebral or non-vertebral fractures. In line with the data on BMD raloxifene had a greater effect on biochemical markers of bone metabolism than bazedoxifene 20 mg and 40 mg.

- Clinical studies in special populations

Renal impairment
No dose adjustment is required for mild or moderate renally impaired patients. However, bazedoxifene has not been sufficiently evaluated in patients with severe renal impairment; caution in this population is therefore advised in sections 4.4 and 5.2 of the SPC.

Hepatic impairment
Safety and efficacy of bazedoxifene have not been evaluated in patients with hepatic impairment; therefore, use in this population is not recommended (see sections 4.4 and 5.2 of the SPC).

Elderly patients
No dose adjustment is necessary based on age.

Paediatric patients
Bazedoxifene is not indicated for use in paediatric patients and has not been investigated in this population.

- Discussion on clinical efficacy

In conclusion the efficacy data available support the assumption that efficacy of bazedoxifene in the treatment indication has sufficiently been established for vertebral fractures, while no effect of bazedoxifene relative to placebo on the incidence of non-vertebral fractures has been established. The efficacy of bazedoxifene appears to be comparable to that of raloxifene. These effects have been investigated on the background of a calcium supplementation (up to 1200 mg) combined with vitamin D (400 IU).
The design of the bazedoxifene phase 3 clinical programme for prevention and treatment of osteoporosis was consistent with the European osteoporosis guideline and scientific advices received at the time it was designed in 2001. Posthoc calculations of the fracture risk using the FRAX™ algorithm and the estimated 10-year absolute risk of fractures in study 301-WW based on the extrapolation of rates from the placebo arm indicate consistency with the current revision 2 of the osteoporosis guideline.

Clinical safety

- Patient exposure

The safety evaluation presented by the applicant is mainly based on results from 2 large scale, outpatient, multicentre, double-blind, randomised, placebo- and raloxifene-controlled, phase 3 studies (300-GL, 2 years treatment, 1,583 postmenopausal women, mean age = 58 years and 301-WW, 3 years treatment, 7,492 postmenopausal women, mean age = 66 years). In addition data from 3 phase 2 studies (200-BR, 204-US/CA, and 205-CN), and 18 phase 1 studies have been evaluated. Data from 9075 women were included in the safety population of the phase 3 studies, 321 bazedoxifene 10 mg, 2208 bazedoxifene 20 mg, 2109 bazedoxifene 40 mg, 1850 raloxifene 60 mg, and 2195 placebo.

Table 7: Patient Exposure in Phase 3 Studies

Study	No. of Subjects	Treatment	Treatment (Months)
300-GL	321	Bazedoxifene 10 mg [a]	24
	322	Bazedoxifene 20 mg	24
	319	Bazedoxifene 40 mg	24
	311	Raloxifene 60 mg	24
	310	Placebo	24
301-WW[b]	1886	Bazedoxifene 20 mg	36
	1872	Bazedoxifene 40 mg	36
	1849	Raloxifene 60 mg	36
	1885	Placebo	36

a. This dose group was not included in the integrated data.
b. Final analysis of 3-year core study.

Based on the duration (2 and 3 years) and size of the phase 3 studies there is an adequate number of women exposed under long-term, controlled conditions. By including raloxifene as an active comparator into these studies, linking to the extensive safety information available with raloxifene, the safety assessment is facilitated.

Safety results from the phase 3 studies were considered individually and pooled for the bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, and placebo treatment groups to provide an overall assessment of the safety profile of bazedoxifene in postmenopausal women. The strategy of considering data sets both pooled and individually is considered acceptable since pooling might generate additional information on rare AE. Pooling mainly across phase 3 data is endorsed as this offers more homogeneous data sets. Subgroups of subjects defined by age (64 years or younger, 65 to 74 years, and 75 years or older) and ethnic origin (Asian, black, and Hispanic populations) were also examined as part of the integrated analyses.

- Adverse events

Data are pooled from all common doses analyzed in studies 300-GL and 301-WW: bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, and placebo. The bazedoxifene 10 mg treatment group from study 300-GL was not included the integrated analyses.

Common Adverse Events

Overall, bazedoxifene 20 and 40 mg doses were well tolerated in postmenopausal women and the adverse event profile of bazedoxifene was consistent with that of raloxifene reported in these studies as well as in earlier clinical trials. Most of the adverse events in the studies were considered to be treatment emergent.

Because of the previous clinical experience with SERMs, particular attention was paid to the analysis of the frequency and distribution of VTEs, selected cardiac AE, cerebrovascular AE, vasodilatation, breast disorders, reproductive system disorders, and leg cramps. Changes in the endometrium and ovaries were monitored in both phase 3 studies by TVU and endometrial biopsies, including measurement of double-wall endometrial thickness and ovarian volumes and determination of the presence of or changes in ovarian cysts. Study 301-WW also included an ECG and a bone histomorphometry substudy. The focus on and the choice of the AE of special interest based on the clinical experience with other drugs from this class is acceptable.

No clinically relevant differences in the overall incidence of TEAE (treatment emergent adverse event) between active treatment groups have been identified with the exception of vasodilatation (table 8).

Table 8: Number (%) TEAE (≥ 5% only) in Phase 3 Integrated Data

Body System a Adverse Event	Overall P-Value	Treatment BZA 20 mg n = 2208	BZA 40 mg n = 2191	Raloxifene 60 mg n = 2160	Placebo n = 2195
Any Adverse Event	0.536	2086 (94.5)	2047 (93.4)	2029 (93.9)	2065 (94.1)
Body as a Whole	0.718	1669 (75.6)	1649 (75.3)	1646 (76.2)	1682 (76.6)
Abdominal Pain	0.110	415 (18.8)	434 (19.8)	460 (21.3)	467 (21.3)
Accidental Injury	0.009**	473 (21.4)	422 (19.3)	413 (19.1)	496 (22.6)
Asthenia	0.657	204 (9.2)	189 (8.6)	210 (9.7)	205 (9.3)
Back Pain	0.729	613 (27.8)	589 (26.9)	609 (28.2)	620 (28.2)
Chest Pain	0.613	158 (7.2)	161 (7.3)	157 (7.3)	141 (6.4)
Flu Syndrome	0.272	495 (22.4)	511 (23.3)	531 (24.6)	538 (24.5)
Headache	0.621	486 (22.0)	480 (21.9)	447 (20.7)	487 (22.2)
Infection	0.688	509 (23.1)	475 (21.7)	479 (22.2)	501 (22.8)
Neck Pain	0.323	149 (6.7)	142 (6.5)	154 (7.1)	172 (7.8)
Pain	0.280	585 (26.5)	592 (27.0)	619 (28.7)	626 (28.5)
Cardiovascular System	<0.001***	893 (40.4)	893 (40.8)	843 (39.0)	772 (35.2)
Hypertension	0.431	376 (17.0)	341 (15.6)	349 (16.2)	377 (17.2)
Vasodilatation	<0.001***	296 (13.4)	307 (14.0)	268 (12.4)	156 (7.1)
Digestive System	0.990	1094 (49.5)	1075 (49.1)	1062 (49.2)	1080 (49.2)
Constipation	0.203	365 (16.5)	372 (17.0)	337 (15.6)	325 (14.8)
Diarrhoea	0.308	190 (8.6)	213 (9.7)	217 (10.0)	195 (8.9)
Dyspepsia	0.326	215 (9.7)	181 (8.3)	189 (8.8)	206 (9.4)
Nausea	0.480	182 (8.2)	192 (8.8)	164 (7.6)	170 (7.7)
Vomiting	0.837	115 (5.2)	125 (5.7)	116 (5.4)	126 (5.7)
Endocrine System	0.434	118 (5.3)	118 (5.4)	97 (4.5)	104 (4.7)
Hemic and Lymphatic System	0.926	184 (8.3)	192 (8.8)	178 (8.2)	183 (8.3)
Metabolic and Nutritional	0.048*	568 (25.7)	554 (25.3)	523 (24.2)	611 (27.8)
Hypercholesteremia	<0.001***	102 (4.6)	87 (4.0)	59 (2.7)	143 (6.5)
Peripheral Edema	0.188	207 (9.4)	181 (8.3)	183 (8.5)	166 (7.6)
Musculoskeletal System	0.232	1034 (46.8)	976 (44.5)	1013 (46.9)	983 (44.8)
Arthralgia	0.737	629 (28.5)	596 (27.2)	616 (28.5)	611 (27.8)
Arthrosis	0.527	149 (6.7)	147 (6.7)	165 (7.6)	146 (6.7)
Leg Cramps	0.011*	235 (10.6)	236 (10.8)	235 (10.9)	182 (8.3)
Myalgia	0.610	101 (4.6)	94 (4.3)	107 (5.0)	111 (5.1)
Nervous System	0.649	831 (37.6)	785 (35.8)	788 (36.5)	811 (36.9)
Anxiety	0.109	92 (4.2)	92 (4.2)	96 (4.4)	121 (5.5)
Depression	0.122	117 (5.3)	137 (6.3)	131 (6.1)	105 (4.8)
Dizziness	0.152	209 (9.5)	172 (7.9)	172 (8.0)	198 (9.0)
Insomnia	0.612	192 (8.7)	175 (8.0)	171 (7.9)	193 (8.8)
Vertigo	0.321	129 (5.8)	117 (5.3)	140 (6.5)	142 (6.5)
Respiratory System	0.795	835 (37.8)	799 (36.5)	792 (36.7)	816 (37.2)
Bronchitis	0.458	185 (8.4)	183 (8.4)	162 (7.5)	162 (7.4)
Cough Increased	0.297	221 (10.0)	200 (9.1)	181 (8.4)	209 (9.5)
Pharyngitis	0.145	173 (7.8)	174 (7.9)	180 (8.3)	210 (9.6)
Sinusitis	0.272	135 (6.1)	113 (5.2)	123 (5.7)	107 (4.9)
Upper Respiratory Infection	0.826	156 (7.1)	142 (6.5)	143 (6.6)	141 (6.4)
Skin and Appendages	0.164	546 (24.7)	505 (23.0)	558 (25.8)	555 (25.3)
Pruritus	0.804	118 (5.3)	112 (5.1)	124 (5.7)	123 (5.6)
Special Senses	0.566	410 (18.6)	405 (18.5)	398 (18.4)	436 (19.9)
Urogenital System	0.224	842 (38.1)	798 (36.4)	848 (39.3)	853 (38.9)
Breast Disorder	0.198	105 (4.8)	102 (4.7)	96 (4.4)	126 (5.7)
Cervix Disorder	0.394	97 (4.4)	107 (4.9)	105 (4.9)	121 (5.5)
Urinary Tract Infection	0.525	186 (8.4)	172 (7.9)	189 (8.8)	168 (7.7)

Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
Overall p-value: p-value for chi-square. Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

In the single-dose safety, tolerability, and pharmacokinetic study 123-CI in 60 Chinese subjects, the most commonly reported AE were changes or abnormalities in ECGs. These ECG abnormalities were reported in all treatment groups, including the placebo group, and occurred with no apparent dose relationship. The QTc study and the ECG substudy of phase 3 study 301-WW did not reveal any effect of bazedoxifene on QTc or ECG abnormalities. In addition the pattern of ECG abnormalities in study 123-CI does not suggest a causal relationship.

Regarding the AE of special interest, although overall number of VTE events is low (see table 9), the incidence of VTE appears to be higher in the bazedoxifene treatment groups than in the raloxifene

treatment group. This issue will be addressed in the proposed post-marketing study which is a crucial part of the RMP

Table 9: Number (%) of Subjects Reporting VTE, Phase 3 Integrated Data

Body System[a] AE	Overall p-Value	Treatment BZA 20 mg n = 2208	BZA 40 mg n = 2191	Raloxifene 60 mg n = 2160	Placebo n = 2195	Total n = 8754
Any AE	0.590	16 (0.7)	15 (0.7)	11 (0.5)	10 (0.5)	52 (0.6)
Deep thrombophlebitis	0.115	2 (0.1)	0	0	0	2 (0.0)
Deep vein thrombosis[b]	0.049*	7[c] (0.3)	11 (0.5)	8 (0.4)	1 (0.0)	27 (0.3)
Pulmonary embolus[d]	0.984	5 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)	17 (0.2)
Retinal vein thrombosis[e]	0.672	2 (0.1)	1 (0.0)	1 (0.0)	3 (0.1)	7 (0.1)
Thrombosis	0.113	0	0	0	2[f] (0.1)	2 (0.0)

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
b. Includes 9 posttherapy events (1 bazedoxifene 20 mg, 3 bazedoxifene 40 mg, 4 raloxifene 60 mg, and 1 placebo).
c. Subject 301-034-002313 (bazedoxifene 20 mg) had an event that was coded as superficial thrombophlebitis and was not included in this table. The subject had experienced pain in her right thigh 8 days after her elective knee replacement surgery. Diagnostic procedures revealed a clot at mid-superficial femoral vein. The subject was treated with antithrombotic therapy (heparin, followed by warfarin). Despite a site data clarification request, the principal investigator declined to report this event as a DVT.
d. Includes 1 subject (bazedoxifene 20 mg) with post-procedural pulmonary embolism and 9 posttherapy events (3 bazedoxifene 20 mg, 2 bazedoxifene 40 mg, 2 raloxifene 60 mg, and 2 placebo).
e. Includes 3 events reported as retinal vein occlusion with the MedDRA coding system (1 bazedoxifene 20 mg, 1 raloxifene 60 mg, and 1 placebo).
f. In bazedoxifene study 300-GL, 2 adverse events were coded as "thrombosis" (placebo group): subject 300-102-003702 was reported with a left lower calf thrombosis and considered a DVT, and subject 300-006-007384 was reported with a blood clot in the left knee, secondary to varicose vein and considered a superficial vein thrombosis.
Overall p-value: p-value for chi-square. Statistical significance at the .05 level is denoted by *.

Safety results on cardiovascular system did not raise a concern. For the cerebrovascular events the overall incidence of ischemic and hemorrhagic cerebrovascular AE did not show a statistically significant difference between treatment groups, but the AE cerebral ischemia and cerebrovascular accident, while not different from the placebo group, were reported numerically more often in the bazedoxifene than in the raloxifene groups. Potential cerebrovascular event cases have been adjudicated/readjudicated. The applicant has provided the results of this process (Cerebrovascular Event Readjudication Report). The results are overall consistent with the non-adjudicated cerebrovascular safety analysis as reported by study investigators and in agreement with the safety assessment based on the initial adjudication of cerebrovascular events. Therefore the results did not alter the benefit-risk assessment based on the non-adjudicated data.

Table 10: Number (%)Reporting Cerebrovascular Events, Phase 3 Integrated Data

Body System [a] AE	Overall p-Value	Treatment BZA 20 mg n = 2208	BZA 40 mg n = 2191	Raloxifene 60 mg n = 2160	Placebo n = 2195	Total n = 8754
All Cerebrovascular Events	0.526	24 (1.1)	30 (1.4)	21 (1.0)	30 (1.4)	105 (1.2)
Cerebral hemorrhage	0.577	1 (0.0)	1 (0.0)	0	2 (0.1)	4 (0.0)
Cerebral infarct	0.307	1 (0.0)	5 (0.2)	2 (0.1)	2 (0.1)	10 (0.1)
Cerebral ischemia	0.968	10 (0.5)	10 (0.5)	8 (0.4)	9 (0.4)	37 (0.4)
Cerebrovascular accident	0.624	10 (0.5)	13 (0.6)	7 (0.3)	11 (0.5)	41 (0.5)
Cerebrovascular disorder	0.032*	0	0	4 (0.2)	1 (0.0)	5 (0.1)
Intracranial hemorrhage	0.568	0	0	1 (0.0)	1 (0.0)	2 (0.0)
Retinal artery occlusion	0.801	1 (0.0)	0	1 (0.0)	1 (0.0)	3 (0.0)
Subarachnoid hemorrhage	0.393	0	0	0	1 (0.0)	1 (0.0)
Vertebrobasilar insufficiency	0.582	3 (0.1)	1 (0.0)	1 (0.0)	3 (0.1)	8 (0.1)

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
Overall p-value: p-value for chi-square.
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

The incidence of the AE vasodilatation is elevated in all treatment groups (bazedoxifene and raloxifene) and numerically slightly higher in the bazedoxifene groups compared to raloxifene.

Table 11: Number (%) Reporting Vasodilatation in the Phase 3 Integrated Data

AE	Overall p-Value[a]	Bazedoxifene 20 mg	Bazedoxifene 40 mg	Raloxifene 60 mg	Placebo
Vasodilatation	<0.001	305 (13.8)	320 (14.6)	280 (13.0)	162 (7.4)

a. Chi-square for among-group comparisons.
b. Vasodilatation events included hot flushes/flashes, night sweats, and facial flushing.

Regarding breast disorders bazedoxifene shows a slightly favourable safety profile compared to both raloxifene and placebo. In study 301-WW the incidence of breast-related AE in the bazedoxifene group was similar to placebo. Among 1,886 subjects treated with bazedoxifene (20 mg), there were 5 cases of breast cancer per 4,591 person-years of follow-up (1.09 per 1,000). Among 1,849 subjects treated with raloxifene (60 mg), there were 7 cases of breast cancer per 4,526 person-years of follow-up (1.55 per 1,000). Among 1,885 subjects treated with placebo, there were 8 cases of breast cancer per 4,604 person-years of follow-up (1.74 per 1,000). In study 300-GL the incidence of breast-related AE (breast tenderness, pain, breast cancer, benign breast neoplasm) in the bazedoxifene 20 mg and raloxifene 60 mg groups were similar to placebo.

Table 12: Number (%) Reporting Breast Disorders, Phase 3 Integrated Data

Body System[a] Adverse Event	Overall p-Value	Treatment BZA 20 mg n = 2208	BZA 40 mg n = 2191	Raloxifene 60 mg n = 2160	Placebo n = 2195	Total n = 8754
All Breast-Related Adverse Event	0.200	194 (8.8)	189 (8.6)	207 (9.6)	226 (10.3)	816 (9.3)
Breast carcinoma	0.469	8[b] (0.4)	4 (0.2)	8 (0.4)	10 (0.5)	30 (0.3)
Breast cyst	0.170	8 (0.4)	9 (0.4)	17 (0.8)	15 (0.7)	49 (0.6)
Breast disorder	0.293	113 (5.1)	113 (5.2)	110 (5.1)	136 (6.2)	472 (5.4)
Breast neoplasm	0.182	16 (0.7)	19 (0.9)	16 (0.7)	28 (1.3)	79 (0.9)
Breast pain	0.646	64 (2.9)	54 (2.5)	63 (2.9)	54 (2.5)	235 (2.7)
Fibrocystic breast	0.011*	6 (0.3)	4 (0.2)	17 (0.8)	10 (0.5)	37 (0.4)

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
b. One (1) subject had a breast finding at study entry that was later diagnosed as breast cancer after enrolment.
Overall p-value: p-value for chi-square. Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

There are no relevant differences between treatment groups regarding reproductive disorder AE. Transvaginal ultrasonography (TVU) of the uterus and ovaries did not reveal any safety concerns. In study 301-WW endometria were evaluated in a subset of women by TVU. After 24 months, there were minimal changes in endometrial thickness in placebo (-0.08 mm, n = 131), bazedoxifene 20 mg (-0.07 mm, n = 129), and raloxifene 60 mg (0.16 mm, n = 110) treated groups. The difference in changes from baseline in endometrial thickness among bazedoxifene, raloxifene and placebo groups was not significant. At 36 month, there were no cases of endometrial cancer and 1 case (0.1%) of endometrial hyperplasia in the bazedoxifene 20 mg-treated subjects. There was 1 case (0.1%) of endometrial cancer, 1 case of sarcoma (0.1%) and 1 case (0.1%) of endometrial hyperplasia in the raloxifene 60 mg-treated subjects. There were 3 cases (0.2%) of endometrial cancer and 1 case (0.1%) of endometrial hyperplasia in the placebo group. Forty-eight (48) subjects were diagnosed with endometrial polyps through month 36, 10 subjects in the bazedoxifene 20 mg treatment group, 17 subjects in the raloxifene 60 mg treatment group, and 11 subjects in the placebo group. In study 300-GL endometrial thickness was evaluated for all subjects at baseline and every 6 months (for 24 months) by TVU. After 24 months, there were minimal changes from baseline in endometrial thickness in placebo (-0.24 mm, n = 154), bazedoxifene 20 mg (-0.06 mm, n = 158) and raloxifene 60 mg (0.01 mm, n = 154) treated groups. The difference in changes from baseline among treatment groups was not significant. The proportion of subjects with endometrial polyps was similar between treatment groups. No cases of hyperplasia or endometrial malignancy were identified in any bazedoxifene- or raloxifene-treated subjects.
The incidence of leg cramps was higher on active treatment compared to placebo, but there were no differences between different active treatment groups.
In study 301-WW 121 bone biopsies were obtained (bazedoxifene 20 mg = 28; bazedoxifene 40 mg = 29, raloxifene 60 mg = 32, placebo = 32) after approximately 24 or 36 months of treatment. Histological assessment of bone biopsies from all treatment groups revealed formation of normal lamellar bone in all treated subjects. There was no evidence of osteomalacia, peritrabecular or marrow

fibrosis, cellular toxicity or woven bone in any of the bone biopsy specimens in any of the treatment groups. Histomorphometric assessment revealed normal mineralization as evidenced by the presence of normal osteoid thickness, normal mineralization lag time, and mineral apposition rate.

- Serious adverse event/deaths/other significant events

Sixty-nine (69) deaths occurred during the phase 3 studies and the post-treatment follow-up period, as well as the deaths that resulted from a process that began during the study, were reported to the sponsor. Deaths were reported as follows: 2 of 321 (0.62%) subjects in the bazedoxifene 10 mg treatment group, 19 of 2208 subjects (0.86%) in the bazedoxifene 20 mg treatment group, 17 of 2191 (0.78%) subjects in the bazedoxifene 40 mg treatment group, 19 of 2160 (0.88%) subjects in the raloxifene 60 mg treatment group, and 12 of 2195 (0.55%) subjects in the placebo group. There were no obvious differences in the incidence and causes of death between the treatment groups.
In the integrated data of studies 300-GL and 301-WW, serious adverse events were evaluated for clinically important differences among treatment groups. Most of the serious adverse events, which showed differences among groups, were reported by a very limited number of subjects, increasing the chance of imbalance in distribution. There was, however, an increased incidence of serious adverse events for DVT in the active treatment groups. The incidence of DVT was similar between the raloxifene 60 mg and bazedoxifene treatment groups. These events are described in more detail later. The most common serious adverse events reported by ≥ 10 subjects in any treatment group were accidental injury, angina pectoris, arthralgia, arthrosis, breast carcinoma, cerebrovascular accident, chest pain, cholecystitis, cholelithiasis, coronary artery disorder, DVT, gastrointestinal carcinoma, hypertension, overdose, pneumonia, and skin carcinoma. No significant differences in the incidence of serious adverse events among treatment groups were observed for cerebrovascular adverse events including ischemic and hemorrhagic cerebrovascular accidents; endometrial events, including endometrial carcinoma, endometrial hyperplasia, and endometrial neoplasia; and breast carcinoma.

Venous thromboembolism (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
In the osteoporosis prevention study, 300-GL, the incidence of VTEs was similar among all treatment groups in postmenopausal women with a mean age 58 years. In the osteoporosis treatment study, 301-WW, an increased incidence of VTEs was observed in all active treatment groups compared with placebo in postmenopausal women with a mean age 66 years. In the osteoporosis treatment trial in 7,492 valuable subjects (mean age=66 years), the bazedoxifene-treated women had an increased risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis). The rate per 1,000 women-years through the 3-year study period was 3.23 in the bazedoxifene 20 mg group and 1.72 in placebo. The relative risk was 1.9 through the 3-year study period. The relative risk decreased over the three years studied (year 1=3.0, year 2=2.5, year 3=0.3).

With regard to DVT there was a statistical significant RR of 4.93 (95% CI: 1.09, 22.39) for bazedoxifene 20 mg compared to placebo. Using adjudicated data, the RR of DVT was 7.0 (95% CI 0.86, 56.81) in the bazedoxifene 20 mg group compared to the placebo group.
Hence, DVT (and VTE) continues to be a significant safety concern with bazedoxifene, to be further addressed in a study, to which the applicant committed as a follow-up measure
Although not statistically significant, the RR for thromboembolic events with bazedoxifene 20mg compared to raloxifene was
- 1.51 (0.71 – 3.22) for any event
- 1.22 (0.48 – 3.09) for DVT
- 1.22 (0.33 – 4.55) for PE
- 1.96 (0.18 – 21.56) for RVT.

An explanation as suggested by the applicant was a lower than expected rate of VTE in the raloxifene group in study 301-WW This explanation was considered not to be fully convincing, and therefore this issue (comparison of VTE risk associated with raloxifene and bazedoxifene) will be addressed in a proposed EU-post-marketing study as a crucial part of the RMP.
Currently, the possibility that the absolute risk of VTE in subjects ≥75 years might be greater than in younger women cannot be excluded. As a consequence, it will be followed up in a post-marketing study and is included in the risk management plan. Also, it cannot be excluded that the risk associated

with bazedoxifene might be higher in obese women. As a consequence, the data obtained in a post-marketing study will also be stratified by BMI.

Cerebrovascular Events

Potential cerebrovascular event cases have been adjudicated/readjudicated. The Adjudication Board determined that overall 52 subjects experienced a stroke (bazedoxifene 20 mg: 12 subjects, bazedoxifene 40 mg: 14 subjects, raloxifene 60 mg: 12 subjects, and placebo: 14 subjects) and 19 subjects experienced a TIA (bazedoxifene 20 mg: 5 subjects, bazedoxifene 40 mg: 7 subjects, raloxifene 60 mg: 3 subjects, and placebo: 4 subjects). Eleven (11) subjects with stroke and 1 subject with TIA reported the events from 4 to 166 days after their last dose of test article. The incidence rate in women-years was determined from the number of events adjudicated as ischaemic stroke, hemorrhagic stroke, stroke unspecified, or TIA and the total exposure for subjects in each treatment group. Follow-up time was uniformly distributed among treatment groups and ranged from 4492 to 4652 women-years for the cerebrovascular events. The frequency and rate of cerebrovascular events per 1000 women-years cumulative (0 to 3 years) is presented in the following table.

Table 13: Frequency and Rate Per 1000 Women-Years of Cerebrovascular Events, Based on Adjudicated Data

	----- n -----				-Rate Per 1000 Women-Years (95% CI)-			
Year	PBO	RLX	BZA20	BZA40	PBO	RLX	BZA20	BZA40
Total stroke								
0-3	14	12	12	14	3.01 (1.65,5.06)	2.63 (1.36,4.59)	2.59 (1.34,4.52)	3.12 (1.70,5.23)
Ischaemic stroke								
0-3	10	10	9	12	2.15 (1.03,3.96)	2.19 (1.05,4.02)	1.94 (0.89,3.69)	2.67 (1.38,4.66)
Hemorrhagic stroke								
0-3	2	1	1	1	0.43 (0.05,1.55)	0.22 (0.01,1.22)	0.22 (0.01,1.20)	0.22 (0.01,1.24)
Stroke, unspecified								
0-3	2	1	2	1	0.43 (0.05,1.55)	0.22 (0.01,1.22)	0.43 (0.05,1.56)	0.22 (0.01,1.24)
Transient ischaemic attack								
0-3	4	3	5	7	0.86 (0.23,2.20)	0.66 (0.14,1.92)	1.08 (0.35,2.52)	1.56 (0.63,3.21)

BZA20 = bazedoxifene 20 mg; BZA40 = bazedoxifene 40 mg; CI = confidence interval; RLX = raloxifene 60 mg; PBO = placebo.
/project/radnor/anarpt/production/tse424/p301_corestudy/cp/programs/ae4_t1.sas -> ae4_t1_301_cva_all_a
Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3068A1 TSE-424/ P301_CORE_STUDY2007/ 301_NDA_CDRs_CORE_STUDY2007/CVA_RE-ADJUDICATION_FINAL/ 3068-301_NDA_CDRS_CORE_STUDY2007 ae4_t1_301_cva_all_a - 21NOV08 11:25.

The rate estimates for the first, second, and third years of the study were similar to that for the first 3 years combined although the 95% CI for the estimates were greater. Overall, the rates for the cerebrovascular events were comparable among the 4 treatment groups with overlapping CIs.
The results of the readjudication analysis are overall consistent with the non adjudicated cerebrovascular safety analysis as reported by study investigators. These results are also in agreement with the safety assessment based on the initial adjudication of cerebrovascular events.

- Laboratory findings

Regarding laboratory adverse events no differences between active treatment groups for hepatology, bone metabolism related measurements or haematology have been identified. Increases in ALT or AST were lower on active treatment compared to placebo.

- Safety in special populations

As can generally be expected, older patients showed more AEs, but differences were small and no specific dose recommendation is required. No definite conclusion on ethnic origin is possible due to low number of participants available within each treatment group. The use of bazedoxifene in subjects with significant renal impairment cannot be endorsed as only limited data regarding the pharmacokinetics in this population are available at present. This is reflected in the SPC and the PIL.

- Safety related to drug-drug interactions and other interactions

For the safety related to drug-drug interactions and other interactions no safety concerns are expected, since no DDI has been identified and these findings are in line with data on raloxifene.

- Discontinuation due to adverse events

Discontinuation due to any AE and to the AE vasodilatation was numerically lower in the raloxifene arm compared to both bazedoxifene arms, The safety analysis of discontinuations due to AE seems to confirm a difference in discontinuations due to the AE vasodilatation between bazedoxifene and raloxifene treatment groups

Table 14: Number (%) Reporting AE Resulting in Withdrawal that Showed a Significant Difference Among Groups, Phase 3 Integrated Data

		Treatment			
Body System [a] Adverse Event	Overall p-Value	BZA 20 mg n = 2208	BZA 40 mg n = 2191	Raloxifene 60 mg n = 2160	Placebo n = 2195
Any Adverse Event	0.391	334 (15.1)	337 (15.4)	316 (14.6)	300 (13.7)
Asthenia	0.026*	5 (0.2)	2 (0.1)	10 (0.5)	2 (0.1)
Infection	0.010*	1 (0.0)	0	6 (0.3)	1 (0.0)
Heart arrest	0.030*	0	0	0	3 (0.1)
Vasodilatation	0.003**	27 (1.2)	28 (1.3)	19 (0.9)	7 (0.3)
Osteoporosis	0.008**	0	0	0	4 (0.2)

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.

Overall p-value: p-value for chi-square. Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

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.

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
VTE – Important identified risk	Included as an endpoint in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs. The observational cohort studies will use computerized administrative databases to compare the incidence of VTE in bazedoxifene users with raloxifene users, stratifying by age and by BMI where possible.	– Risk minimisation actions will consist of communication in the SPC and PIL. SPC Section 4.3: contraindications Active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. SPC Section 4.4: Special warnings and precautions for use Use of CONBRIZA is not recommended in women at an increased risk for venous thromboembolic events (see section 4.8). The risk factors associated with venous thromboembolism (VTE) cases in clinical trials included: advanced age, obesity, immobilisation, surgery, major trauma and malignancy. It should be discontinued prior to and during prolonged immobilisation (e.g., post-surgical

		recovery, prolonged bed rest), and therapy should be resumed only after the patient is fully ambulatory. In addition, women taking CONBRIZA should be advised to move about periodically during prolonged travel. PIL section 2: Take special care with Conbriza – as it may increase your risk of getting blood clots. While very infrequent, these clots can cause serious medical problems, disability or death. Speak with your doctor to see if you are at increased risk for blood clots. – if you are immobile (unable to move) for some time, such as being wheel-chair bound, sitting for a prolonged period of time or having to stay in bed while recovering from an operation or illness. If you are traveling on long trips, you should walk around or exercise your legs and feet at regular intervals. This is because sitting for a long time in the same position may prevent good
Ischemic stroke – Important potential risk	Included as an endpoint in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs.	None, since no increased risk of ischemic stroke has been identified.
Atrial fibrillation – Important potential risk	Included as an endpoint in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs.	None, since no increased risk of atrial fibrillation has been identified.
Renal carcinoma and adenoma - Potential risk from non-clinical studies	Renal cell carcinoma as part of PASS pharmacoepidemiology studies Renal cell carcinoma and adenoma events will continue to be analyzed in the 4 year extension of study 301-WW. Spontaneous reports of related events will be collected, analyzed and reported in PSURs.	SPC Section 5.3 Pre-Clinical Safety Data. In an 18-month bone efficacy study in aged ovariectomized cynomolgus monkeys, bazedoxifene, administered orally to monkeys at dosages of 0, 0.2, 0.5, 1, 5, or 25 mg/kg/day, resulted in exposures, based on surface area (mg/m^2) of approximately 0.2 to 24 times the clinical dose of 20 mg.. Renal cell carcinomas were observed in this study. These tumours are considered as spontaneous renal cell carcinomas that are known to occur in nonhuman primates

		and are unlikely to be relevant to humans.
New presentation or aggravation of pre-existing renal failure or insufficiency - Potential risk from non-clinical studies	Surveillance for renal insufficiency and failure as part of PASS pharmacoepidemiology studies New presentation or aggravation of pre-existing renal failure or insufficiency continue to be analyzed in the 4 year extension of study 301-WW. Spontaneous reports of related events will be collected, analyzed and reported in PSURs.	SPC Section 4.4 Special warnings and precautions for use. Bazedoxifene has not been sufficiently evaluated in patients with severe renal impairment; caution should be used in this population.
Cholecystitis – Potential risks	Included as an endpoint in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs.	None, since no increased risk of cholecystitis has been identified.
Increased triglyceride levels – Potential risks	Included as an endpoint in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs.	No risk minimisation activities proposed, since no increased risk has been identified.
Ischemic/thrombotic cardiac disorders – limited information	Included as an endpoint in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports will be collected, analyzed and reported in PSURs.	None, since no increased risk of ischemic/thrombotic cardiac disorders has been identified.
Elderly – limited information	Age to be used as a stratification factor in the EU and US PASS pharmacoepidemiology studies and in the 4-year extension of study 301-WW. Spontaneous reports in the elderly will be collected, analyzed and reported in PSURs.	No risk minimisation activities proposed for this limited information item.
AE = adverse event; DVT = deep vein thrombosis; EU = European Union; PE = pulmonary embolism; PIL = patient information leaflet; RR = relative risk; RVT = retinal vein thrombosis; SPC = Summary of Product Characteristics; VTE = venous thromboembolism.		

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There was a quality issues that will be resolved as Follow-up Measures within an agreed timeframe. This issue is not expected to have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

All relevant properties of bazedoxifene were investigated in standard PD, PK and toxicology studies.
In rats, treatment with bazedoxifene for approximately one year partially prevented the effects of ovariectomy on numerous skeletal parameters (bone mineral content, bone mineral density, and architecture). In monkeys, treatment with bazedoxifene for 18 months resulted in the partial preservation of cortical and cancellous bone mass as determined by BMD measurements. In both species, the administration of bazedoxifene had no deleterious effects on bone quality and resulted in uterine and mammary gland atrophy without other histological differentiation from untreated animals.

Repeated-dose studies in normally cycling rodents and cynomolgus monkeys revealed a marked stimulation of ovarian follicle growth without ovulation, leading to partly haemorrhagic-ovarian cysts and markedly elevated estradiol levels. This is considered not clinically relevant in post-menopausal women.

Carcinogenicity studies showed a marked decrease in pituitary and mammary tumours; a causative link can be assumed because the pituitary tumours are regarded as oestrogen-dependent prolactinomas whereby the secreted prolactin caused the mammary tumours.
Bazedoxifene caused also corticomedullar nephrocalcinosis and enhanced spontaneous chronic progressive nephropathy (CPN) in male rats. Urine parameters were pathologically changed. In long-term studies renal tumours (adenomas and carcinomas) were observed at all doses tested, most likely as a consequence of this chronic renal damage.
It is plausible to assume that bazedoxifene, via an oestrogen-like action also caused this disease in males. The preclinical kidney findings are mentioned in the SPC to make the prescriber aware of a possible link between bazedoxifene and kidney disease and take a closer look if a patient receiving bazedoxifene develops kidney disease.

Bazedoxifene showed adverse effects on fertility and early embryonic development at low doses (0.03 mg/kg/day) in female rats. Due to lack of prenatal and postnatal developmental studies, including maternal function, toxicity observed in embryo-foetus and lack of knowledge concerning excretion into milk, bazedoxifene is not intended for use in breast-feeding women. Moreover bazedoxifene is only for use in post-menopausal women.

Efficacy

Efficacy was studied in 2 large phase 3 trials. Study 301-WW examined the effect of bazedoxifene 20 mg and 40 mg, as well as raloxifene 60 mg and placebo on new osteoporotic fractures over a period of 3 years. This study is considered the main (pivotal) trial. Based on dose-finding studies, 2 dosages, 20 mg and 40 mg per day of bazedoxifene were studied. The study evaluated 7492 postmenopausal women with a diagnosis of osteoporosis, based on the presence of at least one mild asymptomatic vertebral fracture, or (in the absence of a vertebral fracture) a BMD T-score at the femoral neck or lumbar spine of –2.5 or worse. The primary outcome parameter were new radiographically confirmed vertebral fractures. Among the secondary endpoints were non-vertebral fractures and BMD.
Participants were healthy postmenopausal women with a mean age of 66.4 years; the mean number of years since the last menstrual period was approximately 19.5 years. The mean baseline T-scores at the lumbar spine and femoral neck were -2.4 and -1.7, respectively. About 56% of participants had at least 1 prevalent fracture.

There was a clinically significant reduction in the incidence of new vertebral fractures compared to placebo for both bazedoxifene doses tested. The rate of new vertebral fractures in women treated with bazedoxifene 20mg per day over 3 years was 2.34%, compared with a fracture rate of 4.07% for women on placebo, corresponding to a relative risk reduction of 42%. The effects were independent of baseline status, apparent from 24 month of treatment onwards, statistically significant at 36 month of treatment and comparable to raloxifene treatment. After 36 months of treatment, the Kaplan-Meier rate estimates of cumulative fracture incidence for the bazedoxifene 20 mg and 40 mg, the raloxifene 60 mg and placebo were 2.34%, 2.51%, 2.34%, and 4.07%, respectively. However, in the subgroup with no vertebral fracture at baseline, the difference in fracture rates between bazedoxifene 20 mg and placebo did not reach statistical significance anymore. The treatment effect was similar between bazedoxifene 20 mg and raloxifene 60 mg. The incidence of non-vertebral osteoporotic fractures was not statistically significant different between any active treatment group and placebo. Bazedoxifene 20 mg and raloxifene 60 mg significantly increase BMD at the lumbar spine (1.14% and 1.26%, respectively, at 6 months; 1.41% and 1.49%, respectively, at 3 years).

Study 300-GL examined the effect of bazedoxifene 10 mg, 20 mg, and 40 mg as well as raloxifene 60 mg and placebo on bone mineral density (BMD) over a period of up to 24 months. This study was designed as an "osteoporosis prevention" and the data obtained is considered supportive for the indication finally granted. As in Study 301-WW, all participants received Calcium and Vitamin D supplements.
In this trial, 1583 healthy postmenopausal women > 45 years of age with at least one osteoporosis-related risk factor were analysed. The mean number of years since the last menstrual period was 10.9 years, the mean age was 57 years. The mean baseline T-scores at the lumbar spine ranged from -1.12 to -1.24. Bazedoxifene 20 mg and 40 mg prevented bone loss at both the lumbar spine and total hip. At month 24, lumbar spine and total hip BMD was higher in all groups treated with bazedoxifene compared with the placebo group. All bazedoxifene dose groups met the prespecified criteria for non-inferiority to the raloxifene 60 mg group for lumbar spine and total hip BMD.
Overall, concluded from both trials, the 40 mg bazedoxifene dose did not offer a more favourable benefit/risk profile than the 20 mg dose.

At the request of the CHMP the fracture risk of the population studied was investigated to be in concordance with the 2006 osteoporosis guideline. The applicant provided an analysis of the absolute risk of fractures in the population studied, based on the extrapolation of rates from the placebo arm; upon correction of confounding factors in a model algorithm, the 10-year fracture probability for vertebral fractures was estimated at 11%. This suggest that the study overall was in line with the recommended population of revision 2 of the CHMP guideline on osteoporosis.

During the procedure, the CHMP had requested a GCP inspection of the main (pivotal) clinical trial, 301-WW. A number of critical deviations at one of the study sites investigated were identified, raising in particular concern with regard to underreporting of adverse events in the trial overall.
During the procedure, the applicant performed an adjudication/readjudication process of potential cerebrovascular event cases for both main studies and provided evaluations of the fracture data, as well as SAE data, with and without inclusion of data from the large study site.
The results did not indicate changes in the efficacy in fracture reduction or in the AE profile when data from this site were excluded from the analysis. Moreover, the results were consistent with overall analyses of the entire population. Reassuring was the fact, that the trial was both placebo and active comparator-controlled, suggesting that critical findings identified were independent from treatment strata. Overall, it was therefore concluded by the CHMP that the findings did not impact on the reliability or interpretation of the data, and therefore did not alter the otherwise positive benefit-risk assessment.

Safety

The safety evaluation is mainly based on results from the 2 large phase 3 trials, the scale (data from 9075 women of the phase 3 studies) and length (2 and 3 years) of which were considered adequate. Moreover, the inclusion of raloxifene as a comparator allowed a comparison with raloxifene's extensive existing safety information.

Overall, bazedoxifene 20 and 40 mg doses were well tolerated in postmenopausal women and the adverse event profile of bazedoxifene was consistent with that of raloxifene reported in these studies as well as in earlier clinical trials.
The most frequent drug-related adverse reactions were hot flushes and muscle spasms (including leg cramps).
Safety results with regard to the cardiovascular system did not raise a concern. For the cerebrovascular events the overall incidence of ischemic and hemorrhagic cerebrovascular AE did not show a statistically significant difference between treatment groups. Potential cerebrovascular event cases had been adjudicated/readjudicated, and the outcome was consistent with the initial analysis. Regarding breast disorders bazedoxifene showed a slightly favorable safety profile compared to both raloxifene and placebo. There were no relevant differences between treatment groups regarding reproductive disorder AE, in particular with regard to the endometrium. Bone biopsies were performed in a subset of 121 patients of study 301-WW, and did not show relevant histological differences between groups, in particular with regard to bone structure and mineralisation. There were no obvious differences in the incidence and causes of death between the treatment groups.

There was, however, an increased incidence of serious adverse events for deep vein thrombosis in the active treatment groups. The incidence of DVT was similar between the raloxifene 60 mg and bazedoxifene treatment groups. In study 301-WW in 7,492 valuable subjects, the bazedoxifene-treated women had an increased risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism and retinal vein thrombosis). The rate per 1,000 women-years through the 3-year study period was 3.23 in the bazedoxifene 20 mg group and 1.72 in placebo. The relative risk was therefore 1.9; the relative risk decreased over the three years studied (year 1=3.0, year 2=2.5, year 3=0.3). To address this safety concern with bazedoxifene, the applicant has committed to perform a post-marketing safety study (see also RMP).

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

Overall the user consultation demonstrated that study participants were able to identify and comprehend key safety messages. The results were considered supportive of the proposed PIL and the test conforming to EMEA guidelines.

Risk-benefit assessment

A significant reduction in the incidence of new vertebral fractures was observed after 36 months of treatment for bazedoxifene 20 mg and 40 mg treatment groups. The rate of new vertebral fractures in women treated with bazedoxifene 20mg per day over 3 years was 2.34%, compared with a fracture rate of 4.07% for women on placebo, corresponding to a relative risk reduction of 42%. This reduction was comparable to the risk reduction seen with raloxifene. However, statistical significance of this effect in subgroup analysis was only present in higher risk subjects; in subjects treated with bazedoxifene, the incidence of fractures was related to the baseline fracture risk: the higher the fracture risk, the greater the benefit with bazedoxifene treatment.
Regarding non-vertebral fractures (secondary endpoint) no effect of bazedoxifene or raloxifene was demonstrated. There was a post-hoc subgroup analysis in high risk individuals (T-score ≤ -3 or the presence of fractures) indicating an effect with 20 mg at month 12 and sustained up to month 36, but not with 40 mg bazedoxifene.
Therefore, the efficacy data available support the assumption that efficacy of bazedoxifene in the treatment indication has sufficiently been established for vertebral fractures, while no effect of bazedoxifene relative to placebo on the incidence of non-vertebral fractures has been established in the overall study population.

With regard to secondary outcome parameters, bazedoxifene relative to placebo significantly increased BMD at the lumbar spine, total hip, femoral neck, and femoral trochanter. However, although

treatment effect was demonstrated on BMD in osteoporotic patients, the effect was significantly and consistently lower compared to raloxifene. Significant decreases in levels of bone markers indicating a reduction in bone turnover were demonstrated with all active treatments at all time points in both phase 3 studies.

The safety profile seen in the clinical trials with bazedoxifene was mainly in line with the known safety profile of drugs in the SERM class. This comparison was facilitated by inclusion of both placebo and the active comparator raloxifene in the clinical trials. AE of special interest were venous thromboembolic events, cardiovascular events, cerebrovascular AE, vasodilatation, reproductive disorders including breast disorders, and leg cramps.

Bazedoxifene had a neutral endometrial profile, with endometrial effects similar to placebo. No increased incidence of endometrial neoplasm (polyps), hyperplasia, or carcinoma was observed in the bazedoxifene treatment groups compared with placebo. The overall incidence of breast cancer was low; bazedoxifene treatment groups had a numerically lower incidence of breast cancer compared to placebo. Analysis of bone biopsies after treatment revealed formation of normal lamellar bone in all treated subjects.

There was, in study 301-WW, an increased risk of venous thromboembolism, with a relative risk of 1.9 compared with placebo. This is a known class effect of SERMs. The incidence of VTE appeared to be somewhat higher in the bazedoxifene treatment groups than in the raloxifene treatment group. This overall concern of the CHMP with regard to VTEs will be followed up by a post-authorization safety study of venous thromboembolic events.

The overall incidence of ischemic and hemorrhagic cerebrovascular AE did not show a statistically significant difference between treatment groups, but the AE cerebral ischemia and cerebrovascular accident are reported numerically more often in the bazedoxifene and in the placebo than in the raloxifene groups. Potential cerebrovascular event cases have been adjudicated/re-adjudicated. The results were overall consistent with the non-adjudicated cerebrovascular safety analysis as reported by study investigators and in agreement with the safety assessment based on the initial adjudication of cerebrovascular events.

Overall, the data provided by the applicant clearly demonstrated a significant reduction in the incidence of new vertebral fractures in osteoporotic women treated with bazedoxifene compared to placebo; the effect was comparable to that seen with raloxifene. This was accompanied by significant effects on BMD and biochemical markers of bone turnover. The safety data provided by the applicant indicated no major differences between bazedoxifene and raloxifene. The known AE are adequately addressed in the provided RMP. Therefore bazedoxifene seems to have a favourable safety profile in the treatment of osteoporosis in postmenopausal women.

Due to the fact that the revised 2006 guideline no longer recognizes the prevention indication as a separate indication, an osteoporosis prevention indication of bazedoxifene could not be granted. In conclusion the benefit-risk ratio was considered positive by the CHMP for the treatment of postmenopausal osteoporosis in women at increased risk of fracture regarding vertebral fractures; efficacy on hip fractures has not been established.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that: Additional pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of CONBRIZA in the following indication: “CONBRIZA is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip

fractures has not been established." was favourable and therefore recommended the granting of the marketing authorisation.